What’s New and Important in Pediatric Ophthalmology and Strabismus for 2017
The Complete and Unabridged handout

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1. **AMBLYOPIA**

A pilot randomized clinical trial of intermittent occlusion therapy liquid crystalglasses versus traditional patching for treatment of moderate unilateral amblyopia


In this randomized controlled non-inferiority study, the effectiveness of intermittent occlusion therapy (IO therapy) using liquid crystal glasses was compared to continuous occlusion therapy using traditional adhesive patches for treating amblyopia. Children 3-8 years of age with previously untreated, moderate, unilateral amblyopia (visual acuity of 20/40 to 20/100 in the amblyopic eye) were enrolled. Amblyopia was associated with strabismus, anisometropia, or both. Prior to initiation of treatment all participants had worn any optimal refractive correction for at least 12 weeks without improvement. Subjects were randomized into two treatment groups: a 4-hour IO therapy group with liquid crystal glasses (Amblyz), set at 30-second opaque/transparent intervals (occluded 50% of wear time), and a 2-hour continuous patching group (occluded 100% of wear time). For each patient, visual acuity was measured using ATS-HOTV before and after 12 weeks of treatment. Data from 34 patients were available for analysis. Amblyopic eye visual acuity improvement from baseline was 0.15 +/- 0.12 logMAR (95% CI, 0.09-0.15) in the IO therapy group (n = 19) and 0.15 +/- 0.11 logMAR (95% CI, 0.1-0.15) in the patching group (n = 15). In both groups improvement was significant, but the difference between groups was not (P = 0.73). No adverse effects were reported. In this pilot study, IO therapy with liquid crystal glasses was not found to be inferior to adhesive patching. The authors concluded that it is a promising alternative treatment for children 3-8 years of age with moderate amblyopia. Even though there were some flaws with randomization the study was generally well designed. Some of the limitations were the short follow-up period and the large withdrawal from the study. Previous studies on Amblyz are discussed. It is approved as a medical device by the FDA and this pilot study can be a basis for evidence-based guidelines for prescribing these glasses.
Photoscreening for amblyogenic risk factors in 1-year-olds: results from a single center in Portugal over a 9-year period.


This retrospective study reported the experience of a single center in Portugal with photoscreening 1-year-olds for amblyogenic risk factors over a 9-year period. It also estimated amblyopia prevalence in this population. The records of 11,029 children 11-18 months of age, who were screened for amblyogenic risk factors between 2004 and 2012 were reviewed. Measurements were performed with MTI (until 2008) and plusoptiX S04 (from 2009). The screening was negative in 8,985 children (82%), positive in 519 (5%), unreadable in 201 (2%), and borderline in 1,324 (12%). The overall positive predictive value (PPV) for the presence of at least one amblyogenic risk factor was 56.8%. The estimated prevalence of meaningful refractive errors in this population was 2.2%; of strabismus, 0.3%. The authors conclude that in the presented cohort the rate of unreadable screenings was low. The overall PPV was lower than other large studies, at older ages, but higher than those of the same-age children. This study demonstrates the feasibility of screening 1-year-olds. Even though the cohort is very large, not all patients completed an ophthalmic examination. Hence, sensitivity and the negative predictive value were not available. It is difficult to interpret the clinical relevance of these photoscreeners at this age group, when these values are missing.

Effect of a Binocular iPad Game vs Part-time Patching in Children Aged 5 to 12 Years With Amblyopia
A Randomized Clinical Trial


Binocular treatment of amblyopia represents a paradigm shift in the treatment of this disease. Pilot studies demonstrated an improvement in visual acuity in those treated with a binocular iPad game. This study aims to address the need for a large randomized clinical trial. The authors designed a non-inferiority study comprised of 385 patients with anisometropic, strabismic or combined amblyopia age 5 to 12 years old. Participants were randomized to 2 hours a day of patching the dominant eye or to play a specially designed video game with dichoptic goggles 1 hour a day for 16 weeks. Mean amblyopic eye vision improved by 1.05 lines in the binocular group (2 sided CI 0.85-1.24) and 1.35 (2 sided CI 1.17-1.54) lines in the patching group. Visual acuity overall improved by 1 line. Younger children (age 5 to < 7) with no previous amblyopia treatment improved by about 2.5 lines
in both groups. The adjusted treatment group difference was 0.31 lines favoring patching. This did not exceed the previously specified non-inferiority measure of 0.5 lines but the authors point out that the 1 sided upper limit of the confidence interval did, coming in at 0.53 lines.

Conclusion: A concern about the study is that only 22% of participants in the binocular group completed greater than 75% of the prescribed play. The authors conclude “VA improvement with this particular binocular iPad treatment was not as good as with 2 hours of prescribed daily patching”. Enthusiasm for binocular treatment of anisometropic, mixed and microstrabismic amblyopes may be blunted with this randomized controlled trial. The standard of care of patching, Atropinization or other monocular forms of penalization of the dominant eye should not yet be abandoned.

Binocular Treatment of Amblyopia in Children
Teething Problems on the Path to Clinical Practice

In this invited commentary, Dr. Dahlmann-Noor avers that the most significant clinical finding of the PEDIG paper is that visual acuity improved in the amblyopic eye by 2.5 lines in the binocular group and 2.8 lines in the patching group in the younger cohort, that is, less than age 7 who were treatment naïve, other than glasses. Unfortunately, this subgroup comprised only 38/385 patients and statistical significance could not be determined. She notes that the severe amblyopes in the study (14%) were undertreated in the patching group (2 hours a day vs 6 hours a day) and so the stated mean difference of 0.3 lines in favor of patching may actually have been greater. The author states that the main weakness of the study is the heterogeneity of the groups such as not treated, previously treated, various ages, and different types of amblyopia were all included. Also, the adverse events, such as diplopia, were concerning and this occurred in 16% in the binocular group and 11% in the patching group. The diplopia was persistent in 1 (0.55%) patient in the binocular group, which is rare but present, and should be discussed with parents prior to treatment.

Binocular iPad Game vs Patching for Treatment of Amblyopia in Children A Randomized Clinical Trial

Previous pilot studies of binocular treatment of amblyopia used a falling block style of video game as the intervention in a comparison to part-time patching. Compliance with a Tetris or Pong-style video game was poor, up to 38% of participants. To address the possibility that the game was not interesting enough to engage children to play for the required amount of time, a new game, Digrush, developed with Dr. Robert Hess and Amblyotech and Ubisoft, was used in this randomized clinical trial. This was a crossover trial in which 14 amblyopes in the
part time patching group at the end of 2 weeks, switched into the binocular group so all 28 amblyopes played Digrush for the last 2 weeks of the trial. The game was played one hour a day for 5 out of 7 days a week (10 hours per week). The patching group patched 2 hours a day 7 out of 7 days a week (14 hours per week). 71% of children had prior amblyopia treatment. Compliance was excellent and similar between groups. Age range was 4.6 to 9.5 years and were comprised of anisometropic, mixed and strabismic amblyopes (with a tropia less than 4 prism diopters). Mean amblyopic vision was 20/63 at enrollment. The authors found a greater improvement in the binocular group compared with patching at the 2 week visit (mean increase of 1.5 lines in binocular group vs. 0.7 lines in the patching group). After crossover, patching group caught up and at 4 week study conclusion, there was no significant difference between the groups. Stereoaucity did not improve in either group. Limitations of the study include that there were 5/28 (18%) with severe amblyopia and yet they could be randomized to only 2 (not 6) hours of patching a day, so lack of improvement in patching group at 2 weeks could be because of inclusion of these undertreated severe amblyopes.

Conclusion: Greater compliance was found in amblyopic children who played the binocular game, Digrush, compared with prior studies of random falling blocks. Visual acuity in the amblyopic eye 2 weeks into the study was significantly greater than the amblyopes who patched part time.

New Treatments for Amblyopia—To Patch or Play?

In this invited commentary, Mr. Sloper critiques the 2 studies (Holmes, et.al and Kelly et.al.) on binocular treatment of amblyopia. The mean visual acuity improvement in the best responding groups was only 1.5 lines with a mean difference between binocular and patching groups of only 0.5 lines. He suspects that including older amblyopes, those who had prior treatment, and moderate amblyopia at recruitment (20/63) account for the anemic response to either treatment. Compare with the atropine vs. patching or intense patching of severe amblyopes (ATS by PEDIG) in which participants had 3-4.5 lines of improvement in visual acuity. The more engaging movie provided in the Kelly study may have stimulated the adrenergic system, known to enhance cortical plasticity, and hence the significantly greater visual acuity improvement in the binocular group vs. the patching group at 2 weeks, just prior to crossover. The small improvement in visual acuity in both studies raises the possibility of unconscious bias since the researchers were not masked. Mr. Sloper concludes that further studies should employ masked observers in younger children with amblyopia who are treatment naïve to settle this, as well as other questions, raised in this commentary.

Future Research Using Amblyopia Treatment Dose Monitors

In this invited commentary, the author notes the significant variability in compliance, with some study subjects demonstrating as little as 10% compliance. This
provides an opportunity to identify such patients and give their families educational material that might overcome cultural or socioeconomic barriers to glasses or patching use. The author notes that some study subjects, even with excellent, 80% or more, compliance with glasses wear or patching, did not have optimal visual acuity outcomes. This points to the need for future large scale studies to identify risk factors such as age, type of amblyopia, depth of amblyopia or prior treatment, that might hinder improvement in visual acuity despite excellent compliance.

Association Between Adherence to Glasses Wearing During Amblyopia Treatment and Improvement in Visual Acuity

Poor compliance with amblyopia treatment remains a major reason why visual acuity in the amblyopic eye does not improve. Subjective recall by parents of compliance with amblyopia treatment is not ideal as a measure of compliance. Occlusion dose monitors (ODM’s) were studied as early as the 1990’s to provide objective measures of compliance. However, the monitors were bulky and the child had to carry the data recorder in a shoulder bag. The authors of the current study use a small device attached to the frame of the patient’s glasses which uses the principle of the temperature difference between the skin and the eye to determine compliance with spectacle wear or with patching.

This prospective cohort study was comprised of 20 anisometropic and 20 mixed (strabismic and anisometropic) amblyopes. There was no difference in the severity of the amblyopia between the 2 groups. However, the anisometropic amblyopes were older on average than the mixed group (6.2 vs. 4.9 years P=0.048). Median (SD) adherence to glasses wearing was 70%(25.3%) during the glasses wearing phase and 76.3%(21.5%) during the patching phase. There was no difference between adherence in the 2 groups of amblyopes. A moderate correlation was observed between adherence to glasses wearing and percentage improvement in visual acuity during the glasses phase (r = 0.462; P = .003). This correlation was even higher in the pure anisometropic amblyopes. Adherence to the patching regimen in those study subjects who had to patch, was moderately correlated with visual acuity improvement (r=0.49 P=0.003). There was a strong correlation between adherence to wearing glasses and adherence to patching.

Conclusion: It was interesting that in the 18 week run in phase wearing glasses only, only 2/20 anisometropic amblyopes had resolved their amblyopia, defined as less than a one line interocular difference. The glasses dose monitor (GDM) was assessed for reliability with 4 adult subjects who diaried the amount of time wearing glasses and was consistent with the reading of the GDM to within 6 minutes. Improvement in visual acuity appeared to plateau after 12 weeks (improvement of 2 lines on average in this time period compared with 0.01 lines of improvement from 12-18 weeks in the glasses only run in phase). Also multivariate regression models highlighted the impact of age, type of amblyopia and compliance with glasses wear as key factors in improvement of visual acuity.
Assessing Suppression in Amblyopic Children With a Dichoptic Eye Chart


Suppression has a key role in the etiology of amblyopia, and contrast-balanced binocular treatment can overcome suppression and improve visual acuity. Quantitative assessment of suppression could have a role in managing amblyopia. This study evaluates the use of a novel eye chart to assess suppression in children. This study enrolled children (7–12 years; 63 amblyopic, 25 nonamblyopic with strabismus or anisometropia, 12 controls) in the primary cohort and 22 children (3–6 years; 13 amblyopic, 9 nonamblyopic) in a secondary cohort. Letters were presented on a dichoptic display (5 letters per line). Children wore polarized glasses so that each eye saw a different letter chart. At each position, the identity of the letter and its contrast on each eye’s chart differed. Children read 8 lines of letters for each of 3 letter sizes. The contrast balance ratio was the ratio at which 50% of letters seen by the amblyopic eye were reported. Amblyopic children had significantly higher contrast balance ratios for all letter sizes compared to nonamblyopic children and controls, requiring 4.6 to 5.6 times more contrast in the amblyopic eye compared to the fellow eye (P < 0.0001). Amblyopic eye visual acuity was correlated with contrast balance ratio (r ranged from 0.49–0.57 for the 3 letter sizes). Change in visual acuity with amblyopia treatment was correlated with change in contrast balance ratio (r ranged from 0.43–0.62 for the 3 letter sizes). This study demonstrates that severity of suppression can be monitored as part of a routine clinical exam in the management of amblyopia in children. The association between good acuity and low suppression harmonizes with recent adult data, but contrasts with an older view that posited strong suppression to be a by-product of achieving good acuity. Instead, new binocular treatments for amblyopia are showing success in improving acuity, and depth perception, by reducing suppression. This study furthers our understanding of suppression in amblyopia and provides us with a new tool to assess efficacy of amblyopia treatment in children.

On the Maintenance of Normal Ocular Dominance and a Possible Mechanism Underlying Refractive Adaptation


The purpose of this cross sectional cohort study was to determine if humans with uncorrected anisometropia who have not developed anisometropic amblyopia exhibit a shift in ocular dominance nonetheless, reflecting a more subtle form of deprivation and whether such a change in dominance, if it occurs, is permanent or alterable by an extended period of optical correction. A total of 25 normal controls (mean age 27.5 ± 2.1 years); 28 anisometropes (mean age 20.7 ± 5.6
years) who were fully corrected for more than 16 weeks prior to this investigation; and 24 anisometropes who had never been corrected (mean age 21.2 ± 9.8 years) (aside from 1 hour prior) participated in this study. Sensory eye dominance of observers was measured using the binocular phase combination paradigm to find an interocular contrast ratio at which the contributions of each eye to the binocularly fused percept were equal (i.e., the balance point measure of ocular dominance). Controls exhibited a balance point close to unity (0.91 ± 0.05), while the two groups of anisometropes exhibited a clear binocular imbalance (uncorrected anisometropes, 0.51 ± 0.28; corrected anisometropes, 0.70 ± 0.19); both were significantly different from controls (P < 0.001). The imbalance was less severe in corrected anisometropes compared with uncorrected anisometropes (P = 0.004). This study found that anisometropia is associated with an ocular imbalance even in the absence of amblyopia. This abnormality is weaker in anisometropes who have worn an optical correction for some time, suggestive that a better optical status leads to a better binocular status and that optical correction induces a neuronal change occurs over time. Although the results of this study are intuitive, it is nice to see confirmatory objective data.

Fine Motor Skills of Children with Amblyopia Improve Following Binocular Treatment

The purpose of this study was to determine whether reduced fine motor skills in children with amblyopia improve after binocular treatment provided by dichoptic iPod game play and whether improvements are sustained once treatment has ceased. Fine motor skills (FMS [Bruininks-Oseretsky Test of Motor Proficiency]), visual acuity (VA [Early Treatment of Diabetic Retinopathy Study chart]) and level of binocular function (BF [Randot preschool stereoaucuity and Worth 4 Dot]) were measured in children with amblyopia (n = 20; age: 8.5 ± 1.3 years; 11 anisometropic; 5 strabismic; 4 mixed) and in a group of visually normal children (n = 10; age: 9.63 ± 1.6 years). Eighteen children with amblyopia subsequently completed 5 weeks of binocular treatment provided by home-based dichoptic iPod game play. FMS, VA, and BF were retested at the end of treatment and 12 weeks after treatment cessation. All visually normal children also completed FMS measurements at baseline and 5 weeks later to assess test-retest variability of the FMS scores. This study found that prior to treatment, FMS scores in children with amblyopia were poorer than those in children with normal vision (P < 0.05). In the children with amblyopia, binocular treatment significantly improved FMS scores (P < 0.05). Better baseline amblyopic eye VA and BF were associated with greater improvements in FMS score. Improvements were maintained at 12 weeks post treatment. In the visually normal children, FMS scores remained stable across the two test sessions. Binocular treatment provided by dichoptic iPod game play improved FMS performance in children with amblyopia, particularly in those with less severe amblyopia. This is the first demonstration of an improvement in standardized measure of fine motor skills involved in practical, everyday
tasks following amblyopia treatment. No amblyopia treatment studies to date (including ongoing clinical trials of binocular treatment) include an outcome measurement of visuomotor control. Whether the improvements found in this study are specific to binocular treatment or would also occur with conventional treatment is yet to be determined, but this study provides further evidence that the functional burden of amblyopia goes beyond visual acuity and binocular function.

Refractive Errors and Amblyopia in the UCLA Preschool Vision Program; First Year Results.

Preschool vision screening is essential for the diagnosis of amblyogenic factors in children. The purpose of this study was to report the full eye exam outcomes in the preschoolers in LA county who failed screening by the Retinomax autorefractor during the first year of the UCLA preschool vision program. This was a retrospective cross-sectional study of children screened between August of 2012 and May of 2013. Of the 11,260 children screened, 1,761 of the children failed the screening. Of those, 1,554 were not already being cared for by an eye professional for their eye condition. 65% of those who failed screening and were not under the care of an eye doctor (1,007 children) were examined. Of the children examined, 740 (74%) were prescribed glasses and 79% had at least 1 risk factor for amblyopia according to the 2013 screening criteria. The key point of this paper is that a high percentage of preschoolers who failed the autorefracture and were examined did require spectacles for amblyopia.

Socioeconomic status and utilization of amblyopia services at a tertiary pediatric hospital in Canada

The goal of this study was to determine whether socioeconomic status is associated with equal utilization of amblyopia services at The Hospital for Sick Children (SickKids), a pediatric tertiary hospital in Canada, a publicly funded health-care system. In a retrospective, cross-sectional study, the medical records of children aged under 7 years diagnosed with amblyopia at SickKids from 2007 to 2009 were reviewed. Socioeconomic status was derived from patients' residential postal codes through linking with income data in the 2006 Canadian census report. Patients were divided into 5 income quintiles to compare with amblyopia service utilization. The main outcome measure was the observed distribution of amblyopia patients by socioeconomic status versus the expected distribution of 20% for each quintile. The analyses included 336 patients. Children with amblyopia at SickKids were more likely to come from the richest neighborhood (32.5%), whereas children from each of the 3 lowest quintiles (14.6%-15.5%) were less likely to present at SickKids. These results differed significantly from
the expected 20% for each quintile (p < 0.0001). All types of amblyopia were significantly under-represented for children from the lower socioeconomic groups. When analyses were stratified by travel distance to the hospital, a significant inequality between the lower and higher income quintiles remained for nonmetropolitan Toronto patients, but not for metropolitan Toronto patients. The authors concluded that despite equal health care access, children from lower socioeconomic neighborhoods in distant areas utilize the amblyopia services in a tertiary pediatric center less often than those from higher socioeconomic status.

Randomised controlled trial of video clips and interactive games to improve vision in children with amblyopia using the I-BiT system


In this study, the authors evaluate efficacy of a new treatment for amblyopia that uses virtual reality technology. This includes either DVD footage or computer games that present a common background to both eyes and the foreground, containing the imagery of interest, only to the amblyopic eye. This is a randomized controlled trial performed on patients with amblyopia aged 4–8 years with three treatment arms. All three arms had dichoptic stimulation using shutter glass technology. One arm had DVD footage shown to the amblyopic eye and common background to both, the second used a modified shooter game, Nux, with sprite and targets presented to the amblyopic eye (and background to both) while the third arm had both background and foreground presented to both eyes (non-interactive binocular treatment (non-I-BiT) games). Subjects could have strabismic, anisometropic or mixed amblyopia. Children who had prior treatment with either patching or atropine penalization were eligible. Visual acuity was assessed pretreatment (week 1), after three treatments (week 3), after six treatments (week 6) and 4 weeks after their final treatment (week 10). Treatment consisted of 30 min weekly for 6 weeks in the office. The study randomized 75 patients. Visual acuity improved in all three arms by modest measures, approximately 0.07 logMAR in the amblyopic eye at 6 weeks. There was no difference between I-BiT DVD and non-I-BiT games compared with I-BiT games (stated primary outcome) in terms of gain in vision. Treatment was well tolerated and safe. There was no difference between the three treatments in terms of primary stated outcomes but treatment duration was short and the high proportion of previously treated amblyopia and strabismic amblyopia disadvantaged dichoptic stimulation treatment. Because all three groups were wearing the shutter glasses, perhaps the stimulation did not make as much of a difference. But the study has a serious disadvantage of having extremely short therapy time (total of 3 hours over 6 weeks) and poor patient selection.

Efficacy of an Amblyopia Treatment Program with Both Eyes Open: A Functional Near-Infrared Spectroscopy Study
Vision function was evaluated using the 3-D visual function trainer-ORTe in 10 normal subjects. Occlusion treatment for amblyopia, which is the gold standard, does not promote the development of binocular function; the ORTe treats amblyopia in a binocular state but displaying a target to the amblyopic eye only while both eyes are open. Brain activity measurements were obtained using functional near-infrared spectroscopy (fNIRS) to examining oxygenated hemoglobin (HbO2) concentration change upon visual stimulation. The study found that HbO2 change was significantly higher in subjects with both eyes open compared to patients with one eye occluded with monocular stimulation. The authors conclude that therapies that do not occlude the healthy eye provide better activation of the visual cortex, and are therefore more likely to produce visual improvements in children with amblyopia.

The Necessity of Amblyopia

The visual system relies on environmental stimuli to produce correlated activity that drives binocularity development. Amblyopia is a necessary consequence when visual experience is abnormal. The correlation of corresponding retinal points in each eye will have to be generated by external visual stimulation of aligned eyes. Each cortical cell is influenced by both eyes as it establishes its spatial identity. Anisometropia leads to a decrease in cortical cell activity driven by the blurred eye. With strabismic amblyopia the input from the two eyes is uncorrelated because corresponding points in the two retina are aligned. This leads to spatial distortion and mislocalization within the visual cortex. In strabismus without amblyopia neither eye has an overall advantage but because the activity is uncorrelated and no refinement of binocular correspondence between the two eyes the potential for stereopsis is limited.

Prevalence of amblyopia and strabismus in Eastern China: results from screening of preschool children aged 36–72 months

This is an epidemiologic study evaluating the prevalence of amblyopia and strabismus in preschool children in Eastern China. The Nanjing Pediatric Vision Project was a cross-sectional, population-based cohort study conducted in preschool children aged 36–72 months from 2011 to 2012 in Yuhua District, Nanjing, China, using an age-stratified random sampling procedure. A questionnaire totaling 117 items was sent to be completed by the corresponding parents or legal guardians of each eligible child. Comprehensive eye examinations, including visual acuity, anterior segment examination, autorefraction, cover test and ocular motility, were conducted. Post-cycloplegic refraction and fundus examinations were performed.
if necessary. Amblyopia was present in 68 children (1.20%, 95% CI 0.92% to 1.48%), with no statistical differences in gender (p=0.903) and age (p=0.835). Among these, 27 had bilateral amblyopia and 41 had unilateral amblyopia, including 26 anisometropic without strabismus, 26 binocular refractive, 7 strabismic, 6 combined strabismic/anisometropic and 3 deprivation amblyopia. Strabismus was found in 320 children (5.65%, 95% CI 5.05% to 6.25%), including 43 with concomitant esotropia, 259 with concomitant exotropia (1 esotropia at near but exotropia at distance), 8 with microtropia (3 esotropia and 5 exotropia), 10 with pure vertical strabismus (3 dissociated vertical deviation and 7 oblique muscle dysfunction) and 1 with Type I Duane syndrome. The prevalence of strabismus did not differ by gender, but had significant statistical differences between different age groups (p=0.021). In conclusion, the prevalence of amblyopia and strabismus in preschool children in Eastern China were 1.20% and 5.65%, respectively. It is surprising that the rate of strabismic amblyopia is so low given that there is a significantly higher rate of strabismus found in this population especially among microtropias and comitant esotropias seen in this population.

Perceived visual distortions in juvenile amblyopes during/following routine amblyopia treatment

Perceived visual distortions (PVDs) were measured using a 16-point dichoptic alignment paradigm in 148 visually normal children (9.18 ± 2.51 years of age), and 82 amblyopic children (6.33 ± 1.48 years of age) receiving or following amblyopia treatment. Global distortion and Global uncertainty were compared to age-matched control data, and correlated against clinical parameters of amblyopia (type, monocular visual acuity, pretreatment interocular acuity difference, refractive error, age at diagnosis, motor fusion, stereopsis, near angle of deviation) and amblyopia treatment outcomes (refractive adaption duration, treatment duration, occlusion dosage, post treatment interocular acuity difference, number of lines improvement). Point prevalence of PVDs in amblyopes was 56.1%. Strabismic amblyopes experienced more severe distortions than anisometropic or microtropic amblyopes. Perceived visual distortions severity moderately correlated with the strength of binocular function, and strongly with near angle of deviation. There was no relationship between severity of PVDs and amblyopia treatment outcomes, or the amblyopic visual acuity deficit. Perceived visual distortions persisted in more than one-half of treated amblyopic cases whose treatment was deemed successful. Perceived visual distortions are common symptoms of amblyopia and are correlated with binocular (stereoacuity, angle of deviation), but not monocular (visual acuity) clinical outcomes. This adds to evidence demonstrating the role of decorrelated binocular single vision in many aspects of amblyopia, and emphasizes the importance of restoring and improving binocular single vision in amblyopic individuals.
The initiation of smooth pursuit is delayed in anisometropic amblyopia

Several studies have shown that reaction times of visually guided movements are slower in people with amblyopia, particularly during amblyopic eye viewing. This prospective study of 11 patients with anisometropic amblyopia and 14 visually normal observers sought to test the hypothesis that initiation of smooth pursuit, which is responsible for keeping moving objects on the fovea, is delayed in people with anisometropic amblyopia. Participants were asked to follow a step-rank target moving at ±15°/s horizontally as quickly and accurately as possible. The experiment was conducted under three viewing conditions: amblyopic/nondominant eye, binocular, and fellow/dominant eye viewing. Participants with anisometropic amblyopia initiated smooth pursuit significantly slower during amblyopic eye viewing (206 ±20 ms) (not correlated with severity of amblyopia) than visually normal observers viewing with their nondominant eye (183 ± 17 ms, P = 0.002). However, during binocular and monocular fellow eye viewing, mean pursuit latency in the amblyopes was comparable to that of the visually normal group. Mean open-loop gain, steady state gain, and catchup saccade frequency were similar between the two groups. However, amblyopic participants exhibited more variable steady state gains under all viewing conditions. This study provides evidence of temporally delayed smooth pursuit initiation in anisometropic amblyopia. After initiation, the smooth pursuit velocity profile in anisometropic amblyopia participants is similar to visually normal controls. This finding differs from what has been observed previously in participants with strabismic amblyopia who exhibit reduced smooth pursuit velocity gains with more catch-up saccades.

Binocular rivalry measured 2 hours after occlusion therapy predicts the recovery rate of the amblyopic eye in anisometropic children

This prospective study of 10 children (mean age 6.2 ± 1 years) with moderate anisometropic amblyopia looked at binocular rivalry and visual acuity 2 hours after occlusion therapy, as well as at 1, 2, and 5 months of treatment. Visual stimuli were orthogonal gratings presented dichoptically through ferromagnetic goggles and children reported verbally their visual perception. Bangerter 0.4 filters were used full time for occlusion therapy. Two hours of occlusion therapy increased the nonamblyopic eye predominance over the amblyopic eye compared with pretreatment measures. This boost of the nonamblyopic eye remained at 1 month, and then decreased to pretreatment levels at 2 months of treatment. Across subjects, the increase in nonamblyopic eye predominance after 2 hours of occlusion
correlated ($p= 0.04$) with the visual acuity improvement of the amblyopic eye measured at 2 months of treatment. Homeostatic plasticity operates during occlusion therapy for moderate amblyopia and the increase in nonamblyopic eye dominance observed at the beginning of treatment correlates with the amblyopic eye recovery rate. These results suggest that binocular rivalry might be used to monitor visual cortical plasticity during occlusion therapy. This study is limited by its small size, but does confirm recent work in adults. It is also unclear why Bangerter filters were used in this study for occlusion rather than patch therapy.

**Television Video Games in the Treatment of Amblyopia in Children Aged 4–7 Years**  
Dadeya S, Dnaga S. *Strabismus* December 2016;24(4):146-152.

Subjects were randomly divided into two groups of 20 each: Group A (control), were prescribed patching alone and Group B (study), were made to play action video games on a commercial television set during office visits (12 half-hour sessions each, at weekly intervals), along with patching. Mean age of patients was 6.03 ± 1.14 years. The distance BCVA in the amblyopic eye showed a significant improvement at final follow-up (12 weeks) in both groups: from 0.84 ± 0.19 to 0.55 ± 0.21 LogMARReq in Group A and 0.89 ± 0.16 to 0.46 ± 0.22 LogMARReq in Group B. However, improvement in BCVA was significantly better in group B at all visits ($P=0.002$, 12 weeks). Group B also had a significantly better outcome in terms near visual acuity improvement ($P = 0.006$, 12 weeks) and greater stereo-acuity improvement. The authors conclude that video games supplemental to occlusion may be favorable for visual development in amblyopic children. However, the study is limited by its small sample size, lack of objectively recorded compliance with occlusion and monitoring of home activities, and the fact that the examiner was not masked to the groups.

### 2. VISION SCREENING

A comparison of plusoptiX A12 measurements with cycloplegic refraction.


In this prospective study the accuracy and reliability of the plusoptiX A12 in detecting amblyogenic risk factors were evaluated. Data on 402 eyes of 201 children (mean age, 7.63 +/- 3.41 years) was collected. Each participant completed screening with the plusoptiX A12, cycloplegic refraction, and full ophthalmic examination. American Association for Pediatric Ophthalmology and Strabismus (AAPOS) 2013 guidelines for the detection of amblyogenic risk fac-
tors were used for plusoptiX A12 screening and comparison of the results of both examination modes. Mean (with standard deviation) cycloplegic refraction results were as follows: sphere, 0.88 ± 1.5 D; cylinder, -0.61 ± 0.74 D; axis, 71.17 ± 71.04; and spherical equivalent, 0.68 ± 2.63. The plusoptiX A12 measurements were as follows: sphere, 0.58 ± 1.4 D; cylinder, -0.66 ± 0.77 D; axis, 77.3 ± 68.9; and spherical equivalent, 0.25 ± 1.3. A strong correlation (Pearson) for sphere (r = 0.91), cylinder (r = 0.81), and axis (r = 0.7) was demonstrated. The mean difference of the myopic spherical component between the plusoptiX and cycloplegic refraction was -0.048 ± 0.55 (95% LoA, +1.04 to -1.14 D); for the hyperopic spherical component, 0.37 ± 0.93 (LoA, +2.20 to -1.45 D); and for the cylindrical component, 0.05 ± 0.32 (LoA, +0.68 to -0.57 D). The sensitivity, specificity, positive and negative predictive values for myopia were, respectively, 86%, 93%, 82%, and 94%; for astigmatism, 85%, 98%, 88% and 98%; and for hyperopia, 40%, 100%, 100%, and 98%. The authors conclude that the plusoptiX A12 accuracy is high in the myopic, astigmatic, and anisometropic subgroups. The sensitivity for hyperopic refractive abnormalities was low, possibly resulting in underestimation of hyperopic refractive error. To increase the sensitivity for hyperopic changes the authors suggest lowering the minimal hyperopic criteria to +2.00, by which sensitivity increases to 73% at the cost of examining more children with normal refraction, or performing the plusoptiX measurements under cycloplegia. The results in general seem to indicate that the plusoptiX A12 might not be the most suitable screening tool.

Improving access to vision screening in urban Philadelphia elementary schools.


The Wills Eye Vision Screening Program for Children is a community-based vision screening program for children in urban Philadelphia elementary schools that aims to provide vision screening, remedy refractive error by providing glasses, and refer children with suspected non-refractive eye disease for eye care. In this prospective cross-sectional study, children in grades K-5 from 45 Philadelphia elementary schools were screened for distance and near visual acuity, stereopsis, and color vision from January 2014 to June 2015. Children who failed were assessed by an on-site optometrist and manifest refraction was performed. Two pairs of eyeglasses
were provided at no cost. Children with suspected, non-refractive disease were referred to Wills Eye Hospital Pediatric Ophthalmology and contacted by a social worker to schedule an appointment. Over 84 days, 10,726 children were screened for vision problems at 45 schools. A total of 1,321 children (12%) had refractive error and 1,015 children (77%) returned the consent form and received two pairs of glasses. Of the 509 children (5%) referred to Wills Eye, 215 (42%) returned their consent form, 177 returned consent forms and were not being followed by an ophthalmologist. Of these, 127 children (72%) completed an eye examination at Wills. The authors concluded that the program can provide comprehensive vision screening, with eyeglasses and/or referrals, to children within an underserved community. Some ways to improve consent rate and treatment are discussed. Funding constraints will still remain a challenge.

Efficacy of a vision-screening tool for birth to 3 years early intervention programs


This retrospective study validated the screening tool used to detect unsuspected visual pathway pathology in preschool children under 3 years of age with developmental disabilities enrolled in an early intervention program using guidelines from the Kansas Department of Health and Environment (KDHE). The records of 300 consecutive children screened at a birth to 3 early intervention program from 2011 to 2014 were reviewed. Inclusion criteria were documented KDHE vision screening examinations performed by trained early interventionist and full ophthalmic evaluations by a general ophthalmologist. The evaluation was only considered a pass if it was recorded on the chart and the child did not have any known risk factors. The visual pathway pathology status was determined after comprehensive ophthalmic examination, with the ophthalmologist masked to the vision screening results. Patients were automatically considered screening failures if they required urgent ophthalmologic assessment due to possible 22 listed risk factors, which are listed in the methods. A total of 216 children met inclusion criteria, of whom 137 were referred. The sensitivity was 95.3% (95% CI, 90.8-99.8); specificity, 57.25% (95% CI, 48.3-65.7); positive predictive value, 59.1% (95% CI, 50.4-67.3); negative predictive value, 94.9% (95% CI, 86.8-98.4); and negative likelihood ratio, 0.082 (95% CI, 0.031-0.22). A Pearson chi2 test for fit yielded an approximate P value of <0.0001. The authors concluded that in this study cohort, good sensitivity and negative predictive value were demonstrated by the inexpensive
screening examination coupled with associated risk factors for the 0-3 population of children with developmental disabilities. KDHE screening protocol is also supplied. Authors acknowledge some of the limitations of this study apart from its retrospective nature. The screening procedure was not stratified to determine the effect of the screening test versus the risk factors. Hence, one cannot definitely establish that the risk factors in themselves are not superior to the eight-part screening test. The authors recommend comprehensive ophthalmic assessment for all children enrolled in early intervention programmes, but they recognize that resources are limited and offer us this useful tool for triaging referrals in these situations.

Automated Measurement of Visual Acuity in Pediatric Ophthal-
mic Patients Using Principles of Game Design and Tablet Com-
puters.
Aslam TM, Tahir HJ, Parry NR, et al. 

Accurate measurements of visual acuity are needed to screen children for amblyopia. Recently there has been interest in vision testing via computers and personal electronic devices, but no previous studies have validated this method on children. The purpose of this study was to report on the repeatability and consistency of one of these systems, the Mobile Assessment for vision by interactive Computer for Children (MAVERIC-C) system on children. This system has been previously validated by the same authors in an adult population. The animation and graphics in the system were altered to make them more appealing to children. The authors evaluated 112 children ages 4-16 and found that 126/112 (95%) were able to complete the acuity assessment. The repeatability measurement differences were 0.001 with a standard deviation of +/- 0.136 and the differences in the MAVERIC-C from the EDTRS scores were -0.0879 +/- 0.10. One of the main limitations that the authors point out is that this testing was performed for near acuity only and no distance acuity measurements were done with this system. The key points of this article is that visual acuity testing on a computer is promising in the pediatric population, but needs to be validated and show good repeatability. The pediatric ophthalmology community will have to decide how comfortable they are with a near acuity assessment only as a screening tool.

Study of Optimal Perimetric Testing In Children (OPTIC): develop-
ment and feasibility of the kinetic perimetry reliability meas-
ure (KPRM)

Interpretation of perimetric findings, particularly in children, relies on accurate assessment of test reliability, but no objective measures of reliability exist for kinetic
The authors developed the kinetic perimetry reliability measure (KPRM), a quantitative measure of perimetric test reproducibility/reliability and report its feasibility and association with subjective assessment of reliability. Children aged 5–15 years, without an ophthalmic condition that affects the visual field, were recruited from Moorfields Eye Hospital and underwent Goldmann perimetry as part of a wider research program on perimetry in children. Subjects were tested with two isopters and the blind spot was plotted, followed by a KPRM. Deriving a KPRM involves assessing additional test points at the end of a kinetic testing of each eye. Four points are tested using the largest/brightest (i.e., most peripheral) isopter stimulus used in the test. One point is plotted in each quadrant along a meridian selected from those already used for plotting that isopter. Taking a median value of the unsigned distance (in degrees) between these four KPRM points and the corresponding points previously plotted on the same meridian (with the same, outer isopter stimulus) gives a KPRM score, with higher scores indicating greater test-retest variability. Test reliability was also scored qualitatively using an examiner-based assessment of reliability (EBAR) scoring system, which standardizes the conventional clinical approach to assessing test quality. The relationship between KPRM and EBAR was examined to explore the use of KPRM in assessing reliability of kinetic fields. A total of 103 children (median age 8.9 years; IQR: 7.1 to 11.8 years) underwent Goldmann perimetry with KPRM and EBAR scoring. A KPRM was achieved by all children. KPRM values increased with reducing test quality (Kruskal-Wallis, p=0.005), indicating greater test-retest variability, and reduced with age (linear regression, p=0.015). One of 103 children (0.97%) demonstrated discordance between EBAR and KPRM. In conclusion, KPRM and EBAR are distinct but complementary approaches. Though scores show excellent agreement, KPRM is able to quantify within-test variability, providing data not captured by subjective assessment. Thus, the authors suggested combining KPRM with EBAR to aid interpretation of kinetic perimetry test reliability in children.

**Modified Test Protocol Improves Sensitivity of the Stereo Fly Test**

Angie De La Cruz, Sarah E. Morale, Reed M. Jost, Krista R. Kelly, Eileen E. Birch


The Stereo Fly test is routinely administered to pediatric patients to determine coarse stereopsis (3000 arcsecs) although it yields false negative “pass” due to nonstereoscopic cues. The studies goal was to increase sensitivity but modifying the text with polarized glasses. The modified glasses have polarizers oriented in the same direction for both eyes to eliminate disparity cues. If the child, who tentatively passed the standard Fly Test, pinched above the plate with polarizers on they were deemed as a false negative and the final outcome was a fail. If the child, who tentatively passed the standard Fly Test, touched the plate with the polarizers on they were verified as a true pass. The sensitivity increased from 81% to 90% with the modified protocol.
**Instrument-based pediatric vision screening.**

**PURPOSE:** Review currently available instruments for vision screening in young children.

**FINDINGS:** Instrumentation continues to evolve and are valuable tools for screening young children, especially 5 years and younger, for amblyopia risk factors. Current photoscreeners and autorefractors identify amblyopia risk factors including refractive errors and strabismus. In contrast, the Pediatric Vision Screener (REBIsan Inc.) uses binocular retinal birefringence scanning to identify amblyopia based on abnormalities of foveal fixation. Instrument-based screening results in over referral because amblyopia risk factors are present in 15-20 % of the population where as only 1-5 % of the pediatric population has amblyopia. Guidelines published in 2013 by the AAPOS Vision Screening Committee aim to improve the sensitivity and specificity of instrument-based screening by defining refractive amblyopia risk factors based on age and magnitude of astigmatism, hyperopia, anisometropia and myopia. Instrument-based vision screening is endorsed by the American Academy of Pediatrics and primary care offices can bill CPT code 99174 for instrument-based vision screening.

**SUMMARY:** This is a very good review of instrument-based vision screening, guidelines to increase accuracy and available instrumentation.

**Validation and reliability of the Cardiff Visual Ability Questionnaire for Children using Rasch analysis in a Turkish population**

The authors developed a Turkish version of the 25-item Cardiff Visual Ability Questionnaire for Children (CVAQC) and studied its validity and reliability. The study involved two main phases. The first phase involved a cross-cultural adaptation of the CVAQC from English into Turkish. The second phase involved the completion of the Turkish version of the CVAQC by 150 partially sighted children (6–18 years old) and validity and reliability checks. Extent and construct validity were investigated using Rasch analysis and reliability by internal consistency and person separation index (PSI). An adequate conceptual equivalence was achieved following the linguistic adaptation process. The dataset for validation comprised 150 participants, 88 (58.7%) of whom were male. Evidence of disordered thresholds was found for one item (item 17). This item was recorded by collapsing two categories and ordered thresholds were evident. All items of the CVAQC were found to fit the Rasch model ($\chi^2$ (df)=59.90 (2), p=0.159). The internal construct validity was good (mean item fit (SD) −0.054 (1.132), person fit (SD) −0.629 (2.079)) indicating a single underlying construct. The reliability was good with Cronbach's $\alpha$ of 0.91 and PSI of 0.94. Differential item functioning (DIF) was tested for age, sex, diagnosis, degree of visual impairment, and
comorbidity. Evidence of DIF was found on age for one item (item 10, reading the board at school). The authors concluded that the Turkish version of the CVAQC is a valid, reliable, and unidimensional questionnaire for partially sighted children aged 6–18 years. The Turkish version of the CVAQC has undergone extensive linguistic adaptation process to ensure cultural relevance. This was then carefully studied for validity and reliability.

**Cycloplegic autorefraction versus subjective refraction: the Tehran Eye Study**


This is part of the Tehran Eye Study. In this study, the authors compared cycloplegic autorefraction with non-cycloplegic subjective refraction across all age and refractive error groups. In a cross-sectional study with random stratified cluster sampling, 160 clusters were chosen from various districts proportionate to the population of each district in Tehran. Following retinoscopy and autorefraction with the 0.25 D bracketing (Topcon KR-8000, Topcon, Tokyo, Japan), all participants had a subjective refraction. Then, all participants underwent cycloplegic autorefraction. The final analysis was performed on 3482 participants with a mean age of 31.7 years (range 5–92 years). Based on cycloplegic and subjective refraction, mean spherical equivalent (SE) was +0.31±1.80 and −0.32±1.61 D, respectively (p<0.001). The 95% limits of agreement (LoA) between these two types of refraction were from −0.40 to 1.70 D. The largest difference between these two types of refraction was seen in the age group of 5–10 years (1.11±0.60 D), and the smallest difference was in the age group of >70 years (0.34±0.45 D). The 95% LoA was −0.52 to 0.89 D in patients with myopia and −0.12 to 2.04 D in patients with hyperopia. The study found that female gender (coefficients=0.048), older age (coefficients=−0.247), higher education (coefficients=−0.043) and cycloplegic SE (coefficients=−0.472) significantly correlated with lower inter-method differences. The authors concluded that cycloplegic refraction is more sensitive than the subjective one to measure refractive error at all age groups, especially in children and young adults. The cyclorefraction technique is highly recommended to exactly measure the refractive error in momentous conditions such as refractive surgery, epidemiological researches and amblyopia therapy, especially in hypermetropic eyes and pediatric cases. Sadly, many practitioners ignore cycloplegic refraction. Although the study does not provide substantial new information, it serves to emphasize the importance of cycloplegic refraction.

**Assessing visual function in children with complex disabilities: the Bradford visual function box**

The assessment of children with complex and severe learning disabilities is challenging and the children may not respond to the monochrome stimuli of traditional tests. The authors of this study developed a functional visual assessment tool to assess vision in children with complex and multiple disabilities. The Bradford visual function box (BVFB) comprises a selection of items (small toys) of different size and color, which are presented to the child and the response is observed. The aim of this study was to establish its inter-tester validity in children with severe learning disability. The visual function of 22 children with severe learning disability was assessed using the BVFB. The children were assessed by experienced practitioners on two separate occasions. The assessors were unaware of each other’s findings. The authors found that in 15/22 of the children, no difference was found in the results of the two assessors. The test was shown to have a good inter-tester agreement, with weighted $\kappa=0.768$. The authors conclude that the BVFB is a tool for assessing the visual function in children with severe learning disability in whom other tests fail to elicit a response. However, this study did not compare the traditional tests to BVFB and this claim is not supported by the limited scope of the study design. The authors should be commended for developing an easy to use, portable tool that can provide useful information on visual function of this difficult population.

Vision screening in children: a retrospective study of social and demographic factors with regards to visual outcomes  

Amblyopia and its risk factors are more common among children from low socioeconomic backgrounds. In this study, the authors investigated this association in a region with orthoptic-delivered screening and whole population coverage, and examined the association of the Health Plan Indicator (HPI) with screening outcome. Screening examination outcomes, post-codes and HPIs were extracted from the community child health database for every child who underwent preschool vision screening between March 2010 and February 2011 in Tayside, Scotland. Scottish Index of Multiple Deprivation score for every child was used as a measure of area-based deprivation. They assessed the vulnerability/needs of the individual family through the HPI—‘Core’ (children and families receiving universal health visiting service), ‘Additional’ (receiving additional health/social support) and ‘Intensive’ (receiving high levels of support). The outcomes from follow-up examinations for those who failed screening were extracted from the orthoptic department database. Results show that 4365 children were screened during 2010–2011, of whom 523 (11.9%) failed. The odds of children from the least deprived socioeconomic group passing the visual screening test was 1.4 times higher than those from the most deprived socioeconomic group (OR 1.4, 95% CI 1.07 to 1.89, p=0.01). The odds of a child from a family assigned as ‘Intensive’ failing the preschool visual screening test was three times greater than the odds of a child from a family assigned as ‘Core’ (OR 3.59, 95% CI 1.6 to 7.8, p=0.001). Results of the study confirm that the children from the most deprived back-
grounds and those from unstable homes were more likely to fail preschool vision screening. These findings have implications for future planning of resource allocation and the provision of healthcare.

Cost-effectiveness of School-Based Eye Examinations in Preschoolers Referred for Follow-up From Visual Screening

This is a retrospective cohort study of youngsters who failed a preschool-based vision screening. The authors want to determine cost effectiveness of referral to community based pediatric eye care providers vs referral to a mobile eye care unit brought to the school. Preschool children who failed a vision chart screening or corneal light reflex test were referred to follow up to a community based eye care professional. Preschool children who failed an autorefraction based vision screening (Retinomax) or cover uncover test or corneal light reflex test were referred for follow-up in a mobile eye care unit. 175/3429 (5.1%) preschoolers screened with a vision chart and corneal light reflex test were referred to community based eye care professionals. 204/1524 (13.4%) preschoolers who were screened with an autorefractor, cover test, or corneal light reflex test, were referred to a mobile eye care unit. Main outcome measure was cost effectiveness of 2 referral patterns with referral criteria standardized. 59.4% of those referred to community-based physician attended. 54.9% of those referred to a mobile eye care unit attended. (To receive the examination the student needed to return a signed permission slip and a parent/guardian needed to attend the eye exam, which was free). Follow up for failed vision screen was not correlated with screening visual acuity. Cost effectiveness was defined as total screening and examination costs required per case of amblyopia detected. Costs per case detected were $664 vs $776 respectively.

Importance: Vision screening of 3-5 year olds is important to detect amblyopia and amblyogenic risk factors in a treatable age range. What remains a challenge is obtaining actual follow-up after failed vision screening.

Enhancing the Value of Preschool Vision Screenings

The authors of the above article state that main outcome was cost effectiveness of referral to pediatric eye care professionals vs a mobile eye care unit. However, the study subjects were drawn from different populations, those referred to community pedi eye docs came from vision screen failures using an eye chart. Those referred to a mobile eye care unit came from failed autorefraction based vision screens. The children did come from the same schools, just different years, probably reflecting a change in the vision screening modalities over time. How can referral criteria be consistent from 2 groups, if one group’s referral criteria was based on Snellen acuity and the other on the manufacturer’s refractive error referral guidelines. The invited commentary points out that despite having effec-
tive screening and treatment for amblyopia, a low follow up at either a community based eye care professional or mobile unit is a major barrier to amblyopia treatment. The commentators suggest that parental presence should not be mandated at the follow up mobile eye exam in order to eliminate a barrier to obtaining a higher follow up rate and ultimate treatment of amblyopia.

The Use of a Mobile Van for School Vision Screening: Results of 63 841 Evaluations.

Pediatric vision screening is a priority for the AAO, AAPOS and AAP, however many children are still not screened. This study is a 12 year retrospective study of data gathered by a unique mobile screening program in Cleveland. This screening program, Vision First, is a mobile van where if the child fails the screen (acuity, alignment, pupils, nystagmus, external abnormality), an on-site optometrist completes a full eye exam, writes prescription for glasses (when applicable) and dispenses a free pair of glasses. This study looked at the referral rates to pediatric ophthalmology and the rates of amblyopia and strabismus. Approximately 55% of eligible children were screened, limited mostly by the permission forms signed by the parents. Of those, 10.0% met one or more referral criteria. Glasses were given to 8.4% of children and strabismus and amblyopia prevalence rates were 1.4% and 1.8% respectively. Rates of strabismus, amblyopia, and significant refractive error were stable over 10 years. The authors conclude that a van based model was effective in reaching underserved communities.

Prospective Evaluation of photoscreeners in the pseudophakic eyes of children.

This prospective study compared data of Plusoptix AO9 (Plusoptix, Inc., Atlanta, GA) and Spot( Welch Allen, Skaneateles Falls, NY) photoscreeners with retinoscopy, in pseudophakic eyes of children. A pediatric ophthalmologist was masked to the results of both photoscreeners. In bilateral pseudophakic eyes, one eye was randomly selected. Forty-four eyes were included, with a mean age of 7.4 ± 4.8 years. Refraction was estimated in all eyes using retinoscopy, but a refractive estimate was obtained in only 11.3% (5 of 44) of eyes using the Plusoptix binocularly and 63.6% (28 of 44) of eyes using the Spot. The authors concluded that Refraction was estimated in a higher number of pseudophakic eyes of children using the Spot as compared to the Plusoptix. Although a larger sample size is needed, this is the first study to evaluate and compare the refractive data of Plusoptix and Spot with retinoscopy in pseudophakic children.
Comparison of the Handy Eye Chart and the Lea Symbols Chart in a population of deaf children aged 7-18 years

This study assessed the utility of the Handy Eye Chart in a population of deaf students by comparing participant preference, acuity outcomes and testing duration with the Handy Eye Chart. There were 24 participants, The mean difference in acuity by each chart equates to one optotype. The 95% limits of agreement between the charts was found to be -0.18 to 0.21 log-MAR. The mean difference between the duration of each evaluation was 13.79 seconds (Handy Eye Chart was faster). 17/24 participants preferred the Handy Eye Chart. The Lea Symbols Chart was used without the matching card which could have affected results. The Handy Eye Chart appears to be a fast, valid tool for measuring visual acuity in deaf children ages 7-18 years. It uses hand gesture symbols as optotypes to assess visual acuity.

Validation of photoscreening technology in the general pediatrics office: a prospective study

This study describes the first large-scale, prospective, multi-site evaluation of a commercially available photo screening device in the medical home. Eleven large pediatric practices were recruited to perform photo screening of healthy preschool children with the Spot Vision Screener. Nurses received formal training. Children were between 12 months and 72 months. During an 8-month period, 3134 children were recruited and screened. A formal eye examination was recommended for 306 (9.8%) based on the screening results. The top three reasons for referral were suspected astigmatism (61.8%), suspected anisometropia (17.3%) and strabismus (12.7%). Only 136 of the 306 (44.4%) completed a gold standard examination. Using 2013 AAPOS-VSC guidelines, amblyopic risk factors (ARFs) were detected in 64/136 for a PPV of 47%. PPV was highest for hyperopia and myopia and lowest for strabismus and anisocoria. Using 2003 AAPOS guidelines, the overall PPV increased to 60.3%. An attempt was made to examine children who passed the screening to determine sensitivity rates but show rates were very poor. This is a large study which should help forward the goal of automated vision screening in the medical home. However, this study also shows the very poor rates of family followup with healthy children, but surprisingly even with the children who failed screening. This needs to be strongly considered when designing care plans.

3.REFRACTIVE ERROR
Prevalence and Risk Factors

Clinical factors associated with moderate hyperopia in pre-school children with normal stereopsis and visual acuity


There is controversy concerning early optical correction of moderate hyperopia and its effect on the prevention of strabismus or amblyopia. This is a short preliminary report from PEDIG. A total of 117 children 3-5 years of age with moderate hyperopia (+3.00 D to +6.00 D spherical equivalent [SE]) in at least one eye, age-normal unaided visual acuity, age-normal stereoacuity, no significant anisometropia or astigmatism, and no strabismus were enrolled in a 3-year randomized clinical trial to compare visual outcomes and ocular alignment in children assigned to immediate glasses or to observation and glasses if deterioration of visual acuity, stereoacuity, or alignment occurred. Pearson correlation coefficients were calculated to evaluate relationships among baseline characteristics. A moderate association was found between higher amounts of uncorrected hyperopia and greater accommodative lag (n = 57; R = 0.31; 95% CI, 0.05-0.53). Higher amounts of hyperopia were weakly associated with worse uncorrected distance visual acuity (n = 117; R = 0.24; 95% CI, 0.06-0.41), and better stereoacuity was weakly associated with better uncorrected near acuity (n = 99; R = 0.24; 95% CI, 0.04-0.42). Authors conclude that there is a need for monitoring for potential problems in children with uncorrected moderate hyperopia, even in those with age-normal visual acuity and stereoacuity. Forthcoming results from the randomized trial might shed more light regarding possible effects of delaying prescription of spectacles in moderate hyperopia.

Association Between Myopia, Ultraviolet B Radiation Exposure, Serum Vitamin D Concentrations, and Genetic Polymorphisms in Vitamin D Metabolic Pathways in a Multicountry European Study

Recent large epidemiologic studies point to an inverse relationship of sunlight exposure and myopia. This study seeks to elucidate the mechanism of how increased sunlight exposure inhibits myopia. This is a cross-sectional population based cohort study derived from a random sample of participants in the European Eye Study. The mean age of the study subjects was 72.4 years. A blood sample was taken for analysis. Excluding age related eye problems such as cataract and macular degeneration, 371 had myopia and 2797 did not (defined as -0.75D or more). A standard deviation increase in UV-B exposure age 14-19 (OR 0.81; 95% CI 0.71-0.92) and age 20-39 (OR 0.7; 95% CI 0.62-0.93) was associated with a reduced odds ratio for myopia and those who were in the highest tertile of education had twice the odds ratio of myopia (OR 2.08; 95% CI 1.41.-3.06). Serum vitamin D3 concentrations and genetic polymorphisms for vitamin D metabolism were not associated with myopia. The authors were surprised to find that those study subjects in the highest quintile of plasma lutein concentration had a reduced odds ratio of myopia (OR 0.57; 95% CI 0.46-0.72).

Conclusion: The authors conclude that further study is needed to confirm the association of plasma lutein and myopia. Their paper provides evidence that myopia is not associated with vitamin D concentration or metabolism.

Association of Axial Length With Risk of Uncorrectable Visual Impairment for Europeans With Myopia


The prevalence of myopia is increasing worldwide, especially in urban areas in Asia. Increased risk of permanent visual impairment from glaucoma, cataract, retinal detachment, or myopic macular degeneration in myopes is increased, especially in high myopes, defined as a spherical equivalent of less than -6 diopters. The authors want to determine if there is an association between axial length and permanent visual impairment in myopes. This is a cross-sectional population based study derived from data from the Rotterdam Eye Study. There were 15,693 individuals in the study. Axial length ranged from 15.3 to 37.8 mm; 819 had an axial length of 26 mm or greater. Spherical equivalent ranged from -25 to +14 diopters; 796 had high myopia. Axial length and spherical equivalent were highly correlated. Average age was 61.3 years and 57% were female. Cumulative incidence of visual impairment was 3.8% in those aged 75 years with an axial length of 24 to less than 26mm and greater than 90% with an axial length of 30mm or greater. The cumulative incidence of visual impairment in high myopes increased with increasing age as well. Visual impairment in high myopes (defined by spherical equivalent) was present in 5.7% in those aged 60 years and 39% in those aged 75 years. Permanent visual impairment increased with increasing axial length and myopic spherical equivalent.

Conclusion: Myopia begins in childhood. Identifying genetic and environmental factors in childhood may reduce the burden of visual impairment later, a burden which was elegantly demonstrated in this study. A drawback of this study is that the causes of visual impairment in the participants were not identified.
Myopia—The Silent Epidemic That Should Not Be Ignored

In this invited commentary, the authors emphasize that myopia is not always benign. They affirm that the Tideman study is the first of its kind to establish a dose response relationship between axial length and permanent visual impairment. To further the sense of urgency, they note that the prevalence of myopia and high myopia will increase 5 fold (from 22%) and 2 fold (from 5%) from the year 2000 to 2050. This underscores the need to urgently identify treatments to ameliorate this epidemic.

Development of Experimental Myopia in Chicks in a Natural Environment

Many human studies suggest that increased time outdoors may protect against myopia onset, and may even slow myopia progression. This study looked at the effect of outdoor rearing on form-deprivation myopia in chicks. High intensity indoor laboratory lighting has been shown to increase retinal dopamine production and release and slow form-deprivation myopia in this chick model. In this study, unilaterally goggled cohorts of chicks were maintained in a species appropriate, outdoor rural setting during daylight hours to the extent permitted by weather. Control chicks were reared indoors with incandescent lighting. Myopia developed in the goggled eyes of all cohorts. Whereas outdoor rearing lessened myopia by 44% at 4 days, a protective effect was no longer evident at 11 days. Outdoor rearing had no consistent effect on retinal or vitreous content of dopamine or DOPAC. Outdoor rearing of chicks induces only a partial decrease of goggle-induced myopia that is not maintained, without evidence that retinal dopamine metabolism accounts for the partial myopia inhibition under these outdoor conditions. Although modest, alterations in retinal gene expression suggest that studying circadian signals might be informative for understanding refractive mechanisms. This study illustrates how a simplified view of the effect of sunlight exposure on myopia is insufficient—light doses, mechanisms, and time kinetics have still not been sufficiently explored.

Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention
This is the first systematic review and quantitative meta-analysis of the worldwide prevalence of myopia in childhood and adolescence. The aim of this review was to quantify the global variation in childhood myopia prevalence over time taking account of demographic and study design factors. A systematic review identified population-based surveys with estimates of childhood myopia prevalence published by February 2015. Multilevel binomial logistic regression of log odds of myopia was used to examine the association with age, gender, urban versus rural setting and survey year, among populations of different ethnic origins, adjusting for study design factors. One hundred forty-three published articles (42 countries, 374,349 subjects aged 1–18 years, 74,847 myopia cases) were included. This review found that increase in myopia prevalence with age varied by ethnicity. East Asians showed the highest prevalence, reaching 69% (95% credible intervals (CrI) 61% to 77%) at 15 years of age (86% among Singaporean-Chinese). Blacks in Africa had the lowest prevalence; 5.5% at 15 years (95% CrI 3% to 9%). Time trends in myopia prevalence over the last decade were small in whites, increased by 23% in East Asians, with a weaker increase among South Asians. Children from urban environments have 2.6 times the odds of myopia compared with those from rural environments. In Whites and East Asians, sex differences emerge at about 9 years of age; by late adolescence girls are twice as likely as boys to be myopic. Studies that did not use cycloplegia reported double the odds of myopia than those that did use cycloplegia. This review highlights the marked ethnic differences in age-specific prevalence of myopia. Rapid increases in myopia prevalence over time, particularly in East Asians, combined with a universally higher risk of myopia in urban settings, suggest that environmental factors play an important role in myopia development, which may offer scope for prevention. This study may also provide a guideline as to timing of intervention that is different for boys and girls.

Prevalence and associations of anisometropia in children

This cross-sectional school-based study describes the prevalence and associations of anisometropia in 6,025 children aged 4 to 18 years. Prevalence of anisometropia ≥ 1 diopter was 7.0 ± 0.3% and increased with older age (P<0.001), higher maternal level of education (P=0.004), longer total reading time indoors (P=0.002), higher inter-eye difference in axial length (P<0.001), lower corneal astigmatism (P<0.001), and lower stereoacuity (P<0.001). Prevalence of cylindrical anisotropia ≥ 1 diopter was 3.7 ± 0.2% and was not associated with age after 1 year of age. Anisomyopia, but not hyperopic or cylindrical anisometropia, was associated with lifestyle factors, such as reading time indoors and maternal education. Stereoacuity was strongly influenced by hyperopic anisometropia, but not anisomyopia. Since this is a cross-sectional study, causal relationships cannot be determined. Non-participation may also lead to bias, though this study had a high participation rate of 94.7%. Also, data obtained via interview based on standardized questionnaire could induce some bias. A previous study
demonstrated that more time spent outdoors during school time is associated with a significantly lower incidence of myopia, and this study seems to support this finding.

**Peripapillary Diffuse Chorioretinal Atrophy in Children as a Sign of Eventual Pathologic Myopia in Adults**


In this retrospective case series the authors studied 56 eyes of 29 patients with mean age of 10.2 years for ≥ 20 years of follow-up. Mean axial length was 27.0 mm at baseline and 29.7 mm at the last visit. At the last visit, 19 eyes (34%) had tessellated fundus alone, 31 eyes (55%) had diffuse chorioretinal atrophy, 3 eyes (5%) showed patchy chorioretinal atrophy, and 1 eye (2%) had macular atrophy. Thus, 35 eyes (63%) had pathologic myopia in adulthood. Among the 35 eyes, 29 (83%) already had diffuse chorioretinal atrophy at the initial visit in childhood and the remaining 6 eyes (17%) showed tessellated fundus in childhood. The diffuse chorioretinal atrophy seen in childhood was restricted to the area temporal to the peripapillary region. The presence of peripapillary diffuse chorioretinal atrophy in children with high axial myopia may be an indicator for the eventual development of advanced myopic chorioretinal atrophy in later life.

**Comment:** Figures 1 and 2 provide helpful images of childhood peripapillary chorioretinal atrophy which, by adulthood, had spread to affect the entire posterior fundus in 2 patients. These clues may be helpful to pediatric ophthalmologists in predicting future pathologic myopia.

**Uncorrected Hyperopia and Preschool Early Literacy Results of the Vision in Preschoolers-Hyperopia in Preschoolers (VIP-HIP) Study**


In this prospective cross-sectional observational study, the authors compared literacy of 4- and 5-year-old uncorrected hyperopic children with that of emmetropic children. Literacy was measured using the Test of Preschool Early Literacy (TOPEL), composed of Print Knowledge, Definitional Vocabulary, and Phonological Awareness subtests. Hyperopia was defined as 3.0-6.0 D in the most hyperopic meridian of at least 1 eye and astigmatism ≤ 1.5 D and anisometropia ≤ 1.0 D. Emmetropia was defined as hyperopia up to 1.0 D and astigmatism, anisometropia, and myopia <1.0 D. A total of 492 children (244 hyperopes and 248 emmetropes) participated with mean age of 58 months. Mean of the most hyperopic meridian was 3.78 D in hyperopes and 0.51 in emmetropes. The mean test difference between hyperopes and emmetropes was -4.3 for TOPEL overall, -2.4 for Print Knowledge, -1.6 for Definitional Vocabulary, and -0.3 for Phonological Awareness. Greater deficits in TOPEL scores were observed in hyperopic...
children with 4.0 D than in emmetropes: -6.8, for total score; -4.0, for Print Knowledge. The largest deficits in TOPEL scores were observed in hyperopic children with binocular near VA of 20/40 or worse (-8.5 for total score; -4.5 for Print Knowledge; -3.1 for Definitional Vocabulary) or near stereoacuity of 240 seconds of arc or worse (-8.6 for total score; -5.3 for Print Knowledge) compared with emmetropic children. The author concluded that uncorrected hyperopia associated with reduced binocular near VA or reduced near stereoacuity in 4- and 5-year-old children is associated with significantly worse performance on a test of early literacy.

Comment: The results demonstrate an interesting association of reduced literacy and higher hyperopia. This lays the groundwork for a future interventional study of refractive correction hyperopia. Most the investigators and authors of this paper are optometrists or PhDs affiliated with schools of optometry.

**Reducing the Progression of Myopia**

The acceptability and visual impact of 0.01% atropine in a Caucasian population


Myopia is a condition of enormous public health concern, affecting up to 2.5 billion people worldwide. The most effective treatment to prevent myopia progression is atropine but at the cost of accommodative paresis and mydriasis, necessitating the use of bifocal glasses. Low-dose atropine (0.01%) has been found to be almost as effective with significantly reduced side effects. Since there are well-recognized differences in the effect of atropine between heavily pigmented Asian eyes and Caucasian eyes, this study aimed to determine the acceptability and tolerability of 0.01% atropine (by measuring visual performance and quality of life) as a treatment for myopia control in a Caucasian population exhibiting light irides. The study included 14 university students aged 18–27. Participants received one drop of 0.01% atropine daily into each eye over 5 days in clinic. Distance and near vision, accommodative amplitude, near point of convergence, reading speed using the Wilkins Rate of Reading Test (WPS), and pupil size and response were recorded on day 1, 3 and 5. In addition, visual function using 14 quality of life questionnaire was conducted at baseline and at the final visit. The effect of atropine was statistically significant for pupil size (p=0.04) and responsiveness (p<0.01). While amplitude of accommodation reduced, the change was not statistically significant. Visual acuity (distance and near) and reading speed were not adversely affected. While there was a slight increase in symptoms such as glare, overall there was no quality of life impact associated with the use of low-dose atropine. The authors concluded that 0.01% of atropine was generally well tolerated bilaterally and no serious adverse effects were observed. Therefore, this dose appears to provide a viable therapeutic option for myopia control among Caucasian eyes.
The efficacy of progressive addition lenses (PALs) to slow down the progression of myopia is unclear and various trials have failed to demonstrate clinically meaningful treatment effects. However, several subgroup analyses have suggested that this treatment may be effective in myopic children with near esophoria. PALs, however, do not help in myopic children with exophoria. In this study, the authors evaluated the reading posture (reading distance, head tilt and ocular gaze angles) in myopic children with esophoria, orthophoria and exophoria. Sixty-two myopic children were enrolled in the study (33 boys and 29 girls) aged 7–11 years (mean±SD, 9.6±0.9 years). The children exhibited spherical equivalent refractive errors between −0.75 and −4.75 D (mean±SD, −1.93±0.83 D) in both eyes, <1.00 D of astigmatism, and <1.00 D of anisometropia as measured using non-cycloplegic subjective refraction. They wore SVLs followed by PALs. Eighteen children were esophoric (greater than +1), 18 were orthophoric (−1 to 1) and 26 were exophoric (less than −1) at near. Reading distance, head tilt and ocular gaze angles were measured using an electromagnetic system after adaptation to each lens type. The experiment was performed in a reading laboratory in which the lighting conditions were carefully controlled and maintained at 565 lx (560–570 lx). The desk and chair heights (73 and 41 cm, respectively) were the same as those used in local elementary schools and remained constant during the measurements. Reading distance, head tilt and ocular gaze angles were continuously recorded at 15 Hz with an electromagnetic motion tracking system (Fastrack, Polhemus, USA) that is commonly used for near posture measurements. Data related to the reading of one full page were used for the analyses. Reading distance was defined as the distance from the base of a child's nose to the centre of each line. Head tilt angle was defined as the angle in the sagittal plane between the head and the vertical upright position. Ocular gaze angle was defined as the angle in the sagittal plane between the normal line of the head and the child's line of sight and was corrected for the prismatic effects of the lenses. Results show that the lens type did not influence reading distance or head tilt angle (p>0.05 for both), but ocular gaze angle decreased significantly with the PALs (F=9.25, p=0.004). With the PALs, exophoric children exhibited significantly increased head tilt angle (p=0.003) and reduced ocular gaze angle (p=0.004) compared with esophoric children. Near non-exophoric children exhibited similar eye and head postures when wearing SVLs and PALs, whereas exophoric children exhibited reduced ocular gaze angle (t=−3.18, p=0.04) with PALs compared with SVLs. Using PALs for reading, the mean addition power employed by esophoric children was significantly greater than exophoric children (p=0.04). The authors concluded that myopic esophoric children used a lower
portion of their PALs compared with exophoric children, resulting in greater addi-
tion power. These results may partially explain why myopic children with near
esophoria exhibited superior treatment effects in myopia control trials using
PALs. A major flaw of this study is the use of non-cycloplegic refraction, calling
the study’s reliability into question.

Efficacy Comparison of 16 Interventions for Myopia Control in
Children a Network Meta-analysis
2016;123:697-708

In this meta-analysis of 30 randomized clinical trials of at least 1 year dura-
tion each (total 5422 eyes), the authors compared various myopia treat-
ments to placebo using annual dioptric change in refraction (D/y) and
change in mean in axial length (mm/y). The difference in refraction change
between high-dose atropine and control was 0.68 D/y and difference in axi-
al length was -0.21mm/y. For moderate-dose atropine the differences in re-
fraction and axial length were, 0.53 D/y and -0.21mm/y, respectively. For
low-dose atropine, change was 0.53 D/y and -0.15 mm/y. Each dose of atro-
pine markedly slowed myopia progression. Pirenzepine yielded refraction
change of 0.29 D/y and axial length change -0.09 mm/y. Orthokeratology
and peripheral defocus modifying contact lenses yielded moderate effect of
-0.15 D/y and -0.11 D/y, respectively. Progressive addition spectacle lenses
showed only slight effect.
Comment: Figure 3 is a good summary of interventions such as atropine
and pirenzepine that had a positive effect on refraction and axial length and
some interventions which had no significant positive effect such as rigid
gas-permeable contact lenses, soft contact lenses, timolol, and undercor-
rected single vision spectacle lenses.

Effectiveness study of atropine for progressive myopia in Euro-
peans
J R Polling, R G W Kok, J W L Tideman, B Meskat and C C W Klaver
Eye July 2016; 30: 998-1004; advance online publication, April 22, 2016;
doi:10.1038/eye.2016.78

Most studies examining the efficacy of the use of atropine to slow the progres-
sion of myopia have involved subjects of east Asian ethnicity. In this study involv-
ing 84 children primarily of European ancestry, effectiveness of daily use of atro-
pine 0.5% was investigated. After 12 months of therapy, progression of myopia
decreased from a pretreatment rate of -1.0 D/year to -0.1 D/year. While adverse
effects such as photophobia and reading problems were reported in 82% of pa-
tients, 78% adhered to therapy for the one year study period. The authors con-
clude that atropine 0.5% can slow the progression of myopia in a population of
European ancestry, and use of progressive multifocal lenses can minimize side effects of atropine.

**Miscellaneous**

**Refractive outcomes following the treatment of retinopathy of prematurity in the anti-VEGF era: a literature review**


A growing body of evidence indicates that anti-VEGF therapy is effective in the treatment of retinopathy of prematurity (ROP). Results are presented from a comprehensive literature review on refractive outcomes of anti-VEGF treatments compared to laser treatment or a combination of laser therapy and anti-VEGF injections. Of the 9 studies analyzed, the final mean refractive error was myopic in 3 studies (37%) with intra-vitreal bevacizumab (IVB) monotherapy, 7 studies (87.5%) with laser photocoagulation, and 1 study (50%) with combined therapy. In comparing IVB with laser monotherapy, 6 of 7 studies (86%) reported that final refractive error was significantly more myopic (>1 D) after laser treatment. No study was graded as high quality, and only a single article provided moderate quality of evidence. This review supports the notion that anti-VEGF for ROP leads to less myopia compared to laser therapy. However, the studies included in this analysis were of low quality, they varied in inclusion criteria and in standard of care, and had small sample size. The authors conclude that further studies are needed to elucidate the effect of IVB on refractive error of eyes with ROP.

**Usefulness of refractive measurement of wavefront autorefrac- tion in patients with difficult retinoscopy.**


The ability of the WaveScan WaveFront System (VISX Inc, Santa Clara, CA) to measure refractive errors in patients with difficult retinoscopy was assessed and results were compared to standard cycloplegic retinoscopy in this retrospective case series. The medical records of patients with an ocular condition that could contribute to difficult or unreliable retinoscopy who underwent nondilated, noncycloplegic evaluation with the WaveScan WaveFront System were reviewed retrospectively. Results were compared to a standard cycloplegic retinoscopy. A total
of 60 eyes of 31 patients were included. Wavefront sphere, cylinder, and spherical equivalent measurements were strongly correlated with retinoscopy results; however, the wavefront measured more myopia and more cylinder compared to standard retinoscopy. The mean difference (in absolute values with standard deviation [SD]) between wavefront and retinoscopy sphere was 0.94 ± 0.95 D. The authors concluded that Wavefront can be used to augment and enhance cycloplegic streak retinoscopy. The limitations to this study are directly drawn from its retrospective design.

**Visual Function of Moderately Hyperopic 4- and 5-Year-Old Children in the Vision in Preschoolers - Hyperopia in Preschoolers Study.**

Hyperopia is the most common refractive error in children, yet the threshold for which uncorrected hyperopia compromises vision in this age group is not well understood. This study is a secondary analysis of data from the multicentered prospective and cross-sectional Vision in Preschoolers - Hyperopia in Preschoolers Study (VIP-HIP). In this analysis, the authors evaluated the uncorrected monocular distance and binocular near acuities as well as stereoacuity and accommodative response in 3 and 5 year old preschool children. Moderate hyperopia was defined as 3 to ≤ 6 D and emmetropia as <1D. Their results were that emmetropic children had better visual performance than their hyperopic peers in all areas evaluated. Students with higher magnitudes of hyperopia (4-6 D) were at increased risk to have reduction in one of these functions. The authors point out that this paper does not demonstrate causality. Additionally that it is unclear from this study which spectacle prescription – partial or full correction of the hyperopia – would be best. This study is important because it demonstrates a functional difference for the preschoolers with uncorrected hyperopia and could potentially alter the spectacle prescribing habits of its readers.

**Visual field defect classification in the Zhongshan Ophthalmic Center–Brien Holden Vision Institute High Myopia Registry Study**

Accurate diagnosis of glaucoma in the setting of high myopia poses a clinical challenge. Myopic degeneration can cause similar glaucomatous-like visual fields. This is a registry study looking at Chinese myopes aged 7 to 70 and evaluating their presenting visual field and how they change longitudinally. This article presents initial data. The goal was to describe a new combined myopia and glaucoma visual field classification system in the study population. They found total of 895 eligible participants in the study but only 487 subjects had visual field
data using Zeiss Humphrey SITA-fast. Median age was 17.4 years. Median refraction was -8.6 D and medial axial length was 27.2 mm. From November 2011 to August 2012, a total of 1434 visual fields (including confirmatory repeats of abnormal defects) from 487 high myopes (sphere $\geq -6.0$ D) were analyzed. The predefined classification definitions covering high myopia and glaucoma categories were: normal, enlarged blind spot, abnormal suspect and abnormal with nine subtypes. Two independent graders reviewed the first 150 of 1434 fields for initial grading calibration and the remaining 1284 fields were used to assess intergrader agreement. For the percentage distribution of visual fields, the repeats and unreliable fields were excluded, leaving 894 fields. The intergrader agreement of this combined classification system was a kappa=0.61 (95% CI 0.59 to 0.63). Among the 894 unique fields, the most common visual field was normal at 33.7%, followed by enlarged blind spot at 25.6%. The proportion of ‘arcuate-like’ field defects (combining nasal step, early arcuate and advanced arcuate) was 16.1%, with advanced arcuate at 3.4%. The authors propose a combined visual field classification for high myopia and glaucoma, which demonstrated an acceptable intergrader agreement. A total of 16.1% of defects in young high myopes were found to mimic classic glaucomatous defects. These subjects are being followed prospectively to assess which ones will progress to differentiate myopic from glaucomatous field defects. This study would have more strength if they limited the cohort to 7 to 40. They describe young myopes to include age 7 to 70 in this report and seem to contradict themselves in this report.

**Longitudinal Changes in Refractive Error in a Pediatric referral population in Korea.**


This article investigates the changes in the spherical equivalent (SE) refractive error and astigmatism in a pediatric referral population in Korea with longitudinal follow-up (10 years). In this retrospective case series 221 patients were included aged 3 to 9 years and underwent at least 10 years of follow-up. At the initial visit the subjects were divided into different groups (myopia, $<-0.50$ D, emmetropia, -0.50 to +0.75D, or hyperopia $>+0.75$ D), low($<1.00$ D), moderate(1.00 to 3.00D), and high($>3.00$D) astigmatism. They were also categorized based on the presence of strabismus. The authors showed an overall negative shift in SE refractive error and increasing tendency in astigmatism from age 3 to 16 years. Also, the initial degree of SE refractive error showed a significant association with changes in SE refractive error and the initial degrees of SE refractive error and astigmatism showed a significant association with changes in astigmatism.

**Association Between Ocular Dominance and Anisometropic Hyperopia**

The purpose of the study was to determine the ocular dominance in patients with anisometropic hyperopia. Sighted dominance was determined by the hole-in-the-card test on 223 hyperopic patients (446 eyes). Inclusion criteria included best corrected visual acuity of 20/25 or better in each eye. Right eye ocular dominance was present in 65.5% of patients. As the level of anisometropia increased in the four sub-groups the correlation between ocular nondominance and hyperopia increased. In 100% of patients with anisometropia greater than +2.00D, the nondominant eye was the more hyperopic eye. The authors also found that the shorter axial length correlated with the non-dominant eye.

**Effects of head-mounted display on the oculomotor system and refractive error in normal adolescents.**

This article investigates the clinical effects of head mounted display on the refractive error and oculomotor system in normal adults. Sixty volunteers (age 14.7 +/- 1.3 years, mean SE-3.1 +/- 2.6) watched a three-dimensional movie and virtual reality application of head-mounted display for 30 minutes. The refractive error, angle of deviation at distance (6 m) and near (33 cm), near point of accommodation, and stereoacuity were measured before, immediately after, and 10 minutes after watching the head-mounted display. Refractive error was measured repeatedly after every 10 minutes when a myopic shift greater than 0.15 D was observed after watching the head-mounted display. After 30 minutes of watching the head-mounted display, the SE, near point of accommodation, and stereoacuity in both eyes did not change significantly (all \( P > .05 \)). Immediately after watching the head-mounted display, esophoric shift was observed (0.6 ± 1.5 to 0.2 ± 1.5 PD), although it was not significant (\( P = .06 \)). Transient myopic shifts of 17.2% to 30% were observed immediately after watching the head-mounted display in both groups, but recovered fully within 40 minutes after watching the head-mounted display. The authors conclude that there were no significant clinical effects of watching head-mounted display for 30 min in normal adolescent eyes. This study is limited because it didn’t include adults or children as well as different ethnic groups (all patients were Koreans). Also the time of exposure to the head-mounted display was relatively short.

**4. VISION IMPAIRMENT**

**Procedural Adaptations for Use of Constant Time Delay to Teach Highly Motivating Words to Beginning Braille Readers**
Constant time delay is an evidence-based practice to teach sight word recognition to students with a variety of disabilities. Two previous studies have documented its effectiveness for teaching braille. This study evaluated the effectiveness of constant time delay to teach highly motivating words to 3 beginning braille readers with developmental disabilities. The students (ages 6, 6, and 10 years) had multiple disabilities and were enrolled in a specialized school for students with visual impairments. Variations in this study compared to prior studies included use of a preteaching and assessment tool, a higher criterion for mastery, an increased number of trials per session, and remediated instructional feedback. All 3 students reached mastery in 4 – 12 sessions in less than one hour of instruction. The number of correct responses decreased over time, but long-term maintenance was demonstrated. The results of this small case study have limited generalizability, but suggest that constant time delay is a promising strategy for teaching highly motivating words to early braille readers. The authors conclude that practitioners should incorporate constant time delay into a comprehensive literacy program with opportunities to generalize word reading into other contexts.

Teachers’ Experiences with Literacy Instruction for Dual-Media Students Who Use Print and Braille


Vision loss can affect a student’s proficiency with learning to read and write. Teachers of students with visual impairments (TVIs) are responsible for conducting comprehensive assessments to determine the optimum primary literacy medium for their students and to identify the need for dual-media instruction in both print and braille. Research regarding dual-media learners is limited. This study analyzed the responses from 84 TVIs in the US and Canada who completed an online survey in spring 2015. The teachers introduced braille to their students at the mean age of 7.8 years. The three most common reasons for introducing braille were the student’s diagnosis, print reading speed, and print reading stamina. The amount of instructional time in braille literacy varied, and slightly more than 60% of the students were initially introduced to noncontracted braille. The teachers reported that approximately half of their students were at or above grade level with their print literacy skills, but only about 25% were at or above grade level with their braille literacy skills. Student motivation and confidence appeared to be important considerations in the design and provision of braille literacy instruction.

The study was limited by data that were self-reported from the TVIs and were not verified by the authors, and no work samples to document student reading or writing were collected. However, the authors conclude that many factors should be considered when determining if a student should transition from print to braille.
as a primary literacy medium. Motivating students to want to learn and use braille seems critical, and a comprehensive curriculum is needed for use with established print readers at various reading levels who are transitioning to braille.

A Theory-Based Physical Education Intervention for Adolescents with Visual Impairments

Haegele JA, Porretta DL. *Journal of Visual Impairment & Blindness* 2017 Jan-Feb; 111.1:77.

School-aged individuals with visual impairments tend to be less physically active than their peers without disabilities, though preliminary intervention research suggests that physical activity levels of those with visual impairments can be improved. The purpose of this study was to determine the effects of a social cognitive theory-based physical education program on the leisure-time physical activity among adolescents with visual impairments. Four participants aged 15 – 17 years attending a Midwestern residential school for blind students were sampled. The intervention consisted of 9 instructional lessons; each lesson was infused with one or more social cognitive theory constructs. The school's physical education teacher taught all lessons. Participants 1 and 2 received one session per week over 9 weeks, and participants 3 and 4 received 2 sessions per week over 5 weeks. Physical activity was measured by step counts recorded by Fitbit Zips. For all participants, there were no consistent changes in steps during the intervention. These results conflict with those of a prior study. The authors postulate that residential status of participants and time of year in which the study took place (winter) may have influenced the results. Social validity questionnaires completed by the 4 participants, one physical education teacher, 3 parents, and 2 residential staff supported the program’s social usefulness for enhancing leisure-time physical activity.

The Social Experiences of High School Students with Visual Impairments


This study explored the social experiences of high school students with visual impairments. Experience sampling methodology was used to examine how socially included students with visual impairments feel, the internal qualities of their activities, and the factors that influence a sense of inclusion. 12 students, including 3 with additional disabilities, completed the Psychological Sense of School Membership (PSSM) questionnaire as a measure of inclusion. They were then asked to complete an in-the-moment survey 7 times daily for one week using an iOS device. The survey asked about activities and ratings of internal variables: fitting in, acceptance, loneliness, awareness, and enjoyment. Each student was also interviewed.
In general, the group felt included as measured by the PSSM. Students’ most frequent activity was classwork; doing nothing was rated most negatively and out-of-class activities were rated most positively. In the 3 participants with additional disabilities, the presence of the additional disability appeared to negatively influence a sense of inclusion, fitting in, enjoyment, and loneliness. Interviews revealed a lack of common ground between adolescents with both visual impairments and additional disabilities and their peers. This study revealed that students work hard to maintain parity with peers and they found school more enjoyable if they fit in. The small group of participants in this study had a lower proportion of visually impaired students with additional disabilities than is representative of this population of adolescents; therefore, there may be a higher degree of students struggling at school than is represented in this study.

**Fitness Wearables and Youths with Visual Impairments: Implications for Practice and Application**


Individuals with visual impairments are at risk for chronic health-related illnesses attributed to low physical activity and low fitness levels. This cross-sectional and descriptive study aimed to determine device preferences of 3 physical activity-monitoring wearables for children with visual impairments and to determine beneficial and impeding device components and suggested device changes. 25 individuals aged 9 – 22 years were recruited from a week-long sports camp for youths with visual impairments. Each day for 5 days, five of the participants wore the Nike+ FuelBand ES Activity Tracker, Garmin Vivofit, and Centrios all on the same day. Data was collected via demographic questionnaires and evening focus groups. Responses varied by level of visual impairment, such as with auditory and visual contrast components, and varied slightly by gender, such as with aesthetic components. All responses for beneficial and impeding components and suggested changes fell into nine coded themes: access to data, comfort, display, data measured, auditory, waterproof, aesthetics, goal-setting, and music. The study was limited by the small number of participants and short device usage time for each participant. Also, participants at a sports camp may be inherently more active than the average young population with visual impairments. Nevertheless, this study resulted in conclusions that should be considered in future physical activity promotion research and interventions for youths with visual impairments.

**The Current Experiences of Physical Education Teachers at Schools for Blind Students in the United States**


It has been established that children with visual impairments tend to be less physically active and more delayed in motor skills than their sighted peers. Research has focused on inclusive physical education for these children, but there
is a lack of research on the current status of physical education for children in residential schools. This study sought to gain insight into the experiences of physical education teachers at schools for blind students in the US. A questionnaire was sent to 51 PE teachers from 35 schools for blind students across the country. Data from closed-ended and short-response open-ended questions were analyzed across four main areas: teacher characteristics, teaching practices, student populations, and facilities. Results confirmed that most schools employ certified physical educators, use curricula that are tied to state or national standards, possess a variety of facilities for students to use in physical education, offer a variety of sports, and teach a varied population of students. Concerning factors include the lack of validated assessments in the field of adapted physical education and the subsequent limited use of validated assessments, and the need for additional training for teachers related to children who are deafblind and students with both visual impairments and autism spectrum disorder.

An Artificial Intelligence Tutor: A Supplementary Tool for Teaching and Practicing Braille


This study evaluated the usability and effectiveness of an artificial intelligence Braille Tutor designed to supplement the instruction of students with visual impairments as they learned to write braille contractions. Braille Tutor is an Internet-based tool that uses a form of artificial intelligence known as adaptive computer instruction. 10 students who were taught by 7 teachers of students with visual impairments (TVI) were enrolled. The students were braille readers who did not know either one-cell whole word contractions or short-form words, and they did not have additional significant intellectual disabilities. Each participant was assigned to one of two groups: TVI Only or TVI + Tutor. After finishing their first assigned phase, the students completed a probe using the adapted Assessment of Braille Literacy Skills (ABLS) tool and then switched to the other phase. The student was then probed again to assess maintenance of the contractions learned in the first interventional phase.

Students in the TVI+Tutor phase learned contractions more quickly and tended to get more frequent reinforcement compared to students in the TVI Only phase. In addition, students in the TVI+Tutor phase demonstrated a greater increase in the number of contractions learned during the first day of instruction, and were less likely to demonstrate a notable drop in learning after the first day. The small number of study participants made group analysis difficult, but the raw data suggest that advanced technology can be used along with quality instruction to enhance proficiency in braille literacy.

Binocular Vision in Chronic Fatigue Syndrome

Chronic Fatigue Syndrome (CFS) is characterized by found, disabling fatigue not caused by exertion and not relieved by rest. To diagnose the syndrome patient must also have 4 of the following symptoms within the past 6 months: sore throat, tender lymph nodes, muscle pain, multi-joint pain, post-exertional malaise, unrefreshing sleep, headaches, and impaired memory or concentration. Ocular complaints include pain, photophobia, blurred vision, intermittent diplopia, focusing difficulties, and dry eyes. The authors compared binocular vision measurements, accommodation, and convergence in patients with CFS vs. healthy controls and found that patients with CFS have highly significant smaller fusional amplitudes, reduced convergence capacity, and smaller accommodation range. Treatment for CFS patients with ocular manifestations should include progressive lenses =/- prism and convergence exercises.

Transient Smartphone "Blindness".

The authors present two patients who reported transient monocular “blindness” lasting up to fifteen minutes. After a careful history, the authors determined that the “blindness” occurred in after the patient was lying in bed on her side, with one eye obscured by a pillow and one eye viewing a bright smartphone screen. Thus, one eye became dark adapted and the other light adapted, and subsequent binocular viewing in dim light made the light adapted eye seem “blind.” The authors then subjected themselves to smartphone viewing and electroretinography, showing that the b wave amplitude decreased in the smartphone adapted eye. The effect lasted minutes. As pediatric ophthalmologists, we get questions about smartphone use; this brief report provides an interesting story about transient “blindness” from staring at the bright screen, which we can share with our patients’ families.

Health-Related Physical Fitness among Young Goalball Players with Visual Impairments

This study, which occurred on the day preceding the start of the Brazilian Paralympic School Games, determined the passing rates on health-related physical fitness tests of goalball players, comparing passing rates according to gender and visual impairment classification. 40 Brazilian goalball players (20 male, 20 female, mean age 17.3 years) with visual impairments were administered the Brockport Physical Fitness Test, a health-related, criterion-referenced protocol that evaluated percentage body fat, shoulder stretch, back-saver sit and reach, trunk lift, curl-ups, push-ups, and one-mile run or walk. A significant difference between genders was found only for the one-mile run or walk test. More than half of the participants were able to pass at least 4 of the 7 tests. No significant differ-
ences were found between the groups with varying levels of visual impairment. In both groups, the body fat percentage and trunk lift tests had higher passing rates (80%), and the push-ups and one-mile run or walk test had lower passing rates (<30%). In the one-mile run or walk test, the boys did as well as their sighted peers, whereas the girls did worse than their sighted peers. However, compared to youths with visual impairments who were not involved in regular training, the goalball athletes did better on most of the tests. This cross-sectional study had a relatively small sample size which may have prevented the detection of further differences between groups. In addition, participant motivation to perform the tests given the competition beginning the following day may have prevented participants from achieving their maximum performance. Nonetheless, goalball is a Paralympic sport likely to be of interest to visually impaired children and adolescents, and it seems to support the achievement of ideal physical activity levels in this population, leading to higher levels of physical fitness.

Socialization and Self-Determination in Different-Age Dyads of Students who are Deafblind

Susan Bruce, Mary Zatta, Mary Gavin, Sharon Stelzer. Journal of Visual Impairment and Blindness 2016 May-Jun; 110.3:149.

Deafblindness limits access to social cues and feedback, thus restricting the development of social skills. This collaborative action research study employed grounded theory design to examine how interactions between adolescent students with CHARGE syndrome and younger students with mixed etiologies of deafblindness change over time in the context of an arranged interaction space. Six deafblind students (3 adolescent and 3 elementary school-aged) were selected by their teachers for participation. Four had CHARGE syndrome. The students grouped themselves into dyads based on preferences for a particular activity in an arranged interaction space. The intervention consisted of 6 monthly dyadic interaction sessions in the arranged classroom setting. The older students were instructed to offer a choice of play area to the younger students, and to interact and problem-solve prior to seeking help from the teachers. Each interaction session was followed by a feedback session with the adolescent students. The younger students learned to make toy choices when presented by the adolescent students, though joint attention challenges occurred. The adolescent students in turn learned to interact more effectively with younger students while rehearsing self-determination skills such as goal-setting and problem solving. Although this study involved a small purposeful sample with infrequent and brief interaction sessions, some characteristics of the interactions of deafblind students were elucidated, along with strategies that supported effective interactions. More research on the socialization of deafblind students, and specifically those with CHARGE syndrome, is needed.

Introduction of 3D Printing Technology in the Classroom for Visually Impaired Students

As the importance of visual aids increases, textbooks are including more figures and images to help with students’ understanding. Reading and understanding a textbook poses challenges for students who are visually impaired. This study investigated how 3D printing technology could be used for instructional materials to allow visually impaired students full access to high-quality instruction in history class. Researchers from the 3D Printing Group of the Korea Institute of Science and Technology provided the Seoul National School for the Blind with tactile instructional materials and resizable braille made by 3D printers. The teacher provided hands-on instruction, and students used their hands to independently explore the 3D materials, allowing them to feel the historical pictures, maps, and relics. The 3D instructional materials were provided for use by 4 fifth-grade students for one semester. The students and teachers then evaluated the effectiveness of the 3D instructional materials based on several criteria. Although this was a very small study with no quantitative data, both students and teachers acknowledged the importance and usefulness of the 3D materials. Further study into their potential in teaching visually impaired students seems warranted.

Prevalence and risk factors of vision impairment among children of employees of Telecom, Italy.


Multiple surveys in different countries around the world had looked into the prevalence of vision impairment. It has been stated that there are no recent data on vision impairment in the high-income European countries, and that children from a European Caucasian background remain distinctly underrepresented in existing surveys. In order to define the prevalence, causes, and risk factors of vision impairment (VI) in children, this prospective cross sectional study, examined relatives of Association for Supplemental Health Insurance to the Employees of Telecom members aged 5-16 years in all Italian regions. A standardized record card was used to collect data on medical history; keratometry; objective refraction; uncorrected, presenting, and best-corrected visual acuity (VA); examination of the pupils, adnexa, and anterior segment; direct ophthalmoscopy; posterior segment and fundus examination; and assessment for ocular pathology. Binocular and monocular VI were defined by a VA <20/40. The data was collected during a campaign of preventive medicine in ophthalmology. It included 17,508 children, 12,798 of whom (73.1%) were examined (and 12,740 on whom all VA data were gathered). More than a quarter of the sample (3,319/12,740 [26%]) had not had an eye examination prior to this campaign. The prevalence of uncorrected, presenting, and best-corrected VI in the better eye was 9.0%, 2.51%, and 0.10%, respectively. The following variables were associated with presenting vision impairment: age 10-16 years, family history of myopia, female sex, family history of keratoconus, and hypertension. Myopia was the main cause of vision impairment (82.6%). A total of 96% of children with presenting vision impairment had correctable vision impairment.
very large cohort of patients were analyzed in this study, but authors recognize some of its limitation. The results could be biased because of the 27% of children who were invited but not examined. Another limitation is that test reproducibility for VA measurements between examiners was not reviewed; this was not planned due to the aims of the preventive campaign. The authors concluded that correctable vision impairment because of myopia is an important public health problem in school-age children in Italy.

**State-of-the-art: low vision rehabilitation.**


Low vision rehabilitation (LVR) is today a recognized discipline in Ophthalmology, expanding and improving the quality of life of numerous visually impaired patients. It was not so about a century ago when it all started. Then, charity work aimed at helping blind children was all that LVR was. With advances in science, medicine and public health policy, help for the blind expanded its reach to all who were visually impaired. Devices and re-training of skills have been added to complement diagnosis and charity work. In spite of significant scientific advances and increased awareness of LVR that have occurred recently, it is estimated that today only about 20% to 30% of those who need LVR receive low vision services in westernized countries, and only 10% to 15% in underdeveloped countries. This interesting review presents the challenges of modern LVR. It gives a good historical perspective and supplies an in depth overview of the advances that were made in this field.

5. NEURO-OPHTHALMOLOGY

**Rituximab in the treatment of Neuromyelitis optica: a multicentre Italian observational study**

Pietro A, Capobianco A, Moiola L. F. Patti, J. Frau, A. Uccelli, D. Centonze, . et al. Received: 16 March 2016/Revised: 30 May 2016/Accepted: 31 May 2016/Published online: 10 June 2016 Springer-Verlag Berlin Heidelberg 2016

This is an observational study done to evaluate a favorable dosing schedule for Rituximab in NMO and confirm safety efficacy. The study compares dosing 375 mg/m2/week iv for 4 weeks (RTX-A) and 1000 mg iv twice, 2 weeks apart (RTX-B). The authors find that a single high RTX first dose is favorable rather than an overall higher dose, but spread in a longer period with single lower pulses. This study explores treatment in adults but this may provide insight into treatment management in children.

**Evaluation and Management of Tolosa–Hunt Syndrome in Children: A Clinical Update**
Authors reviewed 16 retrospective case reports in children with Tolosa-Hunt and determined that children have a similar course to adults. Some considerations to note between the two groups involve ophthalmoplegia, pupil dysfunction, imaging and treatment. In children, the third nerve is most frequently involved, followed by the sixth, fourth and fifth cranial nerves. The frequency of pupillary sympathetic dysfunction was higher in children than adults and THS can be present despite normal initial MRI findings. Magnetic resonance angiography may be helpful in the diagnosis. Low dose steroids may be inadequate to manage and prevent recurrence.

Ischemic stroke subtypes and migraine with visual aura in the ARIC study

Patients enrolled in the Atherosclerosis Risk in Communities (ARIC) study, a prospective longitudinal cohort study with enrollment from 1987-1989, were evaluated for migraine with aura or migraine without aura through a headache questionnaire administered at their third study visit (from 1993-1995). 12.6% of patients had a history of migraine, with a male to female ratio of 3:1. Stroke occurred in 6% of the study population after the third study visit. Patients who had migraine with aura had a 1.67 hazard ratio (CI 1.1-2.4) of suffering an ischemic stroke compared to controls, while patient who had migraine without aura did not have an association with ischemic stroke. Patients with migraine with aura had a 3.7 hazard ratio (CI 1.6-8.7) of cardioembolic stroke compared with migraine without aura. Further investigation into the pathophysiology of cardioembolic and cryptogenic stroke in migraine with visual aura is necessary.

Pediatric Optic Nerve Meningioma: Diagnostic and Therapeutic Challenges

Intraorbital meningiomas in children are exceptionally rare. In the pediatric population, optic nerve sheath meningiomas (ONSM) are often associated with neurofibromatosis Type 2. The authors of this paper review the diagnosis and management challenges of this tumor in the pediatric age group. Imaging modalities such as MRI or CT aid in the diagnosis of meningiomas; however meningiomas can have varying imaging patterns. The classic appearance is an intraconal mass surrounding the intraorbital optic nerve with "tram-tracking" but the tumor can also appear as tubular, globular, fusiform and focal optic nerve sheath enlargement. In cases where the diagnosis is uncertain histopathologic analysis is
essential, especially when optic nerve function is compromised. Pediatric meningiomas tend to grow more rapidly and aggressively compared with adult meningiomas. Current treatment options must be interpreted cautiously in the pediatric population. Optic nerve decompressions used in adults may not be as applicable in children. Complete resection is difficult to implement in a reasonably well seeing eye, but concern of compromise of vision to the other eye by extension to the chiasm must be considered. Radiation can put the patient at risk for ocular and systemic complications. Proton beam radiation has been explored and early results seem to show slowing or cessation of tumor growth. One benefit is a narrow radiation delivery zone that presumably produces less surrounding damage to normal tissues. Proton beam radiation may be an effective treatment option for the rare pediatric ONSM.

Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas.


Effective medical therapies are lacking for the treatment of neurofibromatosis type 1–related plexiform neurofibromas, which are characterized by elevated RAS–mitogen-activated protein kinase (MAPK) signaling. This was a phase 1 trial of selumetinib, an oral selective inhibitor of MAPK kinase (MEK) 1 and 2, in children who had neurofibromatosis type 1 and inoperable plexiform neurofibromas to determine the maximum tolerated dose and to evaluate plasma pharmacokinetics. Response to treatment (i.e., an increase or decrease from baseline in the volume of plexiform neurofibromas) was monitored by using volumetric magnetic resonance imaging analysis. A total of 24 children (median age, 10.9 years; range, 3.0 to 18.5) with a median tumor volume of 1205 ml (range, 29 to 8744) received selumetinib. Patients were able to receive selumetinib on a long-term basis; the median number of monthly cycles was 30 (range, 6 to 56). The maximum tolerated dose was 25 mg per square meter (approximately 60% of the recommended adult dose). The most common toxic effects associated with selumetinib included acneiform rash, gastrointestinal effects, and asymptomatic creatine kinase elevation. Treatment with selumetinib resulted in confirmed partial responses (tumor volume decreases from baseline of ≥20%) in 17 of the 24 children (71%). Disease progression (tumor volume increase from baseline of ≥20%) has not been observed to date. Anecdotal evidence of decreases in tumor-related pain, disfigurement, and functional impairment was observed. The phase 1 data suggested that children with neurofibromatosis type 1 and inoperable plexiform neurofibromas benefited from long-term selumetinib treatment without having excess toxic effects. This is an exciting development showing that drug treatment for NF1 patients who have inoperable plexiform neurofibromas is possible.
Orbito- Masticatory Syndrome.

Oscillopsia and diplopia has been reported with mastication after eyelid surgery and more commonly after surgery involving the walls of the orbit. This has been well described in association with orbital wall decompression for of thyroid eye disease. Contraction of the temporalis muscle now readily in contact with orbital contents is the imputed cause. The authors present two interesting cases. One had episodic diplopia and oscillopsia after fronto-temporal-orbitozygomatic craniotomy with osteotomy of the lesser wing of the sphenoid for treatment of an invasive pituitary adenoma. The second developed episodic diplopia and visual field loss due to a bi-lobed arteriovenous malformation in the inferolateral orbital and right temporalis muscle. In both cases, mastication resulted in globe displacement and the associated reported symptoms. In the second case, excision of the AVM resolved the symptoms. A nice fascinoma.

Avoiding Clinical Misinterpretation and Artifacts of Optical Coherence Tomography Analysis of the Optic Nerve, Retinal Nerve Fiber Layer, and Ganglion Cell Layer

This excellent review article is a must read for anyone using OCT. It provides important information that will help the practitioner avoid error in interpretation of this rapidly expanding technology. Data resulting in misinterpretation- unless carefully scrutinized- may be as high as 40%.
RNFL is age dependent. There is a natural decrease in mean RNFL of 0.365 mm per year increase in age so make sure date of birth entered correctly. Signal strength needs to be adequate (this is device dependent) or the results inaccurate and likely non-reproducible. Any media opacity (e.g. dry eye, cataract or vitreous hemorrhage) decreases measurable RNFL and produces regions of dropout which reduce mean RNFL and alter segmentation analysis. Decrease in signal strength can have similar impact. Local areas with a thickness less than 40 mm are typically due to errors in segmentation unless the patient has longstanding extremely severe optic neuropathy. Improper alignment of scan can increase or decrease apparent RNFL and distort segmentation analysis. Papilledema can make it difficult to determine the neural canal opening and can result in measurement of a seemingly large optic disc which is not present, and distorts segmentation of RNFL and may gives areas of non-physiological RNFL drop-out. Increased axial length and myopia above 5 D are associated with reduce measured RNFL which often is most often non-pathologic in nature. These changes may go unrecognized or improperly interpreted in patients post refractive or cata-
ract surgery. Due to the more temporal shift of the RNFL peaks in myopia, the temporal RNFL thickness may appear to be elevated, while the superior and inferior RNFL thickness may be reported as decreased when they are actually “normal” for myopes. Exceptionally hyperopic eyes tend to show a more acute vertical angle of entry of the arcuate bundle also altering the segmentation distribution plot. Cyclo-rotation of the eyes, for example from superior oblique palsy, will cause a change in RNFL profile making it difficult to compare to the normative database. This error has been largely corrected in the Spectralis software. Gliosis of the optic nerve, common after chronic papilledema, can result in an increase in apparent RNFL thickness in the clinical setting of significant optic atrophy. In this case, and in the case of papilledema in general, the macular ganglion cell layer-inner plexiform layer (GCL-IPL) complex available on the macula cube will show atrophy while the peripapillary RNFL appears thickened due to the elevation created by gliosis or edema. Myelinated nerve fiber layer can also lead to an measured increase in RNFL thickness. Acute edema of the inner retina due to artery occlusions, and epiretinal membrane can also cause an increase in measured RNFL thickness that can obscure pathologic loss of axons. Patients with megalopapilla or, conversely those with small neural canals (including optic nerve hypoplasia) may show abnormal cup to disc ratio as software is not designed for these anomalies. The GCL-IPL complex is thickest in the macula, has a larger dynamic range than the RNFL in the papillomacular bundle, and provides a more sensitive measure of neuronal loss than the papillomacular bundle-- and been found to correlate with field loss and optic nerve diseases such as glaucoma, optic neuritis, ischemic optic neuropathy, hereditary optic neuropathy, toxic optic neuropathy, optic nerve glioma, and idiopathic intracranial hypertension. Errors in GCL-IPL segmentation may appear as spoke-like blue regions of thinning called the “propeller sign”. The perifoveal region has much individual variability and thus “abnormalities” need be scrutinized for clinical correlation.

**Ganglion Cell Complex Loss in Chiasmal Compression by Brain Tumors**


Twenty-three patients with chiasmal compression and age matched controls were imaged with Cirrus high-definition optical coherence tomography macula cube protocol, retinal nerve fiber layer protocol and automated,30-2, Humphrey)visual fields. Ganglion cell complex thinning demonstrated in macula cube protocol corresponded to visual field defects and mean deviation correlated more with ganglion cell complex rather than nerve fiber layer thinning. Binasal ganglion cell complex loss was typical for patients with chiasmal lesions. Postoperatively, visual field loss mean deviation improved in 7 of 8 patients with persistent nasal ganglion cell complex thinning and six patients had loss of ganglion cell complex in
spite of normal visual fields. The authors concluded that ganglion cell complex thinning may be detected before loss of retinal nerve fiber layer in some patients with chiasmal lesions and after decompression, many patients demonstrated improvement in visual field even with persistent ganglion cell complex loss. Patients with less ganglion cell loss before decompression had better postoperative visual fields. Macula cube ganglion cell analysis may be a particularly sensitive method to monitor patients with chiasmal lesions.

Saccadic vector optokinetic perimetry in children with neurodisability or isolated visual pathway lesions: observational cohort study


Automated perimetry is highly unreliable in children and often not feasible despite its importance. Saccadic vector optokinetic perimetry (SVOP), by i2EYE Diagnostics, is a new technology that may have improved accessibility, but its accuracy has not been evaluated. This is a study comparing accessibility, testability and accuracy of SVOP by comparing it to results obtained from Goldman visual field testing (GVFT) in children with neurodisability or visual pathway deficits. From October 2013 to May 2014, consecutive patients were enrolled for this exploratory study at children’s eye clinics at a tertiary referral center and a regional child development center. An orthoptist assessed vision and eye movements including saccade and pursuit, a confrontational visual field (CVF) and then a SVOP. There were two groups of children. Group 1 were ages 1 to 16 years old with neurodisability. Group 2 included children 10-16 years old with known or suspected visual field defects. Group 2 also completed GVFT. Full test on SVOP consists of 40 points. The test allows reduced number of points in cases of poor cooperation, that is 14, 12, or 4 can be selected at the discretion of the observer. Of 54 eligible patients, 37 were enrolled: 16 in group 1 and 21 in group 2. In Group 1, testability with full 40-point test was low (12.5%). With reduced test protocols, testability was 100%, but plots may not be clinically meaningful. Children (44%) and parents/carers (62.5%) found the SVOP easy. SVOP and CVF agree in 50%. In Group 2, testability was 62% for the 40-point protocol, and 90.5% for reduced protocols. Corneal changes in childhood glaucoma interfere with SVOP testing. All children and parents/carers find SVOP easy. Overall agreement with GVFT was 64.7%. In conclusion, SVOP has higher accessibility to children, but many cannot complete a full 40-point test. Agreement with current standard tests is moderate to poor.

Choroidal Freckling in Pediatric Patients Affected by Neurofibromatosis type 1.

Aldo Vagge, Leonard Nelson, Paolo Capris, Carlo Enrico Traverso
In this article the authors review the studies that looked at the incidence of choroidal freckling in pediatric patients with Neurofibromatosis TYPE 1 (NF-1) with the use of non-invasive infrared monochromatic light with confocal scanning laser ophthalmoscopy or OCT imaging. All these studies recommend considering freckling as a new clinical marker of the disease although further epidemiologic studies are needed in order to establish choroidal freckling as NIH criterion for the diagnosis of the disease. In addition, both near-infrared reflectance and CT imaging are non-invasive, non-contact, quick and high resolution diagnostic tests that are applicable in children suspected of having NF-1 to determine the presence of choroidal freckling. The authors conclude that there are good evidence to support the correlation between choroidal freckling and NF-1 and that although larger studies are needed in order to confirm its presence in patients with NF-1, the use of choroidal freckling might be a new diagnostic criterion for the diagnosis of the disease.

Optic gliomas in Neurofibromatosis Type 1
Emily Parkhurst, Sridevi Abboy *Journal of Pediatric ophthalmology & Strabismus.* November/December 2017; 53(6): 334-338

The purpose of this study is to report the incidence, presentation and outcome of optic nerve gliomas in children with neurofibromatosis type I (NF-1) in Southern California Kaiser Permanente. Out of 708 patients younger than 21 years of age who were diagnosed with NF-1, only 30(4.2%) had an optic nerve glioma. The average age of diagnosis was 5 years, ranging from 18 months to 12 years. Half of the patients who were diagnosed as having optic nerve glioma, presented with symptoms. Symptomatic patients were diagnosed later than asymptomatic patients through routine screening.63% of the gliomas were bilateral, 23% right-sided and 13% left-sided. Fifty-three percent of the optic glioma patients were involving the optic chiasm. The authors conclude that annual ophthalmologic examination and screening of all children diagnosed with NF-1 is very important for early detection of optic nerve gliomas.

A review of the current practice in diagnosis and management of visual complaints associated with concussion and postconcussion syndrome.

PURPOSE: This review provides information on the diagnosis and management of visual symptoms caused by concussions.

FINDINGS: Concussions are mild traumatic brain injuries due to diffuse axonal injury. Neuroimaging is typically normal in patients with concussions. Visual abnormalities may include: photophobia, diplopia, blurred vision, accommodative
insufficiency, convergence insufficiency and saccadic dysfunction. Vestibular abnormalities may result in dizziness and vertigo. Symptoms present for longer than a month meet the criteria for the diagnosis of postconcussion syndrome which may be associated with impaired school performance, migraine headaches, depression and anxiety. New testing including a brief vestibular/ocular motor screening assessment and near point of convergence measurements may prove beneficial to the diagnosis and identification of patients at greater risk for developing postconcussion syndrome. Multiple tests are available to diagnose concussions, but no test can identify all individuals. Treatment includes rest although no randomized controlled studies have been conducted to assess its effectiveness. Visual symptoms of convergence or accommodative insufficiency are addressed with prisms, convergence exercises or spectacles for near work. Additional studies are necessary to assess the effectiveness of treatment for visual symptoms after concussion.

**SUMMARY:** Ophthalmologists are likely to see more postconcussion syndrome patients in the future and should be aware of how to manage them. There is no a single testing method that can identify all individuals with a concussion. Management of concussion focuses on symptoms. Evidence for the effectiveness of treatment of post concussive symptoms is sparse.

**Pediatric pseudotumor cerebri.**

**PURPOSE:** Review recent literature regarding the epidemiology, diagnosis, and treatment of pediatric pseudotumor cerebri (PTC) or idiopathic intracranial hypertension (IIH).

**FINDINGS:** Revised diagnostic criteria define pediatric IIH as an opening cerebrospinal fluid pressure greater than 28 cm water, papilledema, normal neurologic exam except for cranial neuropathies, absence of a structural lesion on neuroimaging and normal CSF composition. Neuroimaging of a child with suspected IIH should include a MRI with and without gadolinium and a MRV. Adults and children with IIH have similar findings suggestive of increased intracranial pressure on neuroimaging. Obesity is an important risk factor for IIH in post-pubertal children. Obesity and sedation are associated with higher opening pressures. Secondary IIH is caused by medications or conditions including: tetracyclines, withdrawal from chronic steroid use, growth hormone, thyroid replacement, obesity, Down syndrome, chronic kidney disease, cerebral venous sinus thrombosis, Addison disease and anemia. Treatment with diamox and weight loss are effective for IIH patients with mild visual field loss. Patients with severe papilledema, poor visual acuity, and GCL-IPL thickness less than 70 um on SD-OCT at presentation are at increased risk for subsequent visual loss. Further study of pediatric IIH and the relationship between OCT abnormalities and visual dysfunction are necessary.

**SUMMARY:** This is a good review of recent literature that outlines the diagnosis and management of pediatric patients with IIH.
Optic neuropathy in late-onset neurodegenerative Chédiak–Higashi syndrome


The classic form of Chédiak–Higashi syndrome (CHS), an autosomal recessive disorder of lysosomal trafficking with childhood onset caused by mutations in LYST, is typified ophthalmologically by ocular albinism with vision loss attributed to foveal hypoplasia or nystagmus. Optic nerve involvement and ophthalmological manifestations of the late-onset neurodegenerative form of CHS are rarely reported and poorly detailed. This is a case series detailing ophthalmological and neurological findings in three adult siblings with the late-onset form of CHS. All three affected siblings lacked features of ocular albinism and demonstrated significant optic nerve involvement as evidenced by loss of color and contrast vision, central visual field loss, optic nerve pallor, retinal nerve fiber layer thinning by optical coherence tomography (OCT) and abnormal visual evoked potential, with severity corresponding linearly to age of the sibling and severity of neurological disease. Further, unusual prominence of a ‘third line’ on macular OCT that may be due to abnormal melanosomes was seen in all three siblings and in their father. Neurological involvement included Parkinsonism, cerebellar ataxia and spastic paraparesis. This report expands the ophthalmological phenotype of the late-onset neurodegenerative form of CHS to include optic neuropathy with progressive vision loss, even in the absence of ocular albinism, and abnormal prominence of the interdigitation zone between cone outer segment tips and apical processes of retinal pigment epithelium cells on macular OCT.

Visual Deterioration and Herniation of Anterior Cerebral Artery: Unusual Presentation of Empty Sella Syndrome Complicating Decompression of a Rathke Cleft Cyst.


This interesting case report details devastating visual consequences that can occur in patients with an empty sella syndrome who have surgical decompression of a mass or cyst within the region... Surgery and associated scar tissue can cause traction and herniation of adjacent brain contents into the sella. In this case, several weeks after successful decompression of a Rathke cleft cyst in the suprasellar space resulted in herniation of both the anterior cerebral arteries and chiasmal optic nerve into the empty sella. Return to the OR for packing of the region offloaded the cerebral contents but vision only partly recovered.

Systemic Amyloidosis and Extraocular Muscle Deposition

In this case report a 67 year old woman presents with new onset diplopia and progressive restrictive strabismus. CT imaging shows diffuse enlargement of the "involved" extraocular muscles. Workup for thyroid disease and myasthenia are unremarkable and extraocular muscle biopsy demonstrates infiltrative sarcoid. Literature review notes that tissues typically affected in ocular sarcoid are periorbital fat, extraocular muscles, and lacrimal gland, and patients can present with proptosis, ptosis, and/or restrictive strabismus. Whereas some of the clinical presentation resembles thyroid eye disease (absent external inflammation) the neuroimaging is different. Amyloid usually is characterized by diffuse enlargement of involved extraocular muscles, punctate calcifications within the muscles on CT; and heterogeneous hypointense regions on T2 MRI with homogeneous enhancement on fat-suppressed or contrast-enhanced T1 MRI sequences. These features differ from the homogeneous and tendon-sparing fusiform enlargement of extraocular muscles typically documented with neuroimaging in thyroid eye disease. Both disorders can be bilaterally asymmetric or seemingly unilateral and both can appear with or without other obvious non-ocular systemic involvement.

**Fixation Switch Diplopia**


This beautifully written editorial provides an excellent review on the meaning and common causes of fixation switch diplopia. Switch of fixation preference from the previously dominant to the non-dominant eye can result in new onset diplopia without any significant change in strabismus angle. This results from the absence of a paracentral suppression scotoma for the previously dominant eye. Common causes include vision loss in the previously dominant eye from cataract or other aging changes, refractive changes favoring better uncorrected acuity in the previously non-dominant eye (e.g. development of myopia in the previously less hyperopic eye) and use of mono-vision correction. Careful prescreening patients for a history of amblyopia might alert practitioners to those at risk so that interventions likely to result in fixation switch diplopia are avoided.

**The degree of anisocoria in pediatric patients with Horner’s syndrome when compared to children with no disease.**


This study evaluates the degree of anisocoria in a normal pediatric population using the PlusoptiX A08 photoscreener and compares it pediatric patients with known Horner’s syndrome through literature review in order to determine whether or not anisocoria alone should raise suspicion for the diagnosis of Horner’s syndrome.
The medical records of 592 consecutive patients (up to the age of 9 years) were retrospectively reviewed. All patients had complete eye exams including photoscreening with the Plusoptix AO8. A complete literature search of documented pupillary size in pediatric patients with the diagnosis of Horner syndrome was performed. This was then compared to the normative pediatric pupil data from the study. Of the 592 children without Horner syndrome, 372 had an anisocoria of 0.1 to 0.5 mm (62.84%), 167 had an anisocoria of 0.6 to 1.2 mm (28.16%), and 21 had an anisocoria of 1.3 mm or greater (3.70%). There was no correlation between increasing age and severity of anisocoria (P = .55). For pediatric patients with a diagnosis of Horner syndrome, the average level of anisocoria was 1.37 mm in room light and 2 mm in darkness. In room light, three children had anisocoria of 0.1 to 0.5 mm (9.4%), 14 had anisocoria of 0.6 to 1.2 mm (43.8%), and 15 had anisocoria of 1.3 mm or greater (46.9%). In darkness, the level of anisocoria increased in 19 patients, causing the first category, 0.1 to 0.5 mm, to include 1 patient (3.1%), the second group to include 5 patients (15.6%), and the last group to include 26 patients (81.3%). The authors concluded that in the normal pediatric population the average pupilllary size increased with age but the degree of anisocoria remained stable with increasing age. Over half of the children studied had anisocoria up to 0.5 mm (62.84%), but rarely had anisocoria greater than 1.3 mm (3.70%). In children with a diagnosis of Horner syndrome, the majority had anisocoria greater than 1.3 mm, with the discrepancy in pupil size becoming more apparent in low levels of light intensity. The authors concluded that anisocoria greater than 1.3 mm is unlikely to be physiologic in a child; therefore, the child should be carefully evaluated for other localizing signs. This is a study that gives information about the changes in the pupil size in children as well as the degree of anisocoria in children. However the study is limited by the fact that the data from the Horner’s group were extrapolated from the literature.

**Idiopathic Intracranial Hypertension**

**Use of Multi Color imaging in the assessment of suspected papilledema in 20 consecutive children.**


In this prospective study 20 consecutive children with suspected papilledema were recruited to investigate the use of MultiColor Scanning Laser Imaging as an adjunct to traditional imaging modalities in the assessment of children with suspected disk swelling. The investigators wanted to assess whether it can help differentiate true papilledema from pseudopapilledema. MultiColor imaging was performed on all patients in addition to fundus examination, fundus auto-fluorescence, disk spectral domain optical coherence tomography (SD-
OCT), and disk retinal nerve fiber layer thickness (RNFL) measurement. Of the 20 cases (average age 11 years [range, 5-16 years]; 10 males), papilledema was confirmed in 11 (55%) and pseudopapilledema diagnosed in 9 (45%). Of pseudopapilledema cases, there were 4 cases of optic disk drusen, 2 hypermetropic disks, 2 "crowded disks," and 1 anomalous disk. In patients with true papilledema, on the combined MultiColor image, a green shift in the form of an elevated green ring was seen consistently. This ring was also hyperreflective on the blue and green images and surrounded a central "shadow," which was seen best on near infrared reflectance (NIR). The disk margins and vasculature were obscured on the combined, green, blue, and NIR images. These changes were not present in the pseudopapilledema cases. Only patients with suspected true papilledema had undergone further neurological tests including MRI and LP to confirm the diagnosis. The authors conclude that MultiColor imaging of disks with papilledema shows characteristic changes that may prove useful in differentiating true papilledema from pseudopapilledema. It is therefore a useful adjunct to traditional disk imaging modalities in assessing children with suspected disk swelling. They acknowledge that additional studies are required on a larger cohort to further confirm the changes that have been identified, to evaluate their sensitivity and specificity, and to determine whether these changes are consistent in the adult population.

Quality of life at 6 months in the Idiopathic Intracranial Hypertension Treatment Trial
Beau B Bruce, Kathleen B. Digre, Michael P. McDermott, Eleanor B. Schron, Michael Wall Neurology. November 2016; 87:1871-7

This is an analysis of prospectively collected data from the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a double-masked, placebo-controlled treatment trial of patients with idiopathic intracranial hypertension and mild vision loss. Both groups were treated with a low-sodium, weight reduction diet. Patients were administered a vision-specific quality of life (QOL) questionnaire upon enrolment, and either six months later or at the time of failure, whichever occurred first. QOL questionnaires used were the National Eye Institute Visual Function Questionnaire (NEI-VFQ) with Neuro-Ophthalmic Supplement, and the Short-Form 36 (SF-36) to measure overall health-related QOL. Both placebo and acetazolamide treated patients improved in almost all subscales and individual questions. Treatment effects were described with acetazolamide apparent for the Near Activities, Vision blurry, Social Functioning, Mental Health, and Difficulty performing tasks in bright sunlight questions or subscales. NEI-VFQ-25 scores improved with improving visual field pattern mean deviation, as well as self-reported cognitive dysfunction, dizziness/vertigo, and transient visual obscura-
Transient visual obscuration resolution was also associated with improvements in SF-36 scores. Overall treatment with acetazolamide in addition to diet changes were found to improve QOL measures, in addition to previous reports of improvement in visual fields, supporting the use of acetazolamide for treatment of idiopathic intracranial hypertension with mild vision loss.

**Pediatric Idiopathic Intracranial Hypertension: Age, Gender, and Anthropometric Features at Diagnosis in a Large, Retrospective, Multisite Cohort**


In this retrospective study the authors evaluated anthropometric and maturational characteristics at time of diagnosis of pediatric IIH. 233 cases of IIH were identified across 8 sites. In boys, a moderate association between age and BMI Z-scores was noted (Pearson’s correlation coefficient, 0.50; 95% confidence interval [CI], 0.30-0.66; P<0.001; n=72), and in girls, a weak association was noted (Pearson’s correlation coefficient, 0.34; 95% CI, 0.20-0.47; P<0.001; n=161). The average patient was more likely to be overweight at diagnosis at age 6.7 years in girls and 8.7 years in boys, and obese at diagnosis at age 12.5 years in girls and 12.4 years in boys. Compared with age- and gender-matched reference values, early adolescent patients were taller for age (P=0.002 in girls and P=0.02 in boys). Data on Tanner staging, menarchal status, or both were available in 25% of cases. Prepubertal participants (n=12) had lower average BMI Z-scores (0.95+/-1.98) compared with pubertal participants (n=45; 1.92+/-0.60). The authors conclude that 3 subgroups of pediatric IIH exist: a young group that is not overweight, an early adolescent group that is either overweight or obese, and a late adolescent group that is mostly obese. Data also suggest that the early adolescent group with IIH may be taller than age- and gender-matched reference values. Comment: Separating patients by age and onset of puberty helps elucidate the relationship between IIH and BMI. In this study, many IIH patients in the youngest age group were quite underweight.

**Anatomic and visual function outcomes in pediatric idiopathic intracranial hypertension**


There is a paucity of literature describing risk factors for vision loss in pediatric idiopathic intracranial hypertension (IIH). The authors investigated the final visual function, spectral domain optical coherence tomography (SD-OCT) and enhanced depth imaging (EDI)-OCT findings in children with papilledema caused by IIH. This is a retrospective review of 31 patients with pediatric IIH (age ≤17
years) from January 2010 to August 2013. Patients were required to meet the revised diagnostic criteria for IIH proposed by Friedman, Liu and Digre, which includes lumbar puncture opening pressure exceeding 28 cm H$_2$O (or 25 cm H$_2$O if not sedated). Optic disc photographs on presentation and automated perimetry, SD-OCT and EDI-OCT imaging on final follow-up visit were statistically analyzed to identify patient characteristics and anatomic findings associated with irreversible vision loss. Permanent visual acuity or visual field loss developed in 19% of study eyes. Papilledema of modified Frisén grade ≥3 on presentation was highly predictive of permanent vision loss (p<0.001), while associations between pubertal status and visual function outcome failed to reach statistical significance. SD-OCT revealed optic atrophy in 13% and photoreceptor loss in 19% of eyes, with both findings highly associated with vision loss (p<0.0001). Optic disc drusen was noted in 48% of study eyes by EDI-OCT but was not found to be predictive of visual outcome. The authors concluded that clinical observation of high papilledema grade on presentation is predictive of poor visual outcomes. Vision loss is associated not only with optic atrophy but also with photoreceptor damage. Interestingly, a high proportion of study eyes had optic disc drusen, which was not associated with vision loss, but can be a diagnostic challenge in distinguishing true papilledema from pseudopapilledema.

Although the authors gathered information on body habitus, they did not comment on this risk factor in the study. It will be interesting to see whether other studies with pediatric IIH have a similarly high percentage of children with optic disc drusen.

Factors Affecting Visual Field Outcomes in the Idiopathic Intracranial Hypertension Treatment Trial


The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was a multicenter, randomized, double-blind, placebo-controlled trial of patients ages 18-60 designed to determine if weight reduction and a low sodium diet plus acetazolamide was more effective than the same diet plus placebo in reducing vision loss from IIH. The study demonstrated that participants treated with acetazolamide rather than placebo (both plus diet) had significantly improved visual field function, papilledema grade, quality of life measures, and ICP. This paper is a sub study within the IIHTT designed to look at whether worsening visual fields (SITA 24-2) correlated with worsening visual function as opposed to performance failure (inattentiveness to the task of performing a visual field). Performance failure was defined as visual field loss that was transient (visual field returned to baseline by the next interval examination) and associated with stability in all other parameters of visual function. 2950 visual fields of 165 participants were reviewed. True treatment failure was documented in 7/165 (4%) whereas performance failure occurred in 21% of participants. 87% of those with performance failure had fields with false negative/ false positive and fixation losses within the range typically thought to indicate “good” performance. Take-home
message: If visual field decline does not seem in keeping with other clinical data, repeat the test, as it is 5 x more likely to represent performance failure than actual decline in visual function.

**Measuring recovery of visual function in children with papilledema using sweep visual evoked potentials**


This study attempted to determine whether peak contrast sensitivity and grading acuity differ between the children with mild or moderate papilledema and children without papilledema and whether visual function improves following treatment. Sweep VEP was chosen to measure contrast sensitivity. logMAR grating acuity of the papilledema group (currently being treated for the condition) was poorer than controls. There were an insufficient number of cases to allow subgroup analysis between mild and moderate papilledema. The mean peak contrast sensitivity for patients with papilledema and controls was essentially the same. Grating acuity improved both at the first and last examinations after initiating treatment. Contrast sensitivity, followed longitudinally in 5 patients, showed recovery in 4 patients between the first visit (1-2 days before treatment began) and the last visit (1.5-5 months after treatment). The authors comment that sweep VEP can provide an objective measure of visual performance in the context of a swollen optic disk and changing ICP during the course of treatment. This may be especially useful in preverbal children. Sweep VEP had high variability and this combined with the small sample size explains the lack of difference in contrast sensitivity between papilledema and control patients. Contrast sensitivity in this study normalized 2-11 days after shunting surgery for hydrocephalus.

**Perimetry**

**Optic Nerve Imaging**

**Optic pathway glioma volume predicts retinal axon degeneration in neurofibromatosis type 1**


This cross-sectional analysis of patients with NF1 associated optic pathway gliomas (OPG) evaluated optic pathway glioma size and its relationship to axonal damage of the anterior visual pathways. NF1 Children with OPG included in this analysis had to have a high-resolution MRI and an OCT of the RNFL within 2 weeks of each other. The authors found 38 patients, 55 eyes to include, with 20% of the OCTs performed using a hand-held device. For patients with isolated optic nerve gliomas, there was no correlation of RNFL thickness with optic nerve diameter or volume. However, a correlation with increasing anterior visual path-
way volume and decreasing RNFL thickness was found. Each 1mL increase in anterior visual pathway volume let to an approximately 5-micron decrease in RNFL thickness. When anterior visual pathway volume was greater than 3mL it had a positive predictive value (PPV) of 87% for abnormal RNFL (<80 microns). When anterior visual pathway volume was less than 3mL it had a negative predictive value (NPV) (with normal RNFL >80 microns) of 94%. All patients with visual acuity or visual field loss had RNFL thicknesses less than 80 microns. Chiasmal volumes of >1.3mL had a 100% PPV for abnormal RNFL, while volumes <1.3mL had a 95% NPV. This study demonstrates that tumor size is a risk factor for vision loss and axonal damage. Validation of this study may mean that children with smaller OPGs may need to be monitored less frequently, with the converse true for those with larger OPGs. A multi-center prospective study would be ideal to confirm this.

Optic Nerve Head Development in Healthy Infants and Children Using Handheld Spectral-Domain Optical Coherence Tomography

In this prospective cross-sectional study the authors aim to characterize optic nerve head development in full-term infants using handheld spectral-domain optical coherence tomography (SDOCT) without sedation. 352 children aged 1 day to 13 years were imaged with a single scan. Authors collected disc and cup diameter (expressed as distance in micrometers and visual angle in degrees), cup depth, retinal thickness, Bruch’s membrane opening minimum rim width (BMO-MRW) and retinal nerve fiber layer (RNFL; 1700mm and 6 degrees from the disc center). 70% of participants were imaged successfully. Interexaminer reliability was excellent with intraclass correlation coefficients (ICCs) >0.89 for diametric and retinal thickness parameters. Right and left eyes were similar for diametric measurements (ICC,>0.79), but more variable for nasal, RNFL, and retinal thickness. The mean disc and cup diameter increase by 30% and 40%, respectively, between birth and 13 years of age when expressed as a distance measure, but remained constant (at 5-5.5 degrees and 2degrees, respectively) when expressed as a visual angle with reference to the eye nodal point. The peripapillary temporal RNFL demonstrated a marked initial decrease of nearly 35% between birth and approximately 18 months of age. This was followed by a slow increase up to 12 years of age when measured at 1700mm from the disc center, although there was little change when measured at 6 degrees from the disc center.

Comment: This study provides a normative database of the developing optic nerve head. In addition to the data in the paper, the authors provided a helpful animated video cartoon depicting the progression of optic nerve head development from birth to age 13 years. The video is found at aao.org.
Use of Ocular Coherence Tomography in Children With Idiopathic Intracranial Hypertension-A Single-Center Experience.

Anatomical analysis of optic nerve changes with increased intracranial pressure can be evaluated by optical coherence tomography in cooperative children. This is a prospective, single-center study that evaluated 13 children with increased intracranial pressure in the presence and absence of clinical papilledema using Cirrus HD-OCT technology. Results found that in children with clinically apparent papilledema, the RNFL thickness was unequivocally higher than those without clear evidence of papilledema; and measurably higher with increasing disease severity graded on Frisén scale. Telltale symptoms of increased intracranial pressure like headache, pulse synchronis tinnitus and transient visual obscurations were evaluated as well. Headache was a global symptom between both groups, yet was persistent in the group of children without clinically significant papilledema. Pulse synchronous tinnitus and diplopia were absent in children without papilledema. Transient visual obscurations were experienced comparably in both groups. The authors conclude that OCT is an important tool in the decision making related to interventions in patients with IIH.

**This article highlights the significance of OCT technology in evaluating patients with increased intracranial pressure with and without papilledema.

Peripapillary Retinal Nerve Fiber Layer Thickness Corresponds to Drusen Location and Extent of Visual Field Defects in Superficial and Buried Optic Disc Drusen

This retrospective study compares peripapillary RNFL thickness to extent and location of visual field defects in patients with superficial and buried optic nerve head drusen. The cohort studied was 18 years and older. Of 149 eyes, 109 had superficial optic disc drusen and 40 had buried drusen. Peripapillary RNFL thinning was seen in 83.6% of eyes, where optical coherence tomography was performed (n = 61). Eyes with superficial ODD had greater mean peripapillary RNFL thinning (P = 0.0001) and visual field defects (P = 0.002) than eyes with buried drusen. Visual field abnormalities were most typically arcuate and more typically nasal in location. The authors postulate that buried drusen might represent an earlier stage in drusen evolution. They suggest that the actual migration from buried, to superficial, may itself cause NFL damage. This paper confirms the RNFL thinning previously reported in some patients with drusen yet is distinct from the many other studies which associate optic nerve head drusen with increased RNFL thickness and a cause of pseudopapilledema. Perhaps characteristics like location of drusen, and diameter of the optic nerve head may have an impact on RNFL thickness. Age or conditions like chronic papilledema may play a role as well. In a recent study (Gospe SM, et al. Br J Ophthalmol
2015;0:1–5.) on pediatric patients with IIH and papilledema, nearly 50% of patients with true papilledema (that resolved with treatment) had buried ONHD as well resulting in elevation in RNFL thickness. They postulated that chronic stasis of axoplasmic flow might itself result in drusen formation. Take home: Drusen, both buried and superficial, can have a variable impact on RNFL thickness depending on etiology of drusen, age, size of optic nerve head and scleral opening, and co-existent pathology.

**Myasthenia Gravis**

**Increased risk for clinical onset of myasthenia gravis during the postpartum period**

This study analyzed data collected from a cross-sectional population-based cohort from 2 populations, from Norway and the Netherlands. Among women with MG, 11.5% of the Dutch patients, and 18% of the Norwegian patients had their first myasthenia symptoms during pregnancy or during the postpartum period. There was a 5.5 relative risk of developing myasthenia gravis in the postpartum period. The risk of developing MG was higher after the first pregnancy compared to subsequent pregnancies. This suggests that there is an interaction between hormones and immunologic activation in myasthenia gravis that requires further study.

**Myasthenia Gravis**


This review is of relevance to the strabismologist who encounters patients with myasthenia gravis. The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs and a positive test for specific autoantibodies. Antibodies against acetylcholine receptors, muscle-specific kinase, and lipoprotein receptor–related protein 4 (LRP4) are specific and sensitive for the detection of myasthenia gravis, define disease subgroups, and point to pathogenic variations among these subgroups. In antibody-negative cases, neurophysiological tests and a characteristic response to therapy secure the diagnosis. An ice-pack test that reverses ptosis supports the diagnosis. Thymic status should be determined by means of mediastinal imaging. In 15% of all patients with myasthenia gravis, symptoms and signs are confined to ocular muscles. Only half of patients with ocular myasthenia gravis have detectable muscle antibodies. The disease remains restricted to ocular muscles in only a minority of patients. However, 90% of patients with ocular only symptoms after two years will continue to have purely ocular myasthenia gravis and never
develop generalized myasthenia. Myasthenia gravis with muscle-specific kinase antibodies is not manifested as ocular myasthenia, whereas both acetylcholine receptor and LRP4 antibodies can be found in the ocular subgroup. The presence of muscle antibodies increases the risk of subsequent generalized disease.

Coexisting conditions are common in patients with myasthenia gravis. Approximately 15% of patients have a second autoimmune disease, which occurs most frequently in patients with early-onset myasthenia gravis and thymic hyperplasia. Thyroiditis is the most common coexisting condition, followed by systemic lupus erythematosus and rheumatoid arthritis. In patients with ocular myasthenia, thyroid disease is especially common. Neuromyelitis optica with aquaporin-4 antibodies has a prevalence of 40 cases per 1 million population; it has a specific association with myasthenia gravis, and can occur either before or after the onset of myasthenia gravis.

Pyridostigmine is the preferred drug for symptomatic treatment. The dose of pyridostigmine is decided on the basis of the effect on muscle strength and dose-dependent side effects. Typical side effects are diarrhea, abdominal pain or cramps, increased flatus, nausea, and increased salivation, as well as urinary urgency and increased sweating. Most patients are capable of adjusting their own dose, with possible variation from day to day. Most patients with myasthenia gravis need immunosuppressive medication to meet the treatment goals of full or nearly full physical function and high quality of life. Expert consensus and data from limited controlled trials support the use of prednisone or prednisolone in combination with azathioprine as first-line treatment. Alternate-day steroid dosing, which is often used to reduce the side effects of glucocorticoids, does not usually lead to unwanted disease fluctuations, but the evidence for reduced side effects is weak. The dose is usually increased gradually (up to 60 to 80 mg on alternate days) to avoid an initial deterioration. After stable control of symptoms has been achieved and the addition of other treatments has further improved symptom control, the glucocorticoid dose should be slowly reduced to the lowest effective level, which is often 10 to 40 mg on alternate days. In most patients, azathioprine is added to prednisolone because this combination provides a better functional result with fewer side effects than prednisolone monotherapy. The effect of azathioprine on myasthenic weakness often takes months to appear. Most guidelines recommend mycophenolate mofetil for mild or moderate myasthenia gravis. A major aim of treatment for ocular myasthenia gravis is to prevent generalization of the disease. Retrospective and observational studies strongly indicate that prednisolone monotherapy reduces this risk. Low-dose glucocorticoid treatment is therefore recommended by many experts for patients with ocular myasthenia gravis who have persistent symptoms and risk factors such as detectable acetylcholine receptor antibodies, an enlarged thymus, or results of neurophysiological tests showing additional disease involvement of nonocular muscles. Thymectomy is not recommended for patients with
ocular myasthenia, since there is insufficient evidence that surgery prevents generalization or results in remission. However, it has been argued that thymectomy should be considered for the treatment of ocular myasthenia gravis when drug treatment has failed, the patient has acetylcholine receptor antibodies, and neurophysiological tests indicate a risk of generalized disease.

This thorough review on myasthenia gravis increases my appreciation of the nuances of disease management being performed by our neurology colleagues, and I was not aware that prophylactic treatments (prednisone, thymectomy) for ocular myasthenia may prevent generalized disease, even if they have little influence on the ocular symptoms.

**Randomized Trial of Thymectomy in Myasthenia Gravis.**

This was a multi-center, randomized trial comparing thymectomy plus prednisone with prednisone alone for adults with generalized myasthenia gravis with disease duration of less than five years. These were patients without thymomas. The primary outcomes were the average Quantitative Myasthenia Gravis score (on a scale from 0 to 39, with higher scores indicating more severe disease) over a 3-year period, as assessed by means of blinded rating, and the average required dose of prednisone over a 3-year period.

A total of 126 patients underwent randomization between 2006 and 2012 at 36 sites. Patients who underwent thymectomy had a lower average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone (6.15 vs. 8.99, P<0.001); patients in the thymectomy group also had a lower average requirement for prednisone (44 mg on alternate days vs. 60 mg on alternate days, P<0.001). Fewer patients in the thymectomy group than in the prednisone-only group required immunosuppression with azathioprine (17% vs. 48%, P<0.001) or were hospitalized for exacerbations (9% vs. 37%, P<0.001). The number of patients with treatment-associated complications did not differ significantly between groups (P=0.73), but patients in the thymectomy group had fewer treatment-associated symptoms related to immunosuppressive medications (P<0.001) and lower distress levels related to symptoms (P=0.003).

In conclusion, thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous myasthenia gravis. As ophthalmologists involved in the treatment of myasthenia gravis patients, we may see more of our patients undergoing thymectomies.

**International consensus guidance for management of myasthenia gravis**
Donald B. Sanders, Gil I. Wolfe, Michael Benatar, Amelia Evoli, et al.
*Neurology.* July 2016; 87:419-425.
This is a document delineating the determinations of a 15-person panel on treatment of myasthenia gravis, including definitions of treatment goals, Manifestations, remission, ocular myasthenia, myasthenia crisis, refractory myasthenia, etc. This essential document then goes on to recommend initial treatments for myasthenia gravis, including pyrodistigmine, followed by corticosteroids if necessary. Recommendations for nonsteroidal immunosuppressive agents are then made. For refractory cases, treatment by an expert is recommended with therapies such as rituximab, IVIG, PLEX, and cyclophosphamide. The role of thymectomy is discussed. Special considerations such as juvenile myasthenia gravis, MuSK-Ab positive myasthenia, and treatment of myasthenia gravis in pregnancy are also discussed. This treatment guideline is essential for anyone who encounters patients with myasthenia gravis.

**Optic Neuritis**

**Subclinical primary retinal pathology in neuromyelitis optica spectrum disorder.**


The authors of this study examined foveal thickness and its relationship with disease pathology in neuromyelitis optica spectrum disorder (NMOSD) patients and controls using optical coherence tomography (OCT-3). The fovea and retinal nerve fiber layer thickness were studied in all patients. Changes in peripapillary retinal nerve fiber layer thickness was not significant between groups. In all patients with NMOSD, regardless of history of optic neuritis, foveal thinning was significant compared to the control group and may be a predictor of disease.

**Efficacy of glatiramer acetate in neuromyelitis optica spectrum disorder: a multicenter retrospective study.**


This retrospective cohort study reviewed the efficacy of glatiramer acetate (GA) for the prevention of neuromyelitis optica spectrum disorder (NMOSD). The authors evaluated the relapse rate and expanded disability status scale (EDSS) in the patients treated with GA (most aquaporin-4 antibody-positive). Results showed that many of the patients experienced at least one relapse on GA therapy, most occurring after three months of treatment. The clinical disease activity score increased over the course of treatment, necessitating discontinuation of GA therapy in most patients. The authors concluded that GA does not play a therapeutic role in preventing attacks in most patients with NMOSD, particularly in aquaporin-4 antibody-positive cases.
**Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes**

Marianna Spatola, Renaud du Pasquier, Myriam Schluep, Axel Regeniter


Anti-GQ1b antibodies have been previously associated with the Miller-Fisher syndrome. This study analyzed GQ1b antibody titers in Miller-Fisher syndrome, optic neuritis, and acute ophthalmoplegia patients. Serum Anti-GQ1b positivity was found to be strongly associated with Miller-Fisher syndrome (11/12 patients), while CSF Anti-GQ1b less so (2/10 patients). Only one patient with acute ophthalmoplegia had Anti-GQ1b positivity, and none with optic neuritis. This study suggests that serum Anti-GQ1b antibodies therefore appear specific for Miller-Fisher syndrome, and CSF antibodies are unnecessary to obtain.

**Evaluation of the 2015 diagnostic criteria for neuromyelitis optic spectrum disorder**

Jae-Won Hyun, In Hye Jeong, AeRan Joung, Su-Hyun Kim, Ho Jin Kim

*Neurology.* May 2016; 86:1772-9

This study retrospectively applies the 2015 International Panel for NMO Diagnosis criteria to 594 consecutive patients with central nervous system inflammatory diseases. Of the 252 patients who met criteria for NMO spectrum disorder, 226 (90%) had AQP4-IgG positivity. A comparison to 2006 NMO Diagnosis criteria found that 116 patients (46%) who met the 2015 criteria did not meet the previous 2006 criteria for NMOSD. Of interest to the ophthalmologist, optic neuritis was the most frequent initial presentation (41%), and 88% of the patients who were AQP4-IgG negative had optic neuritis at some point during their disease course. This study concludes that the new criteria for diagnosing NMOSD reflects the inclusion of AQP4-IgG antibody testing, and improves the diagnostic yield compared to the 2006 guidelines. Significant limitations for the application of this study include its retrospective nature, solely Asian population, and possible selection bias. Overall the authors find the 2015 criteria to be useful for the diagnosis of NMOSD.

**Other**

**Retinal thinning correlates with clinical severity in multiple system atrophy**

Jeeyun Ahn, Jee-Young Lee, Tae Wan Kim Received: 28 April 2016/Revised: 30 June 2016/Accepted: 4 July 2016

This study evaluates retinal thickness changes in multiple system atrophy (MSA) using optical coherence tomography (OCT) scans. Peripapillary retinal nerve fiber layer (RNFL) thickness and perifoveal retinal thickness were significantly decreased in MSA patients compared to controls. Peripapillary RNFL and perifo-
veal retinal thinning were observed in MSA patients and retinal thinning correlated with the clinical severity of MSA. Structural changes in the retina may reflect the degree and pattern of neurodegeneration occurring in MSA. In conclusion, RNFL and perifoveal retinal thinning were observed in MSA patients. Retinal thinning correlated with clinical severity.

Retinal measures correlate with cognitive and physical disability in early multiple sclerosis

Nabil K. El Ayoubi, Stephanie Ghassan, Marianne Said, Joelle Allam, Hala Darwish, Samia J. Khoury

Received: 6 June 2016/Revised: 11 August 2016/Accepted: 12 August 2016/Published online: 20 August 2016

This paper examines the role of optical coherence tomography (OCT) in the eyes of patients with early relapsing remitting MS and no history of optic neuritis. The authors examined retinal thickness and cognitive as well as physical disability. Adult participants were using interferon beta-1a, or fingolimod therapy with a stable clinical course and did not have a history of optic neuritis. The study found that in patients with early relapsing remitting MS without optic neuropathy, physical disability and cognitive disability could be correlated to retinal thickness, suggesting their potential as biomarkers of axonal loss and neurodegeneration.

A case of ocular neuromyotonia caused by neurovascular compression of the oculomotor nerve by the elongated superior cerebellar artery.

Hashimoto Y, Hideyama T, Yamagami A, Sasaki T, Maekawa R, Shiio Y.


This report describes the case of a 40-year-old woman with 1-year history of involuntary intermittent paroxysmal binocular diplopia, triggered by right gaze, alcohol, and smoking. With 10 s of right gaze and return to primary gaze, her left eye infra-adducted from the primary position. Diplopia in all directions lasted from a few seconds to a few hours. The remainder of the ophthalmic and neurological examination were normal. Magnetic resonance imaging, edrophonium testing and blood test results, including titers of anti-thyroid autoantibodies and thyroid hormone, anti-acetylcholine receptor and anti-voltage-gated potassium channel antibodies were also normal. Magnetic resonance (MR) cisternography in axial planes was performed and showed the left superior cerebellar artery (SCA) was deviated anteriorly from the midbrain and compressed the oculomotor nerve. The authors believe that idiopathic ONM may be caused by vascular compression of the oculomotor nerve and that MR cisternography should be performed because structural abnormalities are not detected by the conventional MRI methods, MR cisternography should also be performed when faced with ONM patients.
Ophthalmoplegia heralding the onset of anti-amphiphysin related paraneoplastic stiff person syndrome.


This report describes a 47 year old female with grade 2 invasive ductal breast adenocarcinoma presenting with neck pain, dizziness and ophthalmoplegia. She demonstrated restricted horizontal pursuit, saccadic eye movements and compensatory head movements. She was diagnosed with paraneoplastic stiff person syndrome. Treatment with intravenous immunoglobulin helped to improve symptoms.

Congenital Cataract With Facial Dysmorphism and Neuropathy: Key Clinical Features.


Molecular studies revealing a homozygous mutation in the CTDP1 gene can confirm the diagnosis of congenital cataract with facial dysmorphism and neuropathy (CCFDN). These children present with motor and intellectual delay, bilateral atrophy of the short toe extensor muscles, externally rotated feet, absent deep tendon reflexes, obesity, rounded face, and a demyelinating neuropathy. Ocular findings include bilateral cataracts, microcornea, microphthalmia, and micropupils. With management of visual disorders, physical therapy, and pharmacologic control of dyskinesia, these patients demonstrate improved quality of life.

A new saccadic indicator of peripheral vestibular function based on the video head impulse test


In conventional head impulse paradigm (HIMP) testing with a patient maintaining fixation on a fixed target while the head is rotated, healthy patients will not make compensatory saccades, while patients with vestibular loss lose fixation on the target and make corrective saccades. This study describes a new test, the suppression head impulse paradigm (SHIMP) in which the patient follows a target that moves with the head. In patients with vestibular loss the eyes move with the head, and no refixation saccades are made. Normal patients without vestibular loss make corrective saccades to refixate on the target, as their vestibulo-ocular reflex causes them to make anti-compensatory saccades. This test can be combined with traditional HIMP testing to determine the presence or absence of vestibular function.

Quantitative MRI criteria for optic pathway enlargement in neurofibromatosis type 1

Robert A.
This retrospective quantitative analysis of MRI data from children with and without NF1 and optic pathway gliomas brings the first quantitative data regarding optic pathway size in these patients. This data will eventually help define criteria for the presence of an optic pathway glioma, whether sporadic or associated with NF1. Children with NF1 had larger brain volumes and larger optic pathways than control patients. A reference range for normal optic nerve diameter, volume, and length, as well as dimensions of the chiasm, optic tracts, whole brain, and entire anterior visual pathway are established. This study is limited by not being able to define the presence of an optic pathway glioma, however it does define size thresholds for enlargement of the anterior visual pathways that may eventually be incorporated into the definition of an optic pathway glioma secondary to NF1.

**Acute disseminated encephalomyelitis in 228 patients**

This retrospective analysis of acute disseminated encephalomyelitis (ADEM) patients of all ages analyzes the presentations and outcomes of patients with this disease. The majority of patients included were children. Of interest to ophthalmologists, the initial presentation included optic neuritis in 16% of children, and only 5% of adults (p=0.009). Rates of other visual disturbances and other cranial neuropathies were similar between adults and children with ADEM. Approximately one quarter of patients experience a relapse. Children who experienced relapses were more frequently diagnosed with multiphasic ADEM in comparison to adults, who were more frequently diagnosed with multiple sclerosis. A large registry study is suggested to help understand ADEM in comparison to other demyelinating diseases.

6. NYSTAGMUS

**The Development of a Nystagmus-Specific Quality-of-Life Questionnaire**

In this prospective cross-sectional study the authors aim to develop a nystagmus-specific quality-of-life (QOL) questionnaire derived from patient concerns. Questionnaire consisting of 37 items was developed through previous interviews of 21 people with nystagmus and then administered to 206 subjects with nystagmus. After consultation with 8 nystagmus experts, 37 items were administered to 206 people with nystagmus. For comparison,
the Visual Function Questionnaire-25 (VFQ-25) was administered to 42 additional participants. Factor analysis revealed that 29 items to comprising 2 distinct subscales reflecting “personal and social” and “physical and environmental” functioning as relating to nystagmus-specific QOL. Cronbach alpha coefficients for the “personal and social” functioning scale and “physical and environmental” functioning were 0.95 and 0.93, respectively. Tests for validity of the measure, consistent with a priori predictions, when compared with the VFQ-25, revealed the “physical and environmental” subscale showed concurrent validity (0.88), whereas the “personal and social” subscale was demonstrated to have discriminative validity (0.81). The authors conclude that their 29-item, nystagmus-specific QOL questionnaire (NYS-29) appropriately addresses physical functioning and psychosocial issues to measure impact of nystagmus on daily living.

Comment: I believe that a validated questionnaire could be helpful in measuring outcomes for various nystagmus intervention studies. Whereas some surgical interventions for nystagmus yield only modest or no improvement in acuity, it is possible that quality of life improves significantly and this tool may be able to measure this.

Perceptual learning in children with infantile nystagmus: effects on reading performance


Perceptual learning improves visual acuity and reduces crowding in children with infantile nystagmus (IN). In this study, 6- to 11-year-old children with IN were divided into two training groups: a crowded training group (n= 18; albinism: n = 8; idiopathic IN: n= 10) and an uncrowded training group (n= 17; albinism: n= 9; idiopathic IN: n= 8). Also 11 children with normal vision participated. Outcome measures were: reading acuity (the smallest readable font size), maximum reading speed, critical print size (font size below which reading is suboptimal), and acuity reserve (difference between reading acuity and critical print size). Reading acuity and critical print size were 0.65 ± 0.04 and 0.69 ± 0.08 log units larger for children with IN than for children with normal vision. Maximum reading speed and acuity reserve did not differ between these groups. After training, reading acuity improved by 0.12 ± 0.02 logMAR and critical print size improved by 0.11 ± 0.04 logMAR in both IN training groups. The changes in reading acuity, critical print size, and acuity reserve of children with IN were tightly related to changes in their uncrowded distance acuity and the changes in magnitude and extent of crowding. This study is the first to show that visual acuity is not the only factor that restricts reading in children with IN, but that crowding also limits their reading performance, and that training improves reading performance.

Perceptual learning in children with infantile nystagmus: effects on visual performance
In this study, 36 children, aged 6- to 11-years, with infantile nystagmus (IN), 18 with idiopathic IN and 18 with oculocutaneous albinism were divided into two training groups matched on age and diagnosis: a crowded training group (n= 18) and an uncrowded training group (n= 18). Also 11 age-matched children with normal vision participated. Training occurred two times per week during 5 weeks (3500 trials per training). Main outcome measures were task-specific performance, distance and near visual acuity (DVA and NVA), intensity and extent of (foveal) crowding at 5 m and 40 cm, and stereopsis. Training resulted in task-specific improvements. Both training groups showed uncrowded and crowded DVA improvements (0.10 ± 0.02 and 0.11 ± 0.02 logMAR) and improved stereopsis (670 ± 249°). Crowded NVA improved only in the crowded training group (0.15 ± 0.02 logMAR), which was also the only group showing a reduction in near crowding intensity (0.08 ± 0.03 logMAR). Effects were not due to test–retest learning. Perceptual learning with or without distractors reduces the extent of crowding and improves visual acuity in children with IN. Training with distractors improves near vision more than training with single optotypes. Perceptual learning also transfers to DVA and NVA under uncrowded and crowded conditions and even stereopsis. Reduced processing time could be an explanation for the improvements in visual acuity. Learning curves indicated that improvements may be larger after longer training. Although this is a small study, it provides compelling evidence that perceptual training improves vision in IN.

A prospective evaluation of retroequatorial recession of horizontal rectus muscles and Hertle-Dell’Osso tenotomy procedure in patients with infantile nystagmus with no definite null position


The authors assessed the effectiveness of the Hertle-Dell’Osso tenotomy procedure (Group 2) as a surgical modality for nystagmus dampening and compared it to large retroequatorial recessions of the horizontal rectus muscles (Group 1). Ten patients total were randomly assigned to either surgery. Although all patients had subjective better acuity there was no statistically significant improvement in binocular vision (Group 1- 1 line, Group 2- none). Contrast sensitivity improved significantly in both groups. Both groups displayed similar improvements in stereoacuity. Nystagmus amplitude decreased in both groups in all gazes on ENG. The authors found no statistical difference between the effectiveness of the two procedures. Patients should be counseled as to what visual parameters can be expected to improve from these procedures, and what parameters will not improve to allow realistic expectations post-operatively.
Pendular Nystagmus Associated With Cerebral Pylomixoid Astrocytoma.

This is a case report of a 5-month-old girl with two week history of pendular nystagmus and tremulous physical behavior. Laboratory and remaining exam findings were within normal limits. CT scan revealed a mass that was resected and found to be a pilomyxoid astrocytoma. While pendular nystagmus has been reported in patients diagnosed with pilomyxoid astrocytoma, understanding the multivectoral and slow nature of pendular nystagmus is important to distinguish from opsoclonus

7. PREMATURITY.

Ophthalmic Features of Premature Infants

Intraocular pressure in premature Low-Birth Weight Infants.

The goal of this study is to establish normative data of intraocular pressure (IOP) and central corneal thickness(CCT) in premature, LBW(low-birth weight, defined as birth weight<=1.500 g or GA ,<=30 weeks) infants as well as to investigate the correlation between the CCT and the GA with the IOP. Forty-five premature, LBW infants were included in the study: their mean IOP was 29.0+/- 9.0 mm Hg( range 12-59 mm Hg), and their mean CTT was 660+/-65.0( range: 517 to 809). The authors found that although IOP and CCT measurements inversely correlate with GAs, there is no correlation between IOP and CCT in premature, LBW infants.

Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study

This study assesses the rates of mortality and morbidity of infants born between 22 and 28 weeks gestation in California. Data was collected from the California Office of Statewide Health Planning and Development between 2007-2011 which provides diagnosis and procedure codes. These codes was linked to hospital discharge, birth certificate, and death records. 6009 infants were included in the study. Twenty-eight percent of all extremely preterm infants died within the first year of life with the greatest risk of mortality at 22 weeks (94%) and decreasing to 28 weeks (6%). A majority of the deaths occurred in the first week of life
(73%). Major neonatal comorbidities included grade III or IV intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity surgery, sepsis, and bronchopulmonary dysplasia. Major morbidity was present in 80% of these infants and multiple morbidities were present in 66% of the 22-23 weeks gestation infants. Improved survival was associated with increased birth weight, female sex, and cesarean delivery for infants requiring resuscitation. This population based evidence about risk of mortality and morbidity can help guide recommendations and care for extremely preterm infants.

**Determination of normal values of intraocular pressure and central corneal thickness in healthy premature infants- a prospective longitudinal study**


This study determined normative IOP and CCT data in healthy premature infants and also evaluated the longitudinal change in these parameters. A total of 110 eyes of 110 infants were enrolled at gestational age of 28 weeks. Looking at the data at 32, 34, 36, 38 and 40 weeks gestational age, the mean IOP was 18.28 mm Hg, 16.13 mm Hg, 14.67 mm Hg, 13.49 mm Hg and 13.21 mm Hg, respectively. The mean CCT was 670.56 μm, 613.67 μm, 579.24 μm, 551.91 μm, 546.18 μm, respectively. The decreased values over time were statistically significant and there was a statistically significant positive linear relationship between IOP and CCT values. Of note, the declining values slow down as term is approached. IOP measurements may have been affected by the wire lid speculum and CCT measurements may have been affected by the use of topical anesthesia.

**Prematurity and Outcomes**

**Ophthalmologic outcomes of Children Born Premature Without ROP: correlations with Gestational Age and Psychomotor Development.**


This article studies the ophthalmologic outcomes of sixty-nine former premature children ( < 37 weeks) and no retinopathy of prematurity at the age of 2 to 7 years and correlates them with neurodevelopmental outcomes. Detailed ophthalmologic examinations were performed and neurodevelopment was assessed using the Peabody Developmental Motor Scale and Wechsler Preschool and Primary Scale of Intelligence. There was a group of 69 healthy children that was used a control. Compared to controls, preterm infants had vision impairment of 19% ver-
sus 1.4%(P=.001), hyperopia of 87% versus 98.5%(P=.21), myopia of 11% versus 1.4%(P=.017) and astigmatism of 39% versus 30.4 %(P=.37).

The authors concluded that premature infants need to be screened for ocular morbidities because they are at higher risk for visual sequelae. When compared to controls, patients with a history of prematurity had significant more myopia and strabismus. These rates didn’t differ by GA or BW, except for the higher prevalence of hyperopia in those with BW greater than 1500g and a GA of 32 weeks or more. No correlations with neurocognitive development were demonstrated. The study is limited by the small number of subjects involved.

Ophthalmologic Outcome of Extremely Preterm Infants at 6.5 Years of Age: Extremely Preterm Infants in Sweden Study (EXPRESS)


Sweden’s national health service is able to ascertain very complete data on all infants. This facilitates prospective longitudinal studies. All extremely premature infants (EPT) who were born within a 3-year period, from 2004 to 2007, were part of a prospective follow-up study of visual outcomes at 6.5 years of age. This group of 486 children was compared with an age-matched group of 300 children born at term. Outcome measures included visual acuity, cycloplegic refraction, and manifest strabismus. These measures were compared with gestational age at birth and whether retinopathy of prematurity (ROP) required treatment.

In the EPT group, 2.1%(9 of 434) were blind, 4.8%(21 of 434) were visually impaired according to the World Health Organization criteria (<20/60), and 8.8% (38 of 434) were visually impaired according to the study criteria (<20/40). Strabismus was found in 17.4% (68 of 390) and refractive errors in 29.7%(115 of 387) of the EPT children compared with 0% (0 of 299) and 5.9% (17 of 289), respectively, of the control children (P < .001). With respect to manifest strabismus, esotropia was almost 4 times as frequent as exotropia. With respect to refractive error, hyperopia was most frequent type.

Major eye and visual problems were defined as visual impairment according to the World Health Organization (WHO) criteria (ie, <20/60), manifest strabismus, or refractive error (ie,myopia >3D, hyperopia >3 D, astigmatism >2 D in the better eye, or anisometropia >2D). By this definition, serious eye abnormalities or visual impairment was present in 37.9%(147 of 388) of infants born <27 weeks gestation and in 55.4% (67/121) of the most immature subgroups.

Importance: Treatment-requiring ROP had a stronger impact on the development of visual impairment and strabismus. However, the development of significant refractive errors was correlated with gestational age and not with treatment-requiring ROP.
ROP and Telemedicine/Screening

Timely implementation of a retinopathy of prematurity telemedicine system

J AAPOS  

This is another report from the NIH-NEI funded, multicenter Telemedicine Approaches to Evaluating Acute-phase ROP (e-ROP) Study. This prospective observational study of premature infants with birth weights of <1251 g in five NICUs in the United States, examined the feasibility of a retinopathy of prematurity (ROP) telemedicine evaluation system of providing timely feedback to a neonatal intensive care unit (NICU) with at-risk premature infants. Infants scheduled for clinically indicated ROP evaluations underwent indirect ophthalmoscopic examinations and digital imaging on the same day. Imaging was performed by non-physician retinal imagers. Times required were determined from obtaining digital images of both eyes to submission via web-based system to a secure server for grading by trained readers at a central reading center to sending back grading results to the clinical center. A total of 1,642 image sets of eyes of 292 infants were obtained, from 823 imaging sessions. The mean turnaround time from submission of image sets of both eyes to return of the grading results to the clinical center was 10.1 ±11.3 hours (standard deviation), with a median of 12.0 hours (1st quartile, 0.9 hours; 3rd quartile, 16 hours). Overall, 95.5% of gradings (95% CI, 93.9%-96.7%) were returned within 24 hours. Subgroup analyses found, for image sets submitted to the reading center before 2 p.m. Eastern Standard Time, median time to report was 1.7 hours (1st quartile, 0.7 hours; 3rd quartile, 15.5 hours) compared with those submitted after 2pm (median, 14.1 hours; 1st quartile, 11.2, hours; 3rd quartile, 16.3 hours). The authors concluded that a ROP telemedicine approach can provide timely feedback to the NICU regarding the detection of potentially serious ROP and thus referral to an ophthalmologist for examination and consideration of treatment. This large well-designed study supports the feasibility of using telemedicine for ROP screening in a timely fashion. Turnaround times may be different outside of the research setting with clinician readers, who would likely have other clinical responsibilities. Ophthalmic consultation might not always be as readily available as the services provided for participating nurseries in this study.

A Tiered Approach to Retinopathy of Prematurity Screening
(TARP) Using a Weight Gain Predictive Model and a Telemedicine System

Incorporating findings from some of the well-designed clinical trials of retinopathy of prematurity into predictive models could improve care of infants with this disease. The authors compare 4 screening approaches and included 242 premature infants with completed exams and known outcomes: ROUTINE (only diagnostic examinations by an ophthalmologist), CHOP-ROP (birth weight and gestational age, with weekly weight gain initiating examinations when the risk cut point is surpassed), e-ROP IMAGING (trained reader grading of type 1 or 2 ROP initiates diagnostic examinations), and TARP (CHOP-ROP alarm initiates imaging, and imaging finding of severe ROP initiates diagnostic examinations)
The mean outcomes were the sensitivity for type 1 ROP, reduction in infants requiring imaging or examinations, numbers of imaging sessions and examinations, and total clinical encounters (imaging sessions and examinations combined.) The sensitivity for detecting type 1 ROP (32 infants) was 100% (95%CI, 89.3%-100%) with each approach.

Conclusion: The tiered approach to ROP screening was associated with a reduced number of examinations and imaging sessions compared with the other approaches. Applying a postnatal growth model and telemedicine system in a tiered approach may reduce the number of clinical ROP interventions more than either approach alone and still retain 100% sensitivity for the detection of Type 1 ROP. Limitations of the study include that it was small, with only 32 infants who developed Type 1 ROP.

Telemedicine for Retinopathy of Prematurity
An Evolving Paradigm

In this invited commentary, the author recognizes that ROP, in addition to other eye conditions like diabetic retinopathy, macular degeneration and glaucoma, is amenable to a telemedicine approach to deliver care. In order to effectively study various aspects of telemedicine, it is critical to establish a gold standard. In diabetic retinopathy, this is well-established and has shown trained non-physician readers as superior in some studies to clinicians in the diagnosis of treatment warranted disease. However, the traditional gold standard for diagnosing ROP of binocular indirect ophthalmoscopy by a pediatric ophthalmologist or retina specialist has been questioned. The greatest number of discrepant cases in the e-ROP study were graded as positive for referral-warranted ROP by the non-physician graders but negative by clinical examination with binocular indirect ophthalmoscopy.
Analysis of Discrepancy Between Diagnostic Clinical Examination Findings and Corresponding Evaluation of Digital Images in the Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity Study

Accurate and timely diagnosis of retinopathy of prematurity (ROP) is essential to provide the best visual outcome for infants with this disease. This study analyzes the differences between clinical exam by expert physicians and digital photos and image grades obtained by trained non-physician readers in arriving at a diagnosis of referral warranted (RW)-ROP during an 18 month period at institutions who participate in the Acute-Phase ROP Cooperative Group. Forty infants were randomly selected from a pool of 100 affected infants and 188 image sets were reviewed. Referral warranted ROP is defined as zone I ROP, stage 3 ROP or worse, or plus disease, a level of severity of disease indicating the need for evaluation by an ophthalmologist to consider treatment. Main outcome measure was consensus evaluation by 4 expert physicians of discrepant image and examination findings for RW-ROP components. The authors looked at image grading presence of RW-ROP (G+) or its absence (G-) and expert examiner detection presence of RW-ROP (E+) or its absence (E-) and calculated ratios based on the clinical data. Out of 5350 image set pairs, there were 161 instances in which image grading did not detect RW-ROP noted on clinical examination (G−/E+) and 854 instances in which grading noted RW-ROP when the examination did not (G+/E−). Expert consensus review of image grade would agree with clinical examination findings in 46.5% of the 161 G−/E+ cases (95%CI, 41.6-51.6) and agree with trained reader grading in 70.0% of the G+/E− cases (95%CI, 67.3-72.8) for the presence of RW-ROP.
Conclusion: There were limitations and strengths for the diagnosis of RW-ROP in remote imaging of disease as well as at the bedside. Improved paradigms of detecting RW-ROP are needed as ROP telemedicine becomes more prevalent.

Influence of Computer-Generated Mosaic Photographs on Retinopathy of Prematurity Diagnosis and Management

Telemedicine is becoming an indispensable approach to diagnosing and managing retinopathy of prematurity, especially given the paucity of physicians available to screen eligible infants in remote areas. This study seeks to determine if there is a benefit to analyzing computer-generated mosaic photographs vs. examining individual fundus photographs on the diagnosis and management of ROP. Mosaic photos, from contact fundus cameras like the Retcam, can help achieve a wid-
er field of view, close to the 200 degree view that ultra wide field non-contact fundus cameras can. In this prospective cohort study, 9 ROP experts reviewed 40 sets of fundus photos, 20 sets of computer generated mosaic and 20 sets of individual fundus photos. They also looked at intraobserver agreement. Diagnosis by mosaic photographs compared with diagnosis by multiple individual photographs showed improvements in sensitivity for diagnosis of stage 2 disease or worse (95.9% vs 88.9%; difference, 7.0; 95% CI, 3.5 to 10.5; P = .02), plus disease (85.7% vs 63.5%; difference, 22.2; 95% CI, 7.6 to 36.9; P = .02), and treatment-requiring ROP (84.4% vs 68.5%; difference, 15.9; 95% CI, 0.8 to 31.7; P = .047). With use of the $\kappa$ statistic, mosaic photographs, compared with multiple individual photographs, resulted in improvements in intergrader agreement for diagnosis of plus disease or not, stage 3 disease or worse or not and type 2 ROP or not. (The kappa coefficient measures interrater agreement for qualitative or categorical items.)

Conclusion: Use of computer-generated mosaic photographs helped improve the accuracy and reliability of the diagnosis of ROP, across many characteristics, and may be a useful tool in the evolving field of telemedicine. However, these results may not be generalizable to the diagnosis of other retinal conditions.

Plus Disease in Retinopathy of Prematurity Improving Diagnosis by Ranking Disease Severity and Using Quantitative Image Analysis

The authors determined expert agreement on ROP disease severity and whether a computer-based image analysis application could model relative disease. The authors complied 2 datasets totaling 134 Retcam ROP photos. 6 expert ROP clinician-scientists ranked ROP severity by average disease classification (classification ranking), by pairwise comparison using the Elo rating method (comparison ranking), and by correlation with the i-ROP computer-based image analysis system. There was variable interexpert agreement on diagnostic classification of disease (plus, preplus, or normal) among the 6 experts (mean weighted $k$, 0.27; range, 0.06-0.63), but high correlation coefficient regarding comparison ranking of disease severity (mean CC, 0.84; range, 0.74-0.93) on the more severe subset of 34 images. Comparison ranking provided a severity ranking that was in good agreement with ranking obtained by classification ranking (CC, 0.92). Comparison ranking on the larger dataset by both expert and nonexpert graders demonstrated good correlation (mean CC, 0.97; range, 0.95-0.98). The i-ROP system was able to model this continuous severity with good correlation (CC, 0.86). The authors concluded that experts diagnose plus disease on a continuum, with poor absolute agreement on classification but good relative agreement on disease severity. These results suggest that the use of pairwise rankings and a continuous severity score, such as that provid-
Risk Score for Predicting Treatment-Requiring Retinopathy of Prematurity (ROP) in the Telemedicine Approaches to Evaluating Acute-Phase ROP Study

In this cohort study, the authors aim to develop a risk score for predicting treatment-requiring retinopathy of prematurity (TR-ROP) in the Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) study. 771 infants with birth weight (BW)<1251 g who had at least 1 imaging session by 34 weeks of post-menstrual age (PMA) and at least 1 subsequent retinopathy of prematurity (ROP) examination for determining TR-ROP by study-certified ophthalmologists were included. Nonphysician trained readers evaluated wide-field retinal image sets for characteristics of ROP, pre-plus/plus disease, and retinal hemorrhage. 85 of the 771 infants (11.0%) developed TR-ROP. In a multivariate model, significant predictors for TR-ROP were gestational age (GA) (odds ratio [OR], 5.7 for ≤ 25 vs. ≥ 28 weeks), need for respiratory support (OR, 7.0 for high-frequency oscillatory ventilation vs.no respiratory support), slow weight gain (OR, 2.4 for weight gain ≤ 12 g/day vs. >15 g/day), and image findings at the first image session including number of quadrants with pre-plus (OR, 3.8 for 4 pre-plus quadrants vs. no pre-plus), stage and zone of ROP (OR, 4.7 for stage1-2 zone I, OR, 5.9 for stage 3 zone I vs. no ROP), and presence of blot hemorrhage (OR, 3.1). Image findings predicted TR-ROP better than GA. The risk of TR-ROP steadily increased with higher risk score and predicted TR-ROP well. Risk score ≥ 3 points for predicting TR-ROP had a sensitivity of 98.8%, specificity of 40.1%, and positive and negative predictive values of 17.0% and 99.6%, respectively. The authors concluded that image characteristics seen at 34 PMA weeks or earlier independently predict TR-ROP. If externally validated in other infants, the risk score calculated from image findings, GA, weight gain, and respiratory support will enable early identification of infants in need of increased surveillance for TR-ROP.

Comment: In addition to insights on potential protocols involving tele-med screening, this paper identifies blot retinal hemorrhage (in contrast to dot, flame or pre-retinal hemorrhage) as a predictor of TR-ROP. This finding may be useful even to clinicians who do not use imaging in screening for ROP.
Facilitated versus self-guided training of non-ophthalmologists for grading pre-plus and plus disease using fundus images on retinopathy of prematurity.

Retinopathy of prematurity (ROP) is an important cause of preventable blindness; these days several barriers exist for the screening of ROP, with the low percentage of ophthalmologists who are trained to perform ROP exam being the most important one. Several studies have shown that trained non-ophthalmologists can accurately grade retinal images for ROP. However, effective training protocols are not established. This study compares the effectiveness of facilitated versus self-guided training of non-ophthalmologists for grading retinal images for pre-plus or plus disease in ROP. Forty-eight undergraduate and graduate students were trained to grade retinal images for the presence of pre-plus or plus disease. Students were randomly assigned to one of two training protocols. Both used identical electronic slideshows: one was guided by an in-person facilitator and the other was self-guided. After completing their respective training, students proficient in grading pre-plus and plus disease graded images in a telemedicine screening scenario. Eighty-three percent (40 of 48) of trained students (91% in the facilitated vs 77% in the self-guided group, \( P = .26 \)) were proficient and qualified to grade the ROP telemedicine screening scenario. Median accuracy for grading normal, pre-plus, or plus disease was 69% (70% in the facilitated vs 68% in the self-guided group, \( P = .91 \)). The authors concluded that self-guided training protocols may adequate to train non-ophthalmologists in order to accurately grade pre-plus and plus disease with high sensitivity. However, the sample size is small and the non-ophthalmologists selected to grade the retinal images were physicians assistants, nurses and engineers. Therefore the results might not be generalized to other non-ophthalmologists.

Trends in the Screening and Treatment of Retinopathy of Prematurity

This study aims to describe the current practice patterns for retinopathy of prematurity (ROP) care in the United States’ level III and IV NICU’s, perceptions of new screening modalities, and current level of medical support available for care of these pre-term infants. A survey of 847 NICU medical directors was mailed and 393 surveys were returned (46%). From this survey information, the directors report following more conservative guidelines for routine screening than current recommendations. For example, 55% screen infants with a gestational age of less than or equal to 31 weeks. 91% used the recommendation of less than or equal to 1500g but only 54% indicated that the clinical course affects the screening decision. Pediatric ophthalmologists and retina specialists performed 90% of
the screening with treatment performed in 39% of cases by a pediatric ophthalmologist and 57% by a retina specialist. 7% of NICU’s utilize retinal imaging devices as the primary screening and these centers are more likely to be smaller, level III, and in rural settings. 14% of NICU’s utilize imaging devices as adjunct to examination. The most common treatment modality was laser photocoagulation (85%) followed by anti-VEGF injection (20%). There is also significant evidence for difficulty in finding and maintaining ophthalmic services in 20% of NICU’s. These centers are more likely to be level 3, suburban, and less likely to have an academic affiliation. The study also investigated attitudes towards telemedicine as another method of screening for ROP. Only 35% of respondents agreed that a retinal imaging device could replace indirect ophthalmoscopy and only 30% agreed that it was a safe practice for ROP screening. The authors conclude that the study highlights the need for continued improvement in screening and treatment for ROP with a focus on maintaining a stable group of physicians willing to screen and treat ROP.

**ROP and imaging**

Impact of number and quality of retinal images in a telemedicine screening program for ROP: results from the e-ROP study

Telemedicine for the detection of retinopathy of prematurity (ROP) is becoming increasingly common; however, obtaining the required multiple retinal images from premature babies may be challenging. Features of referral-warranted ROP (RW-ROP) may be missed if images cannot be obtained or if images are of poor quality and limit visualization of ROP morphology. This is a secondary analysis from the Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) study, a large multicenter study performed in the US and Canada that addresses this issue. It evaluated the detection of RW-ROP by trained non-ophthalmologist readers, when a full set of 5 retinal images could not be obtained. RW-ROP was defined as presence of zone I ROP, stage 3 or worse ROP, or plus disease. A total of 7,905 image sets from 1,257 infants were evaluated. Retinal location of images and image quality were recorded. Sensitivity and specificity of RW-ROP detection by trained readers were calculated by comparing findings in incomplete image sets to the findings on standard eye examination, performed by a trained ophthalmologist. The majority of image sets contained all 5 retinal images (92.8%). But, when image quality was evaluated, about 90% of image sets had 4 or more acceptable quality images present. Sensitivity of detection of RW-ROP was 82.1% when 5 retinal images of acceptable quality were submitted for grading, 67.2% when 4 acceptable images were submitted, and 66.7% for 3 or fewer acceptable images (P = 0.02), with corresponding specificity of 82.2%, 89.0%, and 81.7% respectively (P < 0.0001). The authors concluded that the likelihood of de-
Detecting RW-ROP by telemedicine screening is decreased when a full set of retinal images is not obtained. They suggest repeated imaging or referral for standard ROP examination when fewer than 4 acceptable quality images can be obtained for ROP telemedicine screening. Even though some limitations were raised, the sample size in this study is very large. This study can be used as guidance for the frequency of repeated examinations, when implementing telemedicine for ROP screening.

Retinopathy of Prematurity: Imaging in retinopathy of prematurity: where are we, and where are we going?

This is a short overview on the evolution of ROP diagnosis, imaging and telemedicine. It is part of a symposium on ROP. It explains how advances in imaging had effected the way we can evaluate ROP today. It lists in very general terms the advantages of telemedicine. It is a good source of references on telemedicine that the reader might want to look into.

Expert Diagnosis of Plus Disease in Retinopathy of Prematurity From Computer-Based Image Analysis

One of the most important criteria in assessing high risk Type I ROP, which would require urgent treatment, is determining if there is plus disease. Traditionally, plus disease has been defined by a standard photograph of peripapillary arteriole tortuosity and venous dilatation. Computer modeling of arteriole tortuosity and venous dilatation has been validated. This study seeks to test the accuracy of a computer software program (Imaging and Informatics in ROP, {iROP}) which analyzes photographs and determines if there is plus disease. The gold standard for comparison was a reference standard diagnosis.

This image analysis system was developed using a set of 77 digital fundus images, which classified the images with a reference standard diagnosis (RSD). System performance was analyzed as a function of the field of view (circular crops with a radius of 1-6 disc diameters) and vessel subtype (arteries only, veins only, or all vessels). Routine ROP screening was conducted over 3 years, with a subset of 73 images independently classified by 11 ROP experts for validation. The RSD was compared with the majority diagnosis of experts. The main outcome measure was the percentage of accuracy of the i-ROP system classification of plus disease. Secondary outcome measures included the accuracy of the 11 experts compared with the RSD.

Accuracy of plus disease diagnosis by the i-ROP computer-based system was highest (95%; 95%CI, 94%-95%) when it incorporated vascular tortuosity from
both arteries and veins and with the widest field of view (6–disc diameter radius). Accuracy was 90% or less when using only arterial tortuosity and 85% or less using a 2– to 3–disc diameter view similar to the standard published photograph. Diagnostic accuracy of the i-ROP system (95%) was comparable to that of 11 expert physicians (mean 87%, range 79%-99%).

Importance: In an era of disruptive technologies, computer based diagnosis, even without the use of artificial intelligence, ranks high. Articles in the lay press foresee a future where computer software can analyze data and arrive at a diagnosis, and this study supports the accuracy of making a diagnosis of plus disease in infants with ROP. Thus, this other dimension of telemedicine will likely bring enhanced medical services to all parts of the world.

**Outer Retinal Structural Alternation and Segmentation Errors in Optical Coherence Tomography Imaging in Patients With a History of Retinopathy of Prematurity.**

Patients with a history of ROP have been demonstrated to have abnormal foveal structure on various OCT studies. However no studies to date have systematically compared the structural changes on OCT to visual acuities in these patients. Additionally, patients with abnormal macular structure have OCT results with higher rates of segmentation errors. The authors performed a prospective cohort study on 133 eyes of 133 patients. The patients were grouped into ROP needing treatment, ROP that regressed, other premature patients without ROP, and full term age matched controls. Patients were assessed at a mean of 9.5 years of age (range 4-16years). The authors found that the external limiting membrane (ELM) and cone outer segment tips line (COST) were the least frequently identified structures in patients who received ROP treatment and that visual acuity in these patients correlated with the lack of ELM but not the absence of the COST line. The COST line was detected in 11 (47.8%) of the patients who had history of ROP with treatment and the ELM was identified in 15 (65.2%) of the same patients. Theses results were statistically significant when compared to the other three groups. Segmentation errors occurred in all groups, but were more common in the patients with a history of ROP requiring treatment. The authors concluded that outer retinal abnormalities are more common in patients with a history of ROP treatment and that the increased segmentation errors in SD-OCT might be related to these structural changes. The authors point out the main limitation of the study which is small sample size.

**Choroidal Thickness in Infants with Retinopathy of Prematurity**
This study evaluated choroidal thickness in premature infants and its relationship to stage of ROP using portable SD-OCT. 80 premature infants were studied. Choroidal thickness was measured at the central fovea (CF) and 0.75 mm to 1.5 mm nasal (N1 and N2) and temporal (T1 and T2) to the fovea. Choroidal thickness of CF was significantly greater than nasal and temporal choroidal thickness. There was no significant relationship between stage of ROP and nasal choroidal thickness, though CF and temporal choroidal thickness was significantly lower at higher stage of ROP. In addition, the choroidal thickness of CF was correlated with birth weight but not birth week. Maximum stage of ROP was negatively correlated with choroidal thickness at N1, T1, and T2. Finally, CME was observed in 51.2% of patients, though there was no significant relationship between subfoveal choroidal thickness and the grade of CME. This study was limited by its relatively small sample size, necessitating the lumping of Stage 2 and 3 ROP into one group. Also, newer methods of evaluating the choroid were not employed, and axial length was not measured. Nevertheless, this study demonstrated that subfoveal choroidal thickness can be evaluated in premature infants using portable SD-OCT, and that choroidal thickness decreases with the severity of ROP, most prominently temporally.


The purpose of this study was to describe the retinal imager’s training and certification process and examine the factors that affected image acquisition and image quality in the e-ROP study. The imagers were non physicians who underwent extensive didactic and hands-on training to become certified. A total of 28 imagers from 13 participating clinical centers were trained and certified. Of 3977 image sessions, 3454 (86.8%) completed the required 6 images from each eye. 91.7% had acceptable image quality, 5.6% were poor and 2.7% were missing. Pupil size was a factor in image quality. When comparing pupils <5mm, 5-6mm and >6mm in diameter, acceptable quality images were recorded in 54%, 88% and 93% respectively. Missing images totaled 28%, 3.3% and 2.1% respectively, once again showing the effect of pupil size on acceptable results. Mode of infant ventilatory support also affected image quality. Room air yielded a 94% acceptable image quality rate, while JET/HFOV only yielded a 66% rate, presumably because of difficulty accessing the infant’s eye. Incomplete image sets and quality were also affected by tester experience as the former decreased and the later increased over time. Busier centers had better image quality initially versus less busy centers, but the gap in image quality decreased over time. Overall, pupil size and easier access to the infant were found to yield better images.

**ROP and Anti-Vascular Endothelial Growth Factor Treatment**
Retinopathy of Prematurity: Intravitreal injections of bevacizumab: timing, technique, and outcomes

This report is part of a symposium on ROP and it highlights some of the precautions that need to be applied when using anti-VEGF therapy for ROP. The BEAT-ROP clinical trial was a prospective, randomized, controlled, multicenter clinical trial comparing intravitreal bevacizumab versus conventional laser therapy. It reported improved efficacy in the bevacizumab group for zone I ROP in and decreased high myopia in the bevacizumab group for zone I and posterior zone II ROP. However, delayed recurrences had become a serious problem in follow-up of infants treated by intravitreal bevacizumab, due to lack of guidelines. This report stresses the need for proper case selection (timing). Bevacizumab cannot be administered too early, as a preventive measure, or too late, when stage 4 or 5 have developed. Appropriate injection technique is discussed. Long-term advantageous effects of anti-VEGF are outlined as possible adverse outcomes.

A lower dose of intravitreal bevacizumab effectively treats retinopathy of prematurity

This prospective, non-comparative, interventional case series addresses the question of optimal dose for the treatment of type 1 retinopathy of prematurity (ROP). It included a total of 49 eyes of 25 consecutive infants (24 bilateral and 1 unilateral), who underwent intravitreal injection of a reduced dose (0.25 mg/0.01 mL) of intravitreal bevacizumab. Infants were followed for ROP persistence or recurrence until 90 weeks' postmenstrual age. In this case series ROP regressed in all eyes. No recurrences of plus disease or neovascularization were noted.

In this cohort of patients the lower dose of 0.25mg/0.01ml intravitreal bevacizumab seemed to be effective, with no recurrence of plus disease or neovascularization.

Retinopathy of Prematurity: Anti-VEGF treatment for ROP: which drug and what dose?

This review is part of a symposium on retinopathy of prematurity. It is a very good update on anti-VEGF treatment in ROP. It lists some of the major studies in the field and is a good resource of references on the subject. It highlights some of the major dilemmas regarding anti-VEGF and ROP including: the dilemma around which type of anti-VEGF drug to use for ROP, drug dose, treatment advantages, and side-effects. Four anti-VEGF
treatments are mentioned: bevacizumab (Avastin), ranibizumab (Lucentis), pegaptanib (Macugen), and aflibercept (Eylea). It lists some of the advantages of anti-VEGF treatment compared to laser such as: lower recurrence rate in some reports, less stress to the infant, less myopia and possibly better peripheral vision. On the other hand, it also mentions the concerns that have been raised regarding this treatment modality, including concerns about retinal development, possible systemic effects and delayed neurodevelopment. Hence, the dilemma around the optimal dose. The Pediatric Eye Disease Investigator Group phase 1 dosing study of bevacizumab treatment for severe ROP is mentioned, the results of which are soon to be published. This ongoing study might be able to supply the answer to the dose level question. The author concludes that evidence-based paradigm for anti-VEGF treatment is still incomplete, and that there are many unanswered questions about which drug, what dose, relative benefits and possible side effects. He also stresses the need for more high-quality comparative studies on the matter.

Retinal Vascular Development with 0.312 mg Intravitreal Bevacizumab to Treat Severe Posterior Retinopathy of Prematurity: A Longitudinal Fluorescein Angiographic Study


This study investigated the efficacy of intravitreal bevacizumab (IVB) 0.312 mg per eye in infants with treatment-requiring ROP in Zone 1 and posterior Zone II including APROP, and described the effects of the treatment on the developing retinal vasculature using FA. 0.312 mg is a lower dose than is typically administered to adults, and lower than the dose reported in most previous studies of anti-VEGF therapy for ROP (0.625 mg). 17 premature infants were treated with 0.312 mg IVB because of acute ROP in posterior Zone II or Zone I, including APROP. Infants were examined by FA using RetCam II or III before IVB, within 6 weeks, 8 – 13 weeks, and up to 45 months after treatment. Acute ROP regressed in 19/27 (70%) analyzed eyes, including 100% of posterior Zone II eyes and 80% Zone I eyes, but in only 25% of APROP eyes. Early recurrences (11%, all APROP) and late reactivations (18%) were observed within 1 week and at 9 – 12 weeks, respectively. All eyes demonstrated leakage at the junction of the vascularized zone and capillary malformations on FA prior to treatment. Vessel branching abnormalities and circumferential vessel formation were common features on FA after treatment.

This study was limited by small sample size. In addition, IVB monotherapy was not compared to laser monotherapy, and no control group of imaging data from healthy infants was included. Although FA data from every patient at every time point could not be obtained, a total of 75 FA imaging data sets were examined and reveal interesting new clinical data. That the lower dose of IVB showed simi-
lar results in posterior Zone II and Zone I disease compared to higher doses in other studies is important given the unknown consequences of anti-VEGF medication on developing babies. 0.312 mg IVB was not effective for treating APROP in this study. The authors emphasize that FA may be helpful in defining and diagnosing APROP and other short and long term vessel alterations related to ROP.


This study analyzed the medical records of 101 eyes of 51 consecutive infants with Type 1 ROP in Zone 1. Infants treated between November 2004 – June 2011 received conventional laser photocoagulation (Group I), those treated between July 2011 – October 2012 received combined intravitreal bevacizumab injection and Zone 1 sparing laser (Group II), and those treated between November 2012 – December 2013 received intravitreal bevacizumab with deferred laser treatment (Group III). In Group I, 10 of 44 eyes (22.7%) demonstrated an unfavorable anatomical outcome. However, in Groups II and III, all eyes had favorable anatomical outcomes without reactivation or retreatment. The refractive error was less myopic in Group III (spherical equivalent -1.40 +/- 2.19 D) than in Groups I (-4.62 +/- 4.00D) and II (-5.53 +/-2.21 D).

This study’s major limitation is that it is a historical rather than a simultaneous comparison which may be a source of confounding and bias. Temporal trends such as oxygen treatment protocols and management of sepsis and nutrition might influence the development and behavior of ROP, which would affect treatment outcomes. In addition, the study did not include a group treated with intravitreal bevacizumab alone. Although a prospective study is necessary, the authors conclude that intravitreal bevacizumab with deferred laser may afford a favorable anatomic outcome, lower possibility of reactivation, less frequent examinations after treatment, and preservation of larger unlaunched retinal areas with less myopia than other treatment strategies.

Five years of treatment for retinopathy of prematurity in Sweden: results from SWEDROP, a national quality register


This is a study on how treatment of Retinopathy of prematurity (ROP) was conducted based on registry data in Sweden (SWEDROP) for infants born between
2008-2012. Of note is that their screening criteria changed from < 32 weeks GA to < 31 weeks in July 2012. The international classification for ROP is used for staging and typing of ROP and treatment criteria followed ETROP recommendations for treating type 1 ROP. Laser treatment is the initial treatment of choice. However, anti-vascular endothelial growth factor (VEGF) was administered on a case by case basis when there was a clinical consensus among the pediatric ophthalmologist, retinal surgeon, and neonatologist. Surgery with encircling band and vitrectomy was conducted by retinal surgeons based on their clinical assessment. During 2008–2012, 3488 infants with GA <31 weeks had been screened for ROP in Sweden. Altogether, 30.3% (1057/3488) of the infants developed ROP and 5.2% (181/3488) were treated. Type 1 ROP was found in at least one eye in 83.2% (149/179) of the treated infants. One-third of the eyes (32.2% right, 29.9% left eyes) were treated more than once. Laser was the only treatment in 90% of the eyes. Mean number of laser spots at first laser session was 1177 and 1386 in right and left eyes, respectively. There was no change in frequency of treatment or number of laser spots during the 5-year period. Anti-vascular endothelial growth factor injections were performed in 28 eyes, encircling band was used in five eyes and vitrectomies were performed in seven eyes. Twenty-six retinal surgeons performed 9.4 (range 1–37) treatment sessions in the 181 infants. The authors concluded that this study reveals similar incidences of ROP and frequencies of treatment during the 5-year study period. Many surgeons were involved in treatment of a rather limited number of infants. The results call for national discussions on the organization of ROP treatment.

**Intravitreal Bevacizumab for Zone II retinopathy of prematurity**

This article investigates the treatment outcomes of intravitreal bevacizumab injection when used as monotherapy in treating type I retinopathy of prematurity (ROP). It is a retrospective, non-comparative case series of 14 patients (n=28 eyes), with a mean GA at the day of birth 25.9+/−2.34, and a medial birth weight of 694 g(range 487gr-1740 gr) and at least 3 week of follow-up. One week after intravitreal injection of bevacizumab, 50% of the eyes showed complete regression of ROP, and a partial regression of ROP was observed in 35.7% of the cases. According to the authors, all 28 eyes were treated successfully with intravitreal injection of bevacizumab as monotherapy. No patients showed recurrence of the disease. Also, there was a trend toward a shorter time to full vascularization in the cases with complete regression during the first week compared with the cases of partial regression but it was not statistically significant. This is a study with no power to evaluate the safety of intravitreal injection of bevacizumab in premature babies. VEGF is implicated in the development of the brain, lungs, and kidneys; therefore safety data should include not only ocular but also neurological, pulmonary, renal and bone complications, especially given the fact that recent studies showed that systemic VEGF levels remain inhibited for 8
weeks after intravitreal injection of bevacizumab. It is also retrospective case series, non-comparative with a very short follow-up period. Also, the study lacks any angiographic evidence of complete vascularization.

**Chronic Vascular Arrest as a Predictor of Bevacizumab Treatment Failure in Retinopathy of Prematurity**


In this retrospective interventional study, the authors aim to describe a pattern of ROP disease regression and chronic vascular arrest after intravitreal bevacizumab treatment that is not observed after peripheral laser ablation. 58 eyes in 30 patients treated for type 1 ROP were included. Initial treatment with either a single intravitreal injection of bevacizumab in off-label use (n=33eyes) or peripheral laser ablation (n=25 eyes) as part of standard clinical care. There was bias in recommending off-label bevacizumab for smaller infants with type 1 ROP. All eyes treated initially with bevacizumab demonstrated irregular progression of the leading vascular edge in a stereotyped pattern, suggestive of “scalloped regression.” Recurrence, based on angiographic demonstration of leakage, or chronic vascular arrest, confirmed based on angiographic demonstration of peripheral ischemia, was noted in 30 eyes (91%) in the bevacizumab group, at a median interval of 14.9 weeks after injection (corrected gestational age, 49.3 weeks). Univariate logistic regression indicated that the need for rescue treatment was associated with decreased birth weight (odds ratio [OR],-0.007) and age of initial treatment (OR,-0.35), but not gender, race, or gestational age. Multivariate logistic regression indicated that only decreased birth weight (OR,-0.018) was associated with need for rescue treatment. The authors conclude that treating ROP with intravitreal bevacizumab results in a characteristic “scalloped regression” pattern which in additional to chronic vascular arrest and peripheral retinal ischemia persisting beyond standard screening timelines has significant implications for the management of ROP.

Comment: While not a post-Avastin treatment trial, this paper provides helpful information how long to wait after Avastin injection for full retinal vascularization to occur before moving ahead with peripheral laser ablation even in eyes that do not demonstrate truly reactivated ROP.

**Clinical Management of Recurrent Retinopathy of Prematurity after Intravitreal Bevacizumab Monotherapy**


In this retrospective case series, the authors aimed to determine incidence, risk factors, risk period, and characteristics of recurrent retinopathy of prematurity (ROP) following intravitreal bevacizumab (IVB) monotherapy. IVB monotherapy performed in 241 infants (471 eyes) was studied. Risk factors for recurrence were appearance of neovascularization as acute pos-
terior ROP (P=0.006), extended duration of hospitalization (P=0.01), and lower birth weight (P=0.024). Recurrence risk period was between approximately 45 and 55 weeks adjusted age (mean recurrence of 51.2 weeks adjusted age) and mean interval of 16.2 weeks between treatments. Recurrence characteristics included plus disease (20/20 infants [100%]) and neovascularization, which appeared at the following sites: stage 3+ ROP with confluent neovascularization recurred both at the advancing edge and at the initial ridge and extraretinal fibrovascular proliferative complex (12/14 infants [85.7%]). However, APROP (6/6 infants [100%]) and stage 3+ ROP with nonconfluent neovascularization (2/14 infants [14.3%]) recurred only at the advancing edge. Also, the anterior extent of retinal vascularization was decreased (mean, 1.76 disc diameters [DD] vs. 4.48 DD), and the rate of retinal vascularization was delayed (mean, 0.11 DD/week vs. 0.23 DD/week) in those with versus without recurrence, respectively. After retreatment with IVB, retinal vascularization proceeded minimally and slowly. The authors concluded that premature children with severe ROP are being treated successfully with IVB monotherapy, but recurrence is not uncommon. They recommended vigilant follow-up to ensure timely re-treatment. Knowledge of recurrence incidence, risk factors, risk period, and characteristics allows for tailored clinical management.

Comment: With more treatment options comes more complexity in ROP management decision-making. The study results and fundus photos and angiograms included in the paper are helpful in gaining a better feel for the expected clinical course following injection of Avastin.

Bevacizumab for Retinopathy of Prematurity: Treatment When Pathology Is Embedded in a Normally Developing Vascular System


This editorial by Dr. Good comments on findings of the study by Mintz-Hittner et al published in the same September 2016 issue of Ophthalmology. The editorial highlights several ongoing important clinical questions: 1. What are the systemic effects of Avastin on other organ systems (especially the lungs and brain)? 2. How long is it safe to wait for normal vascularization to commence after Avastin injection? 3. Does peripheral avascular retina without active ROP require treatment? 4. If retreatment is needed, should retreatment be laser or additional Avastin injection(s)?

Comment: This brief editorial does not exactly answers any of these clinical questions but provides additional perspective for the reader of peer-reviewed ROP literature.

Does Bevacizumab Alter Vascularization Potential in Retinopathy of Prematurity?

In this short report of an retrospective interventional study, the authors evaluated outcomes of 5 patients with asymmetric ROP treated with a single Avastin 0.625mg injection. Each patient developed type 1 ROP in only eye and therefore only eye was treated in each patient. The extent of post-treatment peripheral vascularization was similar in the two eyes of each patient. The authors conclude that incomplete vascularization of the peripheral retina may be due to the underlying disease of ROP rather than an arrest of vascularization caused by Avastin. The authors acknowledge the possibility of systemic absorption of Avastin causing some effect on the untreated eye.

Comment: Most of the untreated eyes (4/5) only developed stage 2 ROP. In my experience, the vast majority of eyes with stage 2 ROP ultimately vascularize completely. The fact that these eyes did not fully vascularizes causes me to suspect that Avastin from the treated eye may be affecting the untreated eye to inhibit normal vascularization.

Assessment of plasma cytokine profile changes in bevacizumab-treated retinopathy of prematurity infants

This prospective study compared changes of plasma angiogenesis cytokine profiles in 13 infants treated with bevacizumab for type 1 retinopathy of prematurity (ROP) with 13 age-matched preterm non-ROP infants. Blood samples were collected prior to treatment and 6 weeks after treatment. Plasma levels of 9 cytokines from the angiogenesis growth factor panel and 7 soluble cytokine receptors were measured using a multiplex assay. In bevacizumab-treated ROP infants, multiple plasma angiogenesis growth factor and soluble cytokine receptor levels decreased significantly and some increased significantly. At time 6 weeks, sVEGF-A, sgp130, sIL-6R, sTNFR I, and sTNFR II were lower, and ET-1 level was higher in bevacizumab-treated ROP infants compared to age-matched non-ROP infants. The relationship between VEGF-A and ET-1 has been controversial. The elevation of plasma ET-1 levels could be beneficial to infants by compensating for the loss of VEGF-A. However, this elevation itself could raise other concerns related to the overexpression of ET-1, such as increased smooth muscle cell proliferation, which is seen in persistent pulmonary hypertension of newborn infants. Reductions in SPG130, II-6R, and sTNFR I and sTNFR II could be related to systemic health problems such as decreased humoral immune responses in preterm neonates and chronic lung disease. Though this study is limited by its small size, the results suggest that bevacizumab treatment resulted in significant angiogenic cytokine profile changes in infants with severe ROP. The long-term clinical impact of these changes should be studied carefully.

Involution patterns of retinopathy of prematurity after treatment with intravitreal bevacizumab: implications for follow-up
M Isaac, N Tehrani and K Mireskandari Eye March 2016; 30: 333-341; advance
This is a retrospective study conducted at Toronto Hospital for Sick Children conducted between 2010 and 2014 where the authors examined involution patterns of type 1 ROP treated with a single dose of bevacizumab. 28 eyes were followed for an average of 34 months. Infants who developed type one ROP were treated with bevacizumab 0.625 mg/0.025 ml injected into the vitreous cavity without concurrent treatment with laser and were then followed. Plus disease regressed in 100% by day 8, and Stage 3 and plus disease regressed in 100% by week 4. 17/28 eyes developed recurrence of stage 1 or 2 within 3 months of treatment and none developed recurrence of plus disease. No eyes required re-treatment and none developed unfavorable outcome. At three months 82% of eyes were not fully vascularized. Because of case reports of late onset recurrent neovascularization, despite this studies favorable results the authors continue to recommend exams every 2 weeks until vascularization has arrested in close proximity to the ora serrata, and after 6 month post treatment they recommend fundus fluorescein angiography under general anesthesia to assess for peripheral extra-retinal neovascularization. The study demonstrated the efficacy of mono-therapy treatment of ROP but also emphasizes the importance of long term surveillance which will add cost and multiple examinations and require diligent follow-up by the treating physician.

**Neurodevelopmental Outcomes Following Bevacizumab Injections for Retinopathy of Prematurity**

Julie Morin, Thuy Mai Luu, Rosanne Superstein, Luis H. Ospina, et al. *Pediatrics* April 2016; 137 (4); e20153218

Bevacizumab, a vascular endothelial growth factor, is used to treat retinopathy of prematurity. There is limited information regarding the long-term effects of a systemically absorbed medication on the development of these children. To evaluate the developmental effects, a retrospective study was conducted by the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network. The study identified patients born at less than 29 weeks gestation between 2010-2011 and who were treated with either bevacizumab or laser. Neurodevelopmental outcomes at 18 months were obtained from a database that provided the Bayley Scores of Infant and Toddler Development Third Edition. These developmental tests were administered by pediatricians across Canada. The study showed that infants treated with bevacizumab scored lower on a motor composite score but not on language or cognitive scores. Odds of severe neurodevelopmental disabilities (low Bayley score, cerebral palsy, hearing aids, or bilateral blindness) was 3.1 times higher in infants treated with bevacizumab than laser. The rates were adjusted for variables such as gender, maternal education, and severity of systemic illness. Weaknesses of the study include the observational nature of the research, the lack of information about why an infant received bevacizumab versus laser, and that the bevacizumab group had more severe ret-
Interventions to Prevent Retinopathy of Prematurity: A Meta-analysis


This meta-analysis of previous research surrounding retinopathy of prematurity aimed to evaluate the effectiveness of interventions to reduce the risk of retinopathy of prematurity. A total of sixty-seven randomized or observational studies were identified. These studies estimated the effectiveness of nutritional intervention, oxygen saturation targeting, blood transfusion management, and infection prevention on the development of retinopathy of prematurity and mortality in infants born less than 32 weeks gestation. The results of meta-analysis show that aggressive parenteral nutrition and vitamin A supplementation may reduce any stage of ROP (not severe ROP). In observational studies, breast milk feedings, vitamin E supplementation, and inositol therapy reduce the risk of severe ROP or ROP requiring surgery. Lower oxygen saturation will decrease the risk of both any stage of ROP and severe ROP but it may increase mortality before discharge in these patients. The utilization of transfusion guidelines, erythropoietin, and antifungal agents did not improve the risk of ROP. There is limited high quality evidence that any of these proposed intervention will impact the development and severity of ROP. At the present time, there is no high quality evidence to support a safe intervention that prevents severe retinopathy of prematurity.

Involution patterns of retinopathy of prematurity after treatment with intravitreal bevacizumab: implications for follow-up

M Isaac, N Tehrani and K Mireskandari Eye 30: March 2016: 333-341

The authors conducted a retrospective review of 28 eyes of infants with type 1 ROP treated with intravitreal bevacizumab 0.625 mg at a single center over a 4 year time period. The patterns of ROP regression were described. 100% of plus disease had regressed by day 8 following treatment and 100% regression of both plus disease and stage 3 ROP had occurred by week 4 following treatment. Within the first 3 months of follow-up, 17 of 28 eyes demonstrated recurrence of stage one or two, but none required retreatment and none developed unfavorable structural outcome. At 24 months follow-up, 39% of the eyes were not fully vascularized into zone 3. The study confirms the need to follow these patients closely for long periods of time.
ROP Epidemiology and Outcomes

Postnatal corticosteroids and risk of retinopathy of prematurity


This retrospective study investigated the association between postnatal steroids and retinopathy of prematurity (ROP) in neonates born with birth weights at the limit of viability (<500 g). Data from the Pediatrix BabySteps Clinical Warehouse were retrospectively reviewed. Study population included 1,472 neonates with birth weights of <500 g, who were discharged alive from 167 NICUs between 1996 and 2013. The incidence of any ROP was significantly higher (P <0.0001) in steroid-treated infants (80.5%) than in nontreated infants (66.8%); the incidence of advanced-stage ROP was also significantly higher (P<0.0001) in the former (35.3%) compared to the latter group (21.1%). Steroid-treated infants also had a significantly higher incidence of bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, and intracranial hemorrhage compared to nonsteroid treated neonates. In a multivariate analysis, the odds of any ROP for steroid treated infants was 1.6 (95% CI, 1.2-2.2) compared to nontreated infants; the odds of advanced ROP was 1.7 (95% CI, 1.3-2.3). The authors concluded that in this cohort of critically low birth weight infants, ROP was more common in neonates exposed to postnatal steroids. The investigators had chosen a population of neonates with birthweight of <500 g, because this category of neonates is generally more homogeneous clinically. They were hoping to minimize the clinical differences between treated and untreated groups, but the treated group still had a significantly higher incidence of comorbidities. They corrected for this with multivariate regression analysis. Despite some limitations in the study's design, this study had a very large sample size. Steroid-treated infants in this cohort indeed had significantly increased risk for ROP, but the effect was modest.

Prediction of severe retinopathy of prematurity using the screening algorithm WINROP in preterm infants


An effective screening program for ROP should be able to identify the relatively few preterm infants with treatment-demanding ROP from among the numerous at-risk infants. Weight gain, insulin-like growth factor 1 (IGF-1),
and neonatal retinopathy of prematurity (WINROP) algorithm to predict prolif-erative retinopathy of prematurity has been previously shown to be effective in identifying infants at risk in well-developed countries, such as Sweden and the US. In this retrospective study, the authors wanted to assess the applicability of the WINTROP algorithm in a moderately developed, middle-income country, Turkey. The medical records of infants screened and monitored for ROP from 2007 to 2014 were analyzed, retrospectively. Birth weights of infants born before 32 weeks' gestation were recorded on the WINROP online database system weekly until postmenstrual week 36. The sensitivity, specificity, and positive and negative predictive values of the WINROP algorithm were analyzed. A total of 223 infants were included. WINROP yielded a low-risk result in 106 infants (48%) and a high-risk result (red alarm) in the remaining 117 infants (53%). The sensitivity of the WINROP online system was found to be 84.3% (27/32), whereas its specificity was found to be 52.8% (101/191). In the high-risk group, the time between the first alarm and treatment was 8.59 ± 3.92 (2-15) weeks. The authors conclude that the WINROP online system is a valuable and easy-to-use monitoring system that could decrease the number of infant ROP examinations. Unfortunately, the sensitivity of the WINROP algorithm was not 100% in this cohort. Care must be taken to exclude infants from the WINROP algorithm who develop non-physiologic weight gain, due to excessive edema. In this study, four of 5 infants, who were not identified by the WINROP algorithm had sepsis, Intraventricular hemorrhage IVH, and bronchopulmonary dysplasia. This study was limited by its retrospective nature and the comparably small number of cases.

The association between systemic vascular endothelial growth factor and retinopathy of prematurity in premature infants: a systematic review
Yogavijayan Kandasamy, Leo Hartley, Donna Rudd, Roger Smith

Retinopathy of prematurity (ROP), a vasoproliferative disorder exclusive to premature infants, is an important cause of childhood blindness. The number of premature infants surviving with this condition is expected to increase globally. Animal models of oxygen-induced retinopathy studies have shown vascular endothelial growth factor (VEGF) to be a key player in the pathogenesis of ROP. This has led to increased use of VEGF antagonist as an alternative treatment for ROP. The purpose of this systematic review was to determine the association between VEGF and ROP in human newborn. The literature review identified 12 studies to date that fulfilled the search criteria. Investigators used cord blood, serum, plasma and tissue samples to investigate the association between ROP and VEGF. Studies that measured VEGF in cord blood found mixed results, with low VEGF (at birth) associated with ROP in one study and no difference noted in two others. Mixed results were also seen in studies determining VEGF in postnatal venous samples. Four studies showed no difference in VEGF level between
premature infants with and without ROP, one study showed an increased VEGF level in premature infants with ROP and another study found serum VEGF to be low in premature infants with ROP. The most recent study demonstrated an initial increase in serum VEGF followed by a decline at the time of treatment. These contradictory results indicate that we are yet to fully understand the role of VEGF in human premature infants and call into question the rationale of treating ROP with anti-VEGF. Anti-VEGF therapy results in systemic effect on serum VEGF levels for up to 2 months and this could have an effect on neurodevelopmental outcome. The effect of this on other developing organs is currently unknown. More studies are required to determine the mechanistic relationships between systemic VEGF and ROP in premature infants.

Plus Disease in Retinopathy of Prematurity: A Continuous Spectrum of Vascular Abnormality as a Basis of Diagnostic Variability

The authors identified patterns of interexpert discrepancy in plus disease diagnosis. The authors had compiled 2 dataset totaling 134 Retcam ROP photos and created a reference standard diagnosis based on the past publications. The authors then had 8 independent ROP experts analyze the same 134 Retcam ROP images and classify each image as having plus disease, pre-plus disease or normal. Interexpert agreement was analyzed as well as agreement with the reference standard diagnosis. There was variable interexpert agreement on diagnostic classifications between the 8 experts and the RSD (weighted k, 0-0.75; mean, 0.30). The RSD agreement ranged from 80% to 94% for the dataset of 100 images and from 29% to 79% for the dataset of 34 images. However, when images were ranked in order of disease severity (by average expert classification), the pattern of expert classification revealed a consistent systematic bias for each expert consistent with unique cut points for the diagnosis of plus disease and preplus disease. The 2-way ANOVA model suggested a highly significant effect of both image and user on the average score (dataset A: P < 0.05 and adjusted R2=0.82; and dataset B: P<0.05 and adjusted R2=0.6615). The authors conclude that there is wide variability in the classification of plus disease by ROP experts, which occurs because experts have different cut points for the amounts of vascular abnormality required for presence of plus and preplus disease. This has important implications for research, teaching, and patient care for ROP and suggests that a continuous ROP plus disease severity score may reflect more accurately the behavior of expert ROP clinicians and may better standardize classification in the future. Comment: The authors did a very good job highlighting a very practical problem in ROP clinical care and research. It is worth noting that generally, we do not treat ROP based on the findings in a Retcam image. The use of Retcam photos is good for ensuring that all experts are evaluating the same sample of ROP disease; however, I believe the peripheral retinal find-
ings in a live patient could also influence a clinician’s likelihood of diag-
nosing plus disease which might increase, decrease or have no effect on
overall variability of plus disease diagnosis.

**Reduced utility of serum IGF-1 levels in predicting retinopathy of
prematurity reflects maternal ethnicity**

April 2016;100:501-504

Low insulin-like growth factor 1 (IGF-1) serum levels and poor early or absolute
weight gain (AWG) have recently been shown to be predictors for the develop-
ment of retinopathy of prematurity (ROP). This study aimed at validating the
known risk factors such as gestational age (GA) and birth weight (BW) and iden-
tifying a threshold level for IGF-1 in the development of severe ROP in an ethni-
cally diverse population at a tertiary neonatal unit, 2011–2013. A prospective
masked cohort study was conducted. Serum IGF-1 levels at 31, 32 and 33 weeks
were measured and risk factor data collected including GA, BW, AWG, and ma-
ternal ethnicity. The eventual ROP outcome was divided into two groups: minimal
ROP (Stages 0 and 1) and severe ROP (Stage 2 or worse including Type 1
ROP). A total of 36 patients were recruited: 14 had minimal ROP and 22 severe
ROP. Significant differences between the groups were found in GA, BW, AWG
and IGF-1 at 32 and 33 weeks. There was minimal rise in IGF-1 in Stage 2 pa-
tients and/or black patients (p=0.0013) between 32 and 33 weeks but no prag-
natic threshold level of IGF-1 that could distinguish between minimal or severe
ROP. Many children were transferred from research unit to non-research unit
during the study. The percentage of these infants and the demographics was not
included in the analysis. Among the children included in the study, there were
significant differences in GA, BW, AWG and IGF-1 at 32 and 33 weeks between
those babies with severe ROP and those with minimal ROP. However, there was
no threshold level of IGF-1 at a time point between 31 and 33 weeks that can be
used to exclude a large proportion of babies from screening. The authors found
ethnic differences in IGF-1 levels with infants born to black mothers having signif-
icantly lower IGF-1 levels at 32 and 33 weeks gestation. The determination of
ROP risk using IGF-1 is a race-specific phenomenon. Even with a small sample
size, the authors found that maternal ethnicity has a greater predictive power
than the AWG in an ethnically diverse population.

**Retinopathy of prematurity in Korean infants with birthweight
greater than 1500 g**

2016;100:834-838.

The authors conduct a retrospective observational study to determine the inci-
dence and clinical features of, and risk factors for, retinopathy of prematurity
(ROP) in Korean infants with BW >1500g. From January 2009 to December 2013 they identified 201 infants with BW >1500. The location and the highest stage of retinopathy observed were recorded for each infant. The associated systemic and maternal risk factors in infants with mild or absent ROP were compared with those in infants with treatment-requiring ROP. They found that the total incidence of ROP was 11.9% and that of treatment-requiring ROP was 4.0%. Two patients with gestational age (GA) >32 weeks and BW >1500 g had treatment-requiring ROP. Fifteen eyes from eight infants with type 1 ROP required laser photocoagulation. The mean BWs and GAs in the treatment-requiring ROP group were significantly lower than those in the no or mild ROP group. Total duration of oxygen supplementation, surfactant usage, respiratory distress syndrome, bronchopulmonary dysplasia, antibiotic use for more than 14 days and the number of ROP-associated risk factors significantly increased the likelihood of treatment-requiring ROP. In this study, nearly 4% of infants with BW >1500 developed type 1 ROP. Based on their findings, the authors recommend that the screening criteria be modified (they currently follow AAP guidelines) to include children with BW up to 1750 g.

It is noteworthy that the incidence of Type 1 ROP in this cohort is higher than that found in other populations, such as 2.3% in China but lower than Taiwan at 10%. The reason for these differences seen is not clear. In this retrospective study, it is also not clear how these children were evaluated if they did not meet the screening criteria. AAP guidelines recommend that children with underlying health problems be screened and perhaps this has triggered screening in this children. It would be interesting to know whether all children with >1500 g were included in the study or only those that were requested to be screened due to underlying health problems.

Maternal Diabetes as an Independent Risk Factor for Retinopathy of Prematurity in Infants With Birth Weight of 1500 g or More.

ROP screening guidelines in infants greater than 1500g are not clear and are variable across the globe. Additionally, babies in developing countries have a wider range of birth weight and gestational age compared to those in the US. This was a retrospective case control study to examine the relationship between the development of type 1 ROP and maternal diabetes in one institution in Turkey in infants born at 1500g or more. 336 preterm babies were included in the study, of those 78 had diabetic mothers and the other 258 babies had non-diabetic mothers. The cases and controls were matched based on gestational age and birth year. The authors found that birth weight, rate of any ROP, and rate of type 1 ROP were all significantly higher in the babies from diabetic mothers. Sepsis was also found to be a risk factor for ROP in this study. Sepsis was associated with a 3.5x increase in risk for ROP and maternal diabetes was associated with a 25x increased risk for ROP. The authors found that 78% of babies born to diabetic mothers had any ROP and of those 20% had type 1 ROP. The rate of type 1 ROP was statistically significantly higher in the patients born to di-
abetic mothers when compared to those born to non-diabetic mothers. The au-
thors note that most of the diabetic mothers in this study had uncontrolled diabe-
tes. Additionally, this study is limited because it was a single institution in Turkey
and thus unlikely to be generalizable to a more developed nation. However there
is a strong and independent association between type 1 ROP and maternal dia-
abetes in infants with a birth weight greater than 1500g.

**Practice Patterns in Retinopathy of Prematurity Treatment for
Disease Milder Than Recommended by Guidelines.**
Gupta MP, Chan RV, Anzures R, Ostmo S, et al; Imaging & Informatics in ROP

Multiple studies have noted that pediatric ophthalmologists and retinal specialists
who treat ROP sometimes decide to treat ROP that does not meet the definition
of type 1 ROP. This study used the database from the multi-center i-ROP (Imag-
ing & Informatics ROP research consortium) to look at which babies were treated
and why they were treated when they didn’t meet type 1 ROP criteria as defined
by the ET-ROP. Of the 722 infants in the database, 137 eyes (9.5%) of 70 in-
fants were treated for ROP. Of those, 13 eyes of 9 babies were treated despite
not having ROP meeting type 1 diagnosis. The authors looked closer at these
babies and found that 2 eyes were treated because the fellow eye met type 1 cri-
teria. 9 of the 13 eyes had concerning structural changes, specifically tangential
traction or thick stage 3 membranes with anteroposterior traction. 4 of the 13
eyes were treated because they had persistently active ROP at an advanced
post menstrual age. The authors conclude that the role of individual judgment in
the treatment of ROP remains important. The authors point out that this study
does not describe the expert consensus but rather individual management deci-
sions and that it was not designed to describe the long term outcomes of these
babies.

**Sight threatening retinopathy of prematurity: changing trends in
treatment.**
Kate A. Brown, Rachael C.Heath Jeffery, Barbara Bajuk, Bruce Shadbolt
et al. *Journal of Pediatric Ophthalmology and Strabismus.* March/April

This article studies the incidence and treatment of severe retinopathy of prema-
turity (ROP), in infants younger that 30 weeks of gestational age (GA) in New
South Wales and the Australian Capital Territory, Australia form 2003 to
2008. The data were divided into two groups: the first one( 2003-2008).These da-
ta were also compared to data from previously reported epochs( 1986-1987,
survived, 200 (7.8%) were diagnosed as having severe ROP, and 119 (59.5%)
required laser therapy. No significant difference in the incidence of severe ROP
or treatment rate in infants younger than 27 and 30 weeks' GA from 2003 to 2005
and 2006 to 2008 occurred. Similarly, between 1986 and 2008 there was no difference in the incidence of severe ROP. However, the treatment rate significantly increased during this time. The authors conclude that although the incidence of severe ROP has been stable since 1986, the number of infants receiving laser treatment has significantly increased.

**Neonatal Risk Factors for Treatment-Demanding Retinopathy of Prematurity a Danish National Study**


In this retrospective cohort study, the authors studied 31 candidate risk factors for treatment-demanding ROP while controlling for known risk factors (i.e., gestational age [GA] at delivery, small for gestational age [SGA], multiple births, and male sex). The study included 6490 premature infants found in 3 national registers in Denmark. Mechanical ventilation (odds ratio [OR], 2.84;) and blood transfusion (OR, 1.97) were the only new statistically independent risk factors, in addition to GA at delivery, SGA, multiple births, and male sex. Modification in these prognostic factors for ROP did not cause an increase over the study period in treatment-demanding ROP. 

**Comment:** This large study adds 2 risk factors (mechanical ventilation and blood transfusion) to the list of the known independent risk factors for severe ROP.


The authors sought to assess the level of evidence to support various clinical models for the prediction of ROP by evaluating 23 previously published studies. The authors categorized each study as either a model development study or model validation study. The authors defined criteria in order to also classify each study as Level I evidence (Good quality study), Level II evidence or Level III evidence (Poor quality study). Only 1 study was rated as level I evidence whereas, 3 studies were rated as level II evidence, and 19 studies were rated as level III evidence. Some models suggested reductions in the number of infants screened for ROP. However, the small sample sizes and limited generalizability of the ROP predictive models included in this review preclude their widespread use to make all-or-none decisions about whether to screen individual infants for ROP. Other studies proposed a reduction in the number of examinations per patient in low-risk infants.

**Comments:** The paper provides a good overview of the topic but does not assert a change in ROP screening practice.
Changes in Course of Retinopathy of Prematurity from 1986 to 2013- Comparison of Three Studies in the United States

The authors analyzed the infant characteristics and the onset, severity, and time course of ROP in the CRYO-ROP, ETROP and e-ROP studies to look at trends over the 3 different time periods of these 3 studies. Across the 3 studies, mean BW and mean gestational age (GA) decreased over time from CRYO-ROP (954 g, 27.9 weeks) to ETROP (907 g, 27.4 weeks) to e-ROP (864 g, 27.0 weeks), with an increase in the percentage of infants enrolled weighing <750 g (15.8% CRYO, 24.9% ETROP, 33.4% e-ROP). The percentage of infants who developed ROP varied only minimally (65.8% CRYO, 68.0% ETROP, 63.7% e-ROP). Moderately severe ROP (defined as prethreshold or referral warranted) varied (17.8% CRYO, 12.3% ETROP, 19.4% e-ROP), whereas the time of onset of any ROP did not vary (34.3 weeks CRYO, 34.1 weeks ETROP, 34.8 weeks e-ROP). The BW and GA of infants enrolled in ROP studies in the United States have decreased over the past 27 years, whereas ROP prevalence and onset of disease are stable.

Comment: Although these comparisons were not part of the design of the 3 original studies, this paper benefits from relatively large data sets from each of these well designed studies to demonstrate a decrease in mean BW and gestational age but a stable prevalence and age of onset of ROP.

Diagnostic Discrepancies in Retinopathy of Prematurity Classification

The authors conducted a prospective cohort study to identify the most common areas for discrepancy between experts in classifying retinopathy of prematurity (ROP). Two experts independently evaluated 1553 wide-angle retinal image examinations on 281 infants and classified each exam for zone, stage, plus diseases and overall disease category (no ROP, mild ROP, type II or pre-plus, and type I). The results of the 2 experts were compared with each other and also with the classification by an examiner using binocular indirect ophthalmoscopy. The 2 experts disagreed on the stage classification in 620 of 1553 comparisons (40%), plus disease classification (including pre-plus) in 287 of 1553 comparisons (18%), zone in 117 of 1553 comparisons (8%), and overall ROP category in 618 of 1553 comparisons (40%). However, agreement for presence versus absence of type 1 disease was >95%. There were no differences between image-based and clinical classification except for zone III disease. The most common area of discrepancy in ROP classification was stage, although inter-expert agreement
for clinically significant disease, such as presence versus absence of type 1 and type 2 disease, was high. There were no differences between image-based grading and clinical examination in the ability to detect clinically significant disease. 

Comment: This study provides additional evidence that image-based classification of ROP reliably detects clinically significant levels of ROP with high accuracy compared with the clinical examination.

ROP - Other Topics

Use of a Supplemental Oxygen Protocol to Suppress Progression of Retinopathy of Prematurity

This study compared the progression of retinopathy of prematurity (ROP) before and after institution of an oxygen therapy protocol at the University of Iowa Neonatal Intensive Care Unit to inhibit active proliferation and progression of ROP in premature infants. This was a retrospective cohort study was performed of premature infants undergoing ROP screening before (cohort A) and after (cohort B) implementation of an oxygen therapy protocol to inhibit further progression for those with stage 2 ROP or worse. In cohort B, oxygen saturation target was increased to ≥97% after diagnosis of prethreshold or worse ROP, based on the STOP-ROP trial, which showed a significant reduction in progression of stage 2 to stage 3 ROP. Oxygen saturations were kept at this level until ROP regression began. In cohort A, without oxygen therapy protocol (2002–2007), 44% (54/122) of infants progressed beyond stage 2, compared to 23% (24/103) of infants after protocol implementation (cohort B, 2008–2012) (P = 0.001). No significant differences between cohort A and B were found for gestational age, birth weight, survival, sepsis, bronchopulmonary dysplasia, oxygen at discharge, or need for diuretics. Infants with stage 2 ROP in cohort B, with oxygen therapy protocol, had significantly decreased risk of ROP beyond stage 2 (odds ratio 0.37, 95% confidence interval 0.20–0.67; P = 0.0013), compared to cohort A, correcting for differences in birth weight and necrotizing enterocolitis. Progression from stage 2 to stage 3 ROP in premature infants was significantly decreased after implementation of an oxygen therapy protocol, without a corresponding increase in pulmonary morbidity (unlike in the STOP-ROP trial). The lack of increase in pulmonary morbidity may be a result of the protocol used. In this study, to minimize hyperoxic exposure, effective oxygen exposure was limited to FiO2 ≤ 0.50–0.60 even if this meant that some infants did not consistently achieve the desired oxygen saturation of ≥97%. This study suggests that appropriate oxygen therapy may play a role in inhibiting progression of stage 2 ROP, potentially decreasing the risk of lifelong visual loss in this vulnerable population. Although this study is limited in that it is a retrospective cohort study, limiting the ability to control for nonsystematic changes in clinical practice, the results are compelling and support the im-
Implementation of a standardized targeted supplemental oxygen therapy approach to inhibit the progression of ROP.

The Economic Model of Retinopathy of Prematurity (EcROP) Screening and Treatment: Mexico and the United States.
Rothschild MI, Russ R, Brennan KA, et al

In many middle income countries where infant mortality rates are decreasing and NICU care is improving, a third epidemic of ROP is emerging. There are variable ROP screening guidelines in different countries with variable rates of ROP screening prevalence. This study aims to create an economic model of ROP screening and treatment in Mexico and the United States with the goal of better understanding the cost-effectiveness, cost-utility, and cost-benefit of an ideal ROP screening model. This study calculated direct and indirect costs of blindness in the US and Mexico to create their model. To do this the authors included a survey of the caregivers of blind children. The direct costs calculated included the costs of screening and treatment. The indirect costs were lost productivity of both the patient and the caretaker – this was determined using the surveys of the patients and caregivers and adjusting the numbers based on the country and gender of the caregiver. This study is different from other studies examining ROP cost effectiveness because it also surveyed the families and used region specific economic data to better understand the cost incurred by societal factors when a child is blinded by ROP. The authors measured utility and effectiveness in quality adjusted life years. The authors used this novel model to calculate the incremental net benefit in the US of an ideal ROP screening program as $3,628 per child ($205,906,959 per year) and $5,556 per child ($206,574,333 per year) in Mexico. The authors conclude that ROP screening and treatment is cost effective, cost saving and beneficial for quality of life for both the patient and the caregivers. The authors hope that ministers of health note the cost benefits of ROP screening and will direct resources in this area.

Colorado retinopathy of prematurity model: a multi-institutional validation study

This study assessed the specificity and sensitivity of the CO-ROP model in a larger and more geographically diverse population that the model in which it was first tested. Four institutions were included and records were retrospectively reviewed. This analysis included 858 infants. Of these 83 (9.7%) developed type 1 ROP, 23 (2.7%) developed type 2 ROP, 135 (15.7%) developed low-grade ROP, and 617 (71.9%) did not develop any ROP. Median weight gain for high-grade ROP, low-grade ROP, and no ROP, was 220g, 265g, and 416g respectively which was statistically significant. The CO-ROP algorithm had a sensitivity of
98.8% for type 1 ROP, 95.7% for type 2 ROP and 95.0% for all grades of ROP. The CO-ROP model would have reduced the total number of infants screened with no ROP by 31.3% and 23.9% for overall infants. Using the CO-ROP model, 1 infant with type 1 ROP, 1 with type 2 ROP, and 10 infants with low-grade ROP were missed. An advantage of the CO-ROP model is a simple one-time application formula. The one infant with type 1 ROP who was missed had significant edema so the measured weight at 1 month was non physiologic. This points to adding a small refinement to the algorithm looking for infant instability or non physiologic weight gain as infants who cannot be evaluated simply by this algorithm. The study is limited by its retrospective nature and the small number of infants who developed ROP.

9. STRABISMUS

Strabismus – double vision, binocular vision and visual perception

Extraocular muscle anatomy

Altered Protein Composition and Gene Expression in Strabismic Human Extraocular Muscles and Tendons

The purpose of this study was to determine whether structural protein composition and expression of key regulatory genes are altered in strabismic human extraocular muscles. Samples from strabismic horizontal extraocular muscles were obtained during strabismus surgery and compared with normal muscles from organ donors. Proteomics, standard and customized PCR arrays, and microarrays were used to identify changes in major structural proteins and changes in gene expression in muscles and connective tissue. Strabismic muscles showed downregulation of myosins, tropomyosins, troponins, and titin. Expression of collagens and regulators of collagen synthesis and degradation, the collagenase matrix metalloproteinase (MMP)2 and its inhibitors, tissue inhibitor of metalloproteinase (TIMP)1 and TIMP2, was upregulated, along with tumor necrosis factor (TNF), TNF receptors, and connective tissue growth factor (CTGF), as well as proteoglycans. Growth factors controlling extracellular matrix (ECM) were also upregulated. Among 410 signaling genes examined by PCR arrays, molecules with downregulation in the strabismic phenotype included GDNF, NRG1, and PAX7; CTGF, CXCR4, NPY1R, TNF, NTRK1, and NTRK2 were upregulated. Signaling molecules known to control extraocular muscle plasticity were predominantly expressed in the tendon rather than the muscle component. The medial and lateral rectus muscles displayed similar changes in protein and gene expression, and no
obvious effect of age. Quantification of proteins and gene expression showed significant differences in the composition of extraocular muscles of strabismic patients with respect to important motor proteins, elements of the ECM, and connective tissue. This study supports the emerging view that the molecular composition of strabismic muscles and tendons is substantially altered. This study is the most comprehensive quantitative study to date that surveys changes in expression of both proteins and genes in strabismic human EOMs and supports the growing appreciation that connective tissue, including ECM and fibroblasts surrounding the EOMs, is critical for the function of EOMs and ocular alignment.

Rectus Extraocular Muscle Size and Pulley Location in Concomitant and Pattern Exotropia

In this prospective case-control study, the authors aim to use MRI to determine whether rectus extraocular muscle (EOM) sizes and pulley locations contribute to exotropia. Nine patients with concomitant exotropia, 6 patients with pattern exotropia, and 21 orthotropic normal control participants underwent high-resolution surface-coil MRI scans obtained in contiguous, quasicoronal planes. Rectus pulleys were located differently in patients with A-pattern, versus V- and Y-pattern, exotropia. The lateral rectus (LR) pulleys were displaced significantly superiorly, the medial rectus (MR) pulleys were displaced inferiorly, and the inferior rectus pulleys were displaced laterally in A-pattern exotropia. However, the array of all rectus pulleys was excyclorotated in V- and Y-pattern exotropia. The volume of the medial rectus muscle was statistically subnormal by approximately 29% in concomitant, but not pattern, exotropia (P < 0.05). The LR volume to MR volume ratio in concomitant exotropia was significantly greater than in control participants and those with pattern exotropia (P < 0.05). The authors conclude that abnormalities of EOMs and pulleys contribute differently in pattern versus concomitant exotropia. Abnormal rectus pulley locations derange EOM pulling directions that contribute to pattern exotropia, but in concomitant exotropia, pulley locations are normal, and relatively small medial rectus size reduces relative adducting force.

Comment: This paper contains images and biomechanical analyses that are very convincingly support the authors’ conclusions stated above. This interesting paper sheds a good deal of light on the pathophysiology of a very common clinical entity in the practice of pediatric ophthalmology.

Anterior Segment Optical Coherence tomography of the horizontal and vertical extraocular muscles with measurements of the insertion to limbus Distance.
In many instances such as reoperations, unknown previous muscle surgery, complex strabismus, it is of great importance to know the location of the extraocular muscles, in order to formulate an appropriate plan prior to surgical intervention. This article assesses the possibility of determining the insertion distance from the limbus of horizontal and vertical rectus muscles with anterior segment optical coherence tomography (AS-OCT). The right eyes of 46 patients underwent AS-OCT. The horizontal and vertical extraocular rectus muscle insertion distances from the limbus were measured in a masked fashion by two pediatric ophthalmologists. Forty-two lateral rectus, 43 medial rectus, 35 inferior rectus, and 40 superior rectus muscles of the right eyes of 46 patients were included. Insertion to limbus measurements (mean ± SD) were as follows: lateral rectus = mean 6.8 ± 0.7 mm, range = 4.8 to 8.4 mm; medial rectus = mean 5.7 ± 0.8 mm, range = 4.3 to 7.8 mm; inferior rectus = mean 6.0 ± 0.6 mm, range = 4.8 to 7.0 mm; superior rectus = mean 6.8 ± 0.6 mm, range = 5.5 to 8.1 mm. The intraobserver and interobserver correlation coefficients for the insertion to limbus measurements of all four rectus muscles excellent. This study shows that AS-OCT is capable of imaging all horizontal and vertical muscle insertions as well as the distance from the limbus and that the measurements were consistent and reproducible between different examiners. This might have future implications for the preoperative procedure planning in patients who have had previous surgery.

Classifying medial rectus muscle attachment in consecutive exotropia


This study examined inter observer agreement when classifying medial rectus muscle attachment in patients with consecutive exotropia. Two examiners independently classified the attachment as normal, stretched scar, or slipped muscle. Twenty-six eyes of 25 patients with consecutive exotropia with a mean age of 43.5 years were evaluated. Agreement was found in 15/26 (58%). The majority (n=7) of disagreements were between stretched scar and slipped muscles. The largest source of the diagnostic confusion was muscles having features of both. Therefore the authors opine that these two entities should be combined and termed “abnormal scleral attachment”. The study was small and lacks a “gold standard” for diagnosis. Also the authors reviewed photographs and therefore did not have the opportunity to assess muscle tensile strength.

Spectral domain optical coherence tomography to assess the insertion of extra ocular rectus muscles


This study determined the horizontal rectus muscle insertion distance to the limbus using SD-OCT in a large, white population, to assess reproducibility and determine if there are any correlations with sex, age, and axial length. There were 187 participants and all were self-described as white. The mean age was 43.7
years. The lateral and medial rectus insertions could be identified in 87% and 93.6% of patients respectively. The majority (70%) of failures were due to poor image quality and poor cooperation while the remainder (30%) were technical issues. In children <12 years old imaging success rate was 90%. The mean medial rectus distance to the limbus was 5.22mm and the lateral rectus distance was 6.47mm. Neither age, nor axial length was correlated however males had a larger distance from the rectus insertion to the limbus than females. There was no attempt to look at confounding factors such as height.

**Accessory Extraocular Muscle as a Cause of Restrictive Strabismus**

This paper describes a series of 7 patients with the following clinical characteristics: atypical strabismus, enophthalmos, restriction to eye movements in most fields of gaze, and presence of an anomalous orbital structure that was interpreted on magnetic resonance imaging (MRI) to be an accessory extraocular muscle inserting onto the posterior surface of the globe in the affected eye. The left eye was affected in all 4 males and the right eye was affected in the 3 females. The fellow eye was normal in all cases. Five of the 7 patients underwent surgical correction with partial improvement in only one patient. The authors recommend including an accessory extraocular muscle in the differential diagnosis of patients with atypical restrictive strabismus, especially when globe retraction is observed with the patient looking straight ahead. Orbital computed tomography or MRI are essential for correct diagnosis in these cases. The paper provides good illustrative neuroimaging of the presumed accessory extraocular muscle, however, there was no histopathological confirmation that the anomalous orbital structure consisted of muscle tissue.

**Strabismus – Superior oblique palsy**

Rectus Pulley Displacements without Abnormal Oblique Contractility Explain Strabismus in Superior Oblique Palsy
Suh SY, Le A, Clark RA, Demer JL. *Ophthalmology* June 2016;123:1222-1231

The authors prospectively evaluated 24 patients with superior oblique (SO) palsy and SO atrophy on MRI and 19 age-matched control patients. Pulley locations in oculocentric coordinates in the following subgroups of patients with SO palsy were compared with normal results in subgroups of patients with SO palsy: unilateral versus bilateral, congenital versus acquired, and isotropic (round) versus anisotropic (elongated) SO atrophy. Expected effects of pulley displacements were modeled using Orbit 1.8
computational simulation software. Rectus pulleys typically were displaced in SO palsy. In unilateral SO palsy, on average the medial rectus (MR) pulley was displaced 1.1 mm superiorly, the superior rectus (SR) pulley was displaced 0.8 mm temporally, and the inferior rectus (IR) pulley was displaced 0.6 mm superiorly and 0.9 mm nasally from normal. Displacements were similar in bilateral SO palsy, with the SR pulley additionally displaced 0.9 mm superiorly. However, the lateral rectus pulley was not displaced in either unilateral or bilateral SO palsy. The SR and MR pulleys were displaced in congenital SO palsy, whereas the IR and MR pulleys were displaced in acquired palsy. Pulley positions did not differ between isotropic and anisotropic palsy or between patients with cyclotropia of less than 7 degrees versus cyclotropia of 7 degrees or more. Simulations predicted that the observed pulley displacements alone could cause patterns of incomitant strabismus typical of SO palsy, without requiring any abnormality of SO or inferior oblique strength.

Comment: This interesting paper further elucidates the complexity of the biomechanics of the extraocular muscles and their respective pulleys. However, clinical application of imaging for patients with examination findings consistent with SOP and the direct impact of imaging on outcomes is unclear. This paper suggests that with additional study, imaging may be common in the evaluation of SOP in the future.

Strabismus – Childhood XT and ET

Type 4 Duane syndrome


Duane syndrome encompasses a spectrum of strabismus entities that have common features, including misinnervation and co-contraction of extraocular muscles in addition to enophthalmos with palpebral fissure narrowing. The purpose of this retrospective study was to identify and describe cases of synergistic divergence whose characteristics suggest that this entity is a form of Duane syndrome. The records of all patients with a Duane syndrome diagnosis, including standardized eye position photographs, from the E-Consultation program of Cybersight, Orbis International were analyzed. A total of 350 Duane syndrome cases were identified. Of these, 19 (5%) had features consistent with synergistic divergence, or type 4 Duane syndrome. Of the 19, 16 (84%) were male, 15 (79%) had palpebral fissure narrowing, all had anomalous head posture, and 18 (95%) were exotropic. Only 9 (47%) patients were reported to have undergone surgery. The authors conclude that synergistic divergence is a rare entity with features similar to those of Duane syndrome.
They suggested that this entity be classified as type 4 Duane syndrome, because it has unique findings and an innervation pattern that differs from the other three recognized types. This entity that is described can certainly be considered a type of Duane syndrome or in more general terms congenital cranial dysinnervation disorder (CCDD). Many clinicians tend to shy away from classifying Duane syndrome into types and prefer a more simplified approach looking at the primary deviation and the head position.

Childhood esotropia: child and parent concerns


Few studies to date have evaluated how esotropia affects children in their everyday lives. This cross-sectional prospective study was conducted as a preliminary stage in developing a new patient-reported outcome measures for pediatric eye conditions. The purpose of the study was to identify specific health-related quality of life (HRQOL) concerns affecting children with esotropia as expressed by children or one of their parents (proxy) and concerns affecting the parents themselves. Sixty children with esotropia (0-17 years of age) and 1 parent for each child were enrolled. Individual semi-structured interviews were conducted with children aged 5-17 years (n = 40) and 1 parent each for child ages 0-17 years. Transcripts of recorded interviews were evaluated using NVivo software. Specific concerns were identified from both child and parent interviews and coded. From these specific codes, broad themes were identified. Frequency of each theme was calculated, along with the frequency of specific codes within each theme. Regarding the child's experience 6 broad themes were identified: visual function (mentioned by 32 of 40 children (80%) and by 50 of 60 parents (proxy assessment of child, 83%), treatment (78% and 85%), emotions (65% and 67%), social (58% and 68%), and physical (58% and 32%), and worry (45% and 7%). Regarding the parents' own experience, 5 broad themes were identified: treatment (59 of 60 parents, 98%), worry (97%), emotions (82%), compensation for condition (80%), and affects family (23%). A wide range of concerns were identified from interviews of children with esotropia and their parents. Concerns reflect the impact of esotropia in physical, emotional, and social domains. The authors intend to use specific concerns for the development of questionnaires to quantify the effects of esotropia on children's and parents' quality of life. It seems that the group of chosen participants was very diverse. Eligible participants had a wide range of ocular problems and were
grouped into one: esotropia, exotropia, hypertropia, nystagmus, amblyopia, refractive error, orbital condition, anterior segment, retina, and central nervous system (27% had a concurrent diagnosis). Global delay was noted in 20%. While all patients had a history of esotropia, some were not frankly esotropic at the time of the interview. Authors acknowledge this and state that the aim of the study was to identify concerns from a diverse population of children with esotropia.

A comparative study of adjustable and non-adjustable sutures in primary horizontal muscle surgery in children
A M Kamal, D Abozeid, Y Seif and M Hassan Eye Nov 2016; 30: 1447-1451; advance online publication, July 15, 2016; doi:10.1038/eye.2016.144

The authors conducted a prospective randomized study comparing adjustable vs non adjustable suture technique in the treatment of children with horizontal strabismus. 30 children were in each group. When adjustment was made, it was done with propofol 1-4 hours post op. In the adjustable suture group, 66% were within target at their immediate post op evaluation and did not require adjustment. The results of our study show statistically nonsignificant differences between these two groups. However, the success rate was clinically higher in the adjustable group. The authors conclude that if the long term alignment if better with adjustable sutures, the added time and cost may be justified, but superiority was not demonstrated in this study.

A Randomized Trial Evaluating Short-term Effectiveness of Overminus Lenses in Children 3 to 6 Years of Age with Intermittent Exotropia

In this randomized, clinical pilot trial, the authors aim to evaluate the short-term effectiveness of overminus spectacles in improving control of childhood intermittent exotropia (IXT). 58 children aged 3 to <7 years with IXT were randomly assigned to overminus spectacles (-2.50 D over cycloplegic refraction) or observation (non-overminus spectacles if needed or no spectacles) for 8 weeks. Outcome testing was conducted with children wearing their study spectacles or plano spectacles for the children in the observation group who did not need spectacles. At 8 weeks, mean distance control was better in the 27 children treated with overminus spectacles than in the 31 children who were observed without treatment (2.0 vs. 2.8 points, adjusted difference = -0.75 points favoring the overminus group; 2-sided 95% confidence interval, -1.42 to -0.07 points). Side effects of headaches, eyestrain, avoidance of near activities, and blur appeared similar between treatment groups. The authors concluded that for a pilot study, overminus
spectacles improved distance control at 8 weeks in children aged 3 to<7 years with IXT.
Comment: Whether the improvement in IXT control is lasting or not, overminus glasses may at least be considered to temporize and defer surgery until an older age. PEDIG is currently enrolling IXT patients in a larger study of overminus glasses.

**Accommodative ET-High AC/A Ratio Esotropia: The Case for Glasses**

Presenting the argument for bifocals for patients whom are corrected with 8 prism diopters, monofixational fusion, at distance yet have persistent Over-convergence at near. This is based on the assumption that the patient had single binocular vision prior to the onset of the esotropia and therefor is capable of awakening dormant fusional ability. The author prescribes full cycloplegic refraction with a +2.50 D bifocal on presentation. The Rx is then pulled back as needed, which instills confidence in the family that treatment is working and less is required, versus adding a bifocal at a subsequent visit. Some argue that this weakens the accommodative ability and may cause early presbyopia. The author, and other reports, reason that prolonged accommodation alters the anatomic and physiologic characteristics of the medial rectus muscles which leads to decompensation and need for surgical correction.

**High AC/A Ratio Esotropia: Do We Really Need to Be Using Bifocals?**

Examine the role of bifocals in the treatment of residual esotropia at near despite acceptable distance alignment; is it necessary for all patients? The literature data supporting the use and long term outcomes of bifocal use in patients with a high AC/A ratio is minimal. In fact, the data, which has small sample sizes, states there is no difference in sensory status or deterioration rate between patients treated with bifocals and those that aren’t. Ludwig and Parks observed that children with a high AC/A ratio decompensated, requiring surgery, more often than children with without a high AC/A ratio. This correlation was independent of the use of bifocals, and there was no protective effect from the bifocal. The author also questions why a child does not use their bifocal readily if it produces binocular vision, unlike patients with nerve palsies who adopt a head position to attain single binocular vision. There is also a role for surgery in patients with a distance near discrepancy of the esotropia, and a number of authors have shown that it does not increase the risk of consecutive exotropia and in many cases eliminates the need for bifocals and even glasses all together.
Intermittent Exotropia: Characteristics and Overview

Intermittent divergent misalignment of the eyes occurs more frequently in females, people at sunny latitudes, monozygotic twins, and with a positive family history. There are four types of Intermittent exotropia: 1) Basic: Near and Distance deviation within 9 prism diopters, 2) Divergence excess: Distance deviation > 10 prism diopters than near, 3) Simulated divergence excess: the near deviation is initially < 10 prism diopters than distance but this equalizes with monocular occlusion, 4) Convergence Insufficiency: near deviation > 10 prism diopters than distance. Deviation control has been traditionally described as poor, fair, and good. There have been a number of scales/scores in the literature but they are not widely used. There is also a great deal of variability in control from moment to moment. The angle of deviation can also vary, and determining the amount of real change is dependent on the baseline angle. Stereoacuity is also a function monitored for deterioration and threshold is defined as a change of two octaves on test-retest data. We also must take into account symptoms and quality of life scores in our decision

Accommodative and Fusional Convergence in Intermittent Exotropia

The article is a review of 50 relevant articles to look at the role of accommodation and fusional convergence on intermittent exotropia. One hypothesis is that since accommodation and convergence are synkinetically linked that explains the distance/near disparity. Monocular occlusion for 1 hour should disrupt the fusional convergence and decrease the disparity. Over-minus therapy improves intermittent exotropia control by stimulating accommodation, this has not been shown to alter the underlying refractive error. For patients whose fusional convergence is triggered by retinal image disparity over-minusing may not work, but those triggered by retinal blur may improve with over-minus. The evaluation and management of intermittent exotropia required the assessment of fusion, control, accommodation, and convergence.

Intermittent Exotropia and Mental Illness

Children with intermittent exotropia have a three-fold increase in the incidence of mental illness in early adulthood, worse in males than females. There is a known negative psychosocial impact on patients with strabismus; it affects their self-esteem, academic performance, interpersonal relationships, athletic achievement, and gainful employment. Two correlations between exotropia and mental illness have been made, a link between constant exotropia and schizophrenia in adults linked to gene PMX2B and a higher incidence of strabismus in children of
schizophrenics. Successful surgery was not associated with a decrease in the incidence of mental illness in patient with intermittent exotropia according to Kilgore. The author concludes that frank mental illness in patients with exotropia has little to do with the psychosocial aspect and more to go with genetic predisposition or multifactorial factors.

**Historical Perspective: Nonsurgical Treatment of Intermittent Exotropia**


The first documented treatment for exotropia, a mask, was in 600 A.D and it was used until the 1700s. Occlusion therapy of the sound eye was introduced by Saint Yves and Buffon in the 1700s and the stereoscope was invented in 1838 to stimulate convergence. In the 1860s the father of orthoptics, Louis Emil Javal discovered that strabismus is an anomaly of binocular vision and promoted occlusion therapy to inhibit suppression and encourage fusion. The amblyoscope was invented in the early 1900s by Cla...
tenotomy, plication, hang-back procedures, and single muscle recessions all can be found in very early writings on strabismus. New progress has been made with the use of Botox and Bupivacaine injections. The area which further progress is needed is determining the amount of initial over-correction to aim for.

**Current Nonsurgical Management of Intermittent Exotropia**

Three nonsurgical management strategies for pediatric intermittent exotropia are observation, part-time occlusion, and over-minusing. The incidence of deterioration in observational studies is low, 7-12%, making it a very reasonable option. Based on the theory that part-time occlusion has an anti-suppression effect which than improves control and reduces incidence of deterioration, it is a commonly used therapy for intermittent exotropia in patients that have stereocuity. A PEDIG multicenter randomized clinical trial showed no statistical difference between part-time patching and observation alone. Over-minus spectacles improve control by one of two theoretical mechanisms: stimulating accommodation or fusional convergence. Preliminary data suggests that over-minus spectacles improves control of intermittent exotropia at distance.

**Congenitally impaired disparity vergence in children with infantile esotropia**

This study looked at 19 children aged 5-12 years and treated successfully (to ≤6 PD of strabismus) for infantile esotropia (ET) with short duration (≤3 months, n=10) compared with long duration (≥5 months, n=9) of constant misalignment prior to correction, and healthy controls (n=22). Eye movements during disparity vergence and accommodative vergence were recorded using an EyeLink 1000 binocular eye tracker. Mean response gain was compared between and within groups to determine the effect of duration of misalignment and viewing condition. Compared with controls, children with short (P = 0.002) and long (P < 0.001) duration infantile ET had reduced response gains for disparity vergence (28% and 49% reductions respectively), but not for accommodative vergence (P = 0.19). Regardless of duration of misalignment, children with infantile ET had reduced disparity vergence, consistent with a congenital impairment of disparity vergence in infantile ET. However, it is also clear that disparity vergence may be further degraded when constant misalignment is prolonged early in life. Although early correction of misalignment increases the likelihood that some level of binocular disparity sensitivity will be present, normal levels may never be achieved. This study challenges the currently accepted acquired explanation for a disparity vergence impairment that is supported by studies showing that early intervention can result in normal disparity vergence in nonhuman primate models of infantile ET.
Longitudinal development of refractive error in children with accommodative esotropia: onset, amblyopia, and anisometropia

This retrospective study looked at longitudinal changes in refractive error in children with accommodative esotropia over the first 12 years of life. Children had to have hyperopia > +4.00 D at initial cycloplegic refraction, which had to be prior to 4 years of age, at least 3 visits, and at least one visit between 7 and 12 years of age. Children were classified as infantile (n=30, onset ≤12 months) or late-onset (n=78, onset 18-48 months) accommodative esotropia. The initial visit right eye spherical equivalent refractive error was similar for the infantile (+5.86 ± 1.28) and late-onset (+5.67 ± 1.26) groups. Neither group had a significant decrease in hyperopia before 7 years of age, but after 7 years, the infantile group experienced a myopic shift of -0.43 D/year. The late-onset group did not experience a myopic shift at 7-12 years. Among amblyopic children, a slower myopic shift occurred in the amblyopic eye. Among anisometropic children, the more hyperopic eye experienced more myopic shift than the less hyperopic eye. Patient care was at the discretion of the referring ophthalmologists, and the study did not assess whether weaning of glasses prescription, small residual deviations with full correction, or larger residual deviations requiring surgery influences refractive changes over time. In addition, it is possible that some of the late-onset patients were actually infantile accommodative esotropes that were diagnosed late. Still, this study does provide a compelling reference for clinicians to describe longitudinal prognosis for patients with accommodative esotropia.

Bifocals Fail to Improve Stereopsis Outcomes in High AC/A Accommodative Esotropia
Whitman MC, MacNeill K, Hunter DG
*Ophthalmology* April 2016;123:690-696

In this retrospective cohort study the authors reviewed the charts of 180 patients with high AC/A relationship (77 used bifocals and 103 used single-vision lenses) to assess whether stereopsis outcomes are better after treatment with bifocal than with single vision lenses. The authors compared the two groups regarding stereopsis at final follow-up, difference in stereopsis between final and initial visits, progression to strabismus surgery, included final near and distance deviations. Bifocals did not improve stereopsis outcomes compared with single-vision lenses. In both groups, stereopsis was similar at the initial and final visits, with similar improvement in both groups. Children in the bifocal group had a 3.6-fold higher rate of strabismus surgery than children in the single-lens group (P=0.04.) Additionally, children in the bifocal group had near deviations 4 PD larger than those with single lenses at final follow-up, even after controlling for
age and initial deviation (P=0.02). These results did not change if surgical patients were eliminated or in the subgroup with initial distance deviation of 0 PD in full hyperopic correction.

Comment: The data provide interesting and sobering perspective on the commonly accepted practice of prescribing bifocals in the management of high AC/A ratio. However, since this is a retrospective study, patients were not randomized to bifocals vs single vision glasses. One might hypothesize that possibly the “worse” cases of high AC/A ratio received bifocal and more mild cases were treated with single vision glasses given that the mean initial near angle was significantly greater in the bifocal patient group than in the single vision glasses group. I am curious to know if bifocals were used in the more mild cases whether a better sensory outcome would be achieved in the mild cases.

Acute acquired concomitant esotropia and decompensated monofixation syndrome: a sensory-motor status assessment
Savino G, Abed E, Rebecchi MT, Spreca M, Tredici C, Dickmann A

Acute acquired concomitant esotropia (AACE) is characterized by the acute onset of large-angle esotropia and diplopia in the absence of significant refractive errors. The differential diagnosis of AACE includes central nervous system (CNS) diseases, acute comitant refractive esotropia and decompensated monofixation syndrome (MFS). It is very important to discriminate between AACE and decompensated MFS because the surgical treatment of these two forms of strabismus has different functional and aesthetic outcomes. In AACE, correct surgical management may lead to a complete eye alignment with restoration of normal binocular vision (NBV) and stereopsis. Conversely, in decompensated microtropia, the treatment may achieve only a small-angle strabismus with incomplete stereopsis. Distinguishing between the two entities may be challenging. The authors’ objective, in this retrospective, comparative case series was to characterize the sensory-motor status and clinical features of these two entities, AACE and MFS, under environmental conditions and after prismatic adaptation test and progressive prism test. They enrolled 26 patients with a confirmed postoperative diagnosis of acute acquired concomitant esotropia (group A) (N=14, mean age 17.6 years, range 4–40 years) and monofixation syndrome (group B) (N=12, mean age 10.3 years, range 5–19 years). The diagnosis was established retrospectively, postoperatively, patients with normal binocular vision, normal fusional central vergences, and a stereoscopic acuity ≥120″ after surgery were defined as having AACE. Conversely, for cases with postoperative suppression or abnormal retinal correspondence (ARC) and a stereoscopic acuity <120″, a diagnosis of decompensated MFS was established. All of the patients of group A and 4 patients (33%) of group B experienced diplopia under viewing conditions in the Worth’s 4 dot and Bagliolini striated glass tests. The TNO stereo test showed the total absence of
stereopsis in six patients in group B and a significantly lower stereo acuity in the remaining six patients compared to group A (p < 0.0001). The value of the angle of deviation after the progressive prism test was significantly higher in group B than in group A (p=0.02). At the end of the progressive prism test, all of the patients in group A and only 2 patients in group B were orthotropic (p=0.01). Even though this case series is small, the sensorimotor characteristics of the two groups are substantially different. Unfortunately there are several limitations that could lead to potential bias. Apart from being retrospective, the demographic characteristics of the two groups are different by age and gender (Group A is predominantly female). The authors conclude that Bagolini striated glass and Worth’s 4 dot tests under viewing conditions and responses under prisms allow for the differentiation of the 2 forms and lead to an accurate aesthetic and functional prognosis.

Symptoms in Children with Intermittent Exotropia and Their Impact on Health-Related Quality of Life

35 children (5-13 years) with intermittent exotropia (IXT) completed a 22-item symptom and a health-related quality of life (HRQOL) questionnaire. The most frequently reported symptoms were: rubbing the eye (83%), problems with eyes in the sun (63%), and the eyes feeling tired (63%). Interestingly, 29% of children reported diplopia, a much higher rate than reported in previous studies. Worse child IXTQ HRQOL scores were associated with symptoms of difficulty focusing eyes (P=0.0007), double vision (P=0.007), eyes hurting (P=0.006), and problems with eyes in the sun (P=0.06). The authors propose the use of a symptom survey with just the 7 questions associated with reduced HRQOL to better understand the effects of IXT on an individual child and possibly help direct management. The sample size was small so the findings should be validated in a larger, more heterogeneous population.

Strabismus – Convergence / Divergence insufficiency

Adult-onset chronic divergence insufficiency esotropia: clinical features and response to surgery
Ridley-Lane M, Lane E, Yeager LB and Brooks SE. J AAPOS 2016;20:117-120.

This study investigated baseline characteristics and surgical outcomes of patients with adult-onset chronic divergence insufficiency esotropia treated with unilateral or bilateral recession of the medial rectus muscle. This was a retrospective review over a 12 year period of patients >=45 years of
age with adult onset esotropia (distance deviation exceeded the near deviation by at least 10 prism diopters). There were a total of 27 patients (23 females, all caucasian) with an average age at presentation of 72.3 years and a mean follow-up of 14.2 months. The census data from this region of the country and a random sampling of 60 patients from the practice showed a % of females of 51 and 58 respectively and a caucasian % of 77 and 73 respectively. The study group had a statistically significant greater population of females and caucasians. 12/27 study patients had very mild abduction deficits preoperatively. Eighteen patients underwent bimetal rectus resections; no patient in this group was overcorrected and two required additional surgery. Nine patients underwent a unilateral medial rectus recession; no patient in this group was overcorrected and 1 required additional surgery. Surgical dose-response was significantly lower in both groups compared to expected. Interestingly the dose-response was found to correlate directly with the preoperative angle of strabismus. The authors feel that in this group of patients the findings are consistent with a mechanism involving gradual decreased medial rectus elasticity.

**Strabismus – Acquired**

Is strabismus the only problem? Psychological issues surrounding strabismus surgery


This prospective cross-sectional study of 220 consecutive adult patients undergoing strabismus surgery, was presented as the Philip Knapp Lecture at the 40th Annual Meeting of APPOS in April, 2014. Strabismus can have a negative psychosocial effect on an individual’s quality of life. While correction of strabismus may improve quality of life, this is not always the case, even if realignment is achieved. Surgeons need to understand patients’ expectations of postsurgical outcomes and the impact surgery has on their psychosocial well-being. All participants had completed clinical assessments before surgery and again 2 weeks and 3 months after surgery. Standardized self-reported psychological questionnaires were completed preoperatively and 3 and 6 months postoperatively. Of 220 patients included in the study (mean age, 45 years), 54% were female, 81% were Caucasian, and 58.6% had a concomitant deviation. Prior to surgery, 24% of study participants were experiencing clinical levels of anxiety; 11% were suffering clinical levels of depression, which are 10 times higher than the general population. Quality of life improved and anxiety and depression were reduced after surgery. Approximately 6% of the sample regretted having undergone surgery either at 3 or 6
months after treatment. Authors conclude that it is important to identify patients who are experiencing significant psychosocial distress and to assess their postsurgical expectations in order to improve the outcomes of strabismus surgery. They also suggest that presurgical psychosocial support should be considered for these patients. Unfortunately, the data in this study is presented in a more descriptive form and is not fully statistically analyzed. Hence, the impact of surgery the patients’ well-being is not fully appreciated and possibly moderated. Limitations were also not discussed, such as selection bias. Despite all of this, this work highlights the importance of understanding the psychological issues that are associated with strabismus surgery, which is seminal for good patient-doctor communication.

Incidence and Etiologies of Acquired Third Nerve Palsy Using a Population-Based Method

The incidence and etiology of acquired 3rd nerve palsies are not well-known. One of the most potentially life-threatening etiologies is brain aneurysm. This study analyzes date from the Rochester Epidemiology Project, which captures medical data on all the residents of Olmstead County, Minnesota. The study period was 1978-2014. The authors found 45 newly diagnosed cases of acquired third nerve palsy which yielded an age- and sex-adjusted annual incidence of acquired third nerve palsy of 4.0 per 100 000. Older patients, specifically older than 60 had a higher incidence that patients who were younger than 60 (12.5 vs 1.7 per 100 000; P < .001). The most common causes of acquired third nerve palsy were presumed microvascular (42%), trauma (12%), compression from neoplasm (11%), post-neurosurgery (10%), and compression from aneurysm (6%). Ten patients (17%) with microvascular third nerve palsies had pupil involvement, while pupil involvement was seen in 16 patients (64%) with compressive third nerve palsies. Compared with previous studies, there was a higher incidence of microvascular disease than compressive lesions. Of the 9 patients with aneurysm, the location in 3 patients was posterior communicating artery and in 5 patients was cavernous sinus.

Conclusion: Although this study highlights the importance of identifying whether an acquired 3rd nerve palsy involves the pupil, there were patients who presented with a compressive lesion without pupil involvement. Therefore thorough neurologic evaluation, including neuroimaging, is vital for all patients with acquired 3rd nerve palsies.

Third Nerve Palsies—Less Frequent but Just as Concerning
In this invited commentary, the author notes that the study’s results are more likely generalizable because it is a population-based analysis, which minimizes referral bias. However, she notes that there are problems with retrospective studies. For example, if the encounter is not coded properly, this may underrepresent certain etiologies, for example 3rd nerve palsies caused by posterior communicating artery aneurysm, the most feared etiology because of its high mortality and morbidity. Fifteen percent of patients die before getting to the hospital, another 40% die in the hospital, and more than one third of survivors suffer major neurological deficits. Thus non-invasive vascular neuroimaging is indicated and approaches almost 100% detection rate of PCA aneurysms large enough to cause a 3rd nerve palsy. She cautions though, that an experienced neuroradiologist is key in interpreting an MR or CT angiogram, since PCA aneurysms have been missed, with dire consequences.

**Strabismus in Adults Older than 60 years.**

This study investigates the epidemiology of adult strabismus, its etiology and treatment methods in patients older than 60 years of age in a tertiary care center. A total of 291 patients were included in the study. The most common cause of presentation was diplopia. The majority of the patients had an acquired etiology of strabismus (non-neurologic such as divergence insufficiency, sensory exotropia, after glaucoma or retinal surgery, and after orbital trauma), 11.3 % presented with a cranial nerve palsy, 19.2% had thyroid eye disease, and 7.9 % had presumed myotoxic causes related to strabismus post cataract surgery. Surgical (extraocular muscle surgery or botulinum toxin injection) and non- surgical (prism glasses, orthoptic exercises, occlusion of an eye) methods were used to address their main complaint. The most common treatment was prism glasses (37%). The authors conclude that this epidemiologic study can be used to prevent, diagnose and treat patients 60 years old and older through greater awareness and increased education of both primary care physicians and general ophthalmologists.

**Development of Monofixation Syndrome After Extraction of Dense Cataract.**

This article tests the hypothesis that decreased macular input caused by dense cataracts may cause monofixation syndrome in adults. A retrospective chart review identified twenty-one patients(n=21) with dense unilateral cataract (best-corrected visual acuity of 20/200 or worse), present for at least 3 months. Patients (n=17) with unilateral cataract present for at least 3 months and best-corrected visual acuity of 20/30 were included in the control
The study is limited by the small number of subjects, the fact that there were no data available of patients prior to developing dense cataracts as well as the lack of a detailed strabismus examination preoperatively.

**Strabismus – Misc**

**Changes in the axis of astigmatism and in fundus torsion following inferior oblique muscle weakening.**


The aim of this prospective cross-sectional study was to investigate whether changes in fundus torsion after inferior oblique (IO) weakening would be associated with similar torsional changes in the axis of astigmatism in corneal topography. The degree of fundus torsion and corneal astigmatism were prospectively evaluated before and 3 months after IO myectomy in consecutive patients with IOOA grade +2 or more in one or both eyes and an astigmatic error of 1 D or more. Fundus torsion was evaluated by measuring the disk foveal angle (DFA) using fundus photography. The axis of astigmatism was identified from the anterior sagittal map using Pentacam corneal imaging. A total of 54 eyes of 27 patients were included. Patients were divided into two groups: those with esotropia and those with exotropia. All patients had a preoperative DFA >8 degrees, which decreased postoperatively in both groups (P < 0.01). Postoperatively, there was incyclorotation of the axis of astigmatism by >5 degrees in 80% of the esotropic group and 75% of the exotropic groups (P < 0.01). The present study showed incyclorotation of the axis of astigmatism after IO myectomy. The authors conclude that the measurement of the change in the axis of astigmatism can be used to
assess torsional changes after IO myectomy in patients with IOOA. However, the study could not demonstrate a statistically significant correlation between the disk foveal angle and the degree of change in axis of astigmatism.

**Improvement of Eye Alignment in Adult Strabismic Monkeys by Sustained IGF-1 Treatment**

The goal of this study was to determine if continuous application of insulin-like growth factor-1 (IGF-1) could improve eye alignment of adult strabismic nonhuman primates and to assess possible mechanisms of effect. The theory behind this study is that sustained delivery of IGF-1, and the potential slow and gradual changes associated with such delivery, would avoid the large single change in eye alignment often associated with surgical intervention and, therefore, allow plasticity mechanisms in the visual system and/or ocular motor system to adapt to the change in eye alignment. A continuous release pellet of IGF-1 was placed on one medial rectus muscle in two adult nonhuman primates (M1, M2) rendered exotropic by the alternating monocular occlusion method during the first months of life. Eye alignment and eye movements were recorded for 3 months, after which M1 was euthanized, and the lateral and medial rectus muscles were removed for morphometric analysis of fiber size, nerve, and neuromuscular density. Monkey 1 showed a 40% reduction in strabismus angle, a reduction of exotropia of approximately 11° to 14° after 3 months. Monkey 2 showed a 15% improvement, with a reduction of its exotropia by approximately 3°. The treated medial rectus muscle of M1 showed increased mean myofiber cross-sectional areas. Increases in myofiber size also were seen in the contralateral medial rectus and lateral rectus muscles. Similarly, nerve density increased in the contralateral medial rectus and yoked lateral rectus. This study demonstrates that in adult nonhuman primates with a sensory induced exotropia in infancy, continuous IGF-1 treatment improves eye alignment, resulting in muscle fiber enlargement and altered innervational density that includes the untreated muscles. This supports the view that there is sufficient plasticity in the adult ocular motor system to allow continuous IGF-1 treatment over months to produce improvement in eye alignment in early-onset strabismus. Although this is not yet refined enough for practical application of this in humans, this study suggests that sustained delivery of IGF-1 has potential for augmenting strabismus surgery and providing lasting results.

**A simple and novel grading method for retraction and overshoot in Duane retraction syndrome**
Strabismus in Duane retraction syndrome is frequently associated with significant globe retraction and overshoots. However, there is no method to objectively grade retraction and overshoot. In this report, the authors propose a novel objective grading method to standardize measurements. The authors describe grading for globe retraction that ranges from 0 with no narrowing to 4 with ≥75% of narrowing. Vertical lid fissure height measurements were done on external eye movement photographs in lateral gazes comparing the involved vs. non-involved eye. In this grouping, bilateral Duanes were excluded. Grading for overshoots were also graded 0 to 4. On photographs, a straight line parallel to intermedial canthal line was drawn. Grade of 0 means that the line bisects the pupil of the involved eye. When the cornea disappears below the lid is considered grade 4. Photographs were then graded by two strabismologists. Interobserver agreement was calculated using Cohen’s kappa. The study included 60 patients with unilateral DRS. Among these, 45 had photograph grading and 15 patients had clinical grading. Globe retraction showed good interobserver agreement defined as kappa >0.7 using photographs and clinic grading. Grading of overshoot showed excellent agreement defined as >0.8, both using photographs and clinical assessment. The authors discuss the importance of taking photographs with proper degree of adduction. This grading system does not apply to bilateral DRS and type 4 DRS (synergistic divergence). Also, this will not work for cases with coexisting vertical deviation.

Assessing Geographic Variation in Strabismus Diagnosis among Children Enrolled in Medicaid

In this retrospective cohort study, the authors sought to determine how strabismus diagnosis varies within a given community and across communities among children with Medicaid health insurance. The likelihood of being diagnosed with strabismus was determined for each zip code in Michigan and North Carolina for 10-year-old children enrolled in Medicaid. Over 1 million children were included in the study. Of the 519,212 eligible children in Michigan, 7535 (1.5%) received a strabismus diagnosis, and in North Carolina, 5827 of 523,886 eligible children (1.1%) were diagnosed with strabismus. In both states, the proportion receiving a strabismus diagnosis among black (0.9% in Michigan; 0.7% in North Carolina) and Hispanic (1.1% in Michigan; 0.8% in North Carolina) children was lower than the proportion for white children (1.8% in Michigan; 1.6% in North Carolina). Children living in poorer communities in both states were less likely to be diagnosed with strabismus independent of their race/ethnicity. The author concluded that a child’s likelihood of being diagnosed with strabismus is associated with characteristics of the residential community where he or she resides. The findings of this study highlight the importance of ensuring
that children who live in less affluent communities have access to the necessary services and eye care professionals.

Comment: The study provides insights on healthcare disparities. The authors site relevant limitations of their study; but overall, the study appears to be an objective and appropriate interpretation of big data.

**Incorporating Health-related Quality of Life Into the Assessment of Outcome Following Strabismus Surgery**


Outcomes for strabismus surgery in adults are usually measured by the post op angle of deviation. However subjective quality of life improvement is often noted by patients who fall in to the surgical failure category. This study was prospective cohort study evaluating quality of life in post op adult strabismus patients who were classified as surgical failures. The authors evaluated the patients’ health-related quality of life (HRQOL) scores at 1 year post op to better characterize subjective improvement after strabismus surgery. 21 of 39 patients (54%) who were classified as surgical failures by motor and diplopia criteria showed improvements on the HRQOL scores. The authors propose that HRQOL criteria should be included in determining adult strabismus surgical outcomes.

**Relationship Between Binocular Summation and Stereoacuity After Strabismus Surgery.**


This study is a prospective case series of 130 post op strabismus patients. The authors studied the relationship between binocular summation and stereoacuity. The authors point out that many strabismic patients have deficits in fusional tasks and impaired depth perception, and that there is an increased interest in determining how both eyes working together may be synergistic in the brain due to neural summation. In this study, the authors excluded patients under 3, older than 65, patients with dissociated deviations, nystagmus, neurologic disease or amblyopia. They did not exclude patients based on when the strabismus began or based on their post op eye alignment. Stereoacuity was evaluated using the Randot Stereotest at both near and far. Sloan acuity was tested using the ETDRS protocol with low contrast levels of 2.5% and 1.25% at 3 meters. High contrast acuity was tested using the ETDRS protocol at distance. The authors found that patients with stereoacuity had statistically significantly more binocular summation in 2.5% low contrast acuity than those without stereoacuity. The authors point out that there is no causal relationship proven in this study nor did they compare pre and post surgical results, however they conclude that stereopsis and binocular summation are significantly correlated in patients who have had strabismus surgery.
Strabismus Following Scleral Buckling Surgery

This study assessed the incidence of strabismus after scleral buckling surgery for retinal detachment. A retrospective analysis of 344 patients (360 eyes) with a mean age of $38.45 \pm 18.12$ years was done. Strabismus was detected in 48/344 (13.95%) patients at 6 weeks after scleral buckling surgery, however, the incidence of persistent strabismus decreased to 4.65% after 6 months. Horizontal deviation was the commonest type. 47/48 patients had a scleral buckle in direct proximity to one or more of the recti. Restricted ocular rotation in the direction away from the rectus muscle was seen in 29/48 patients (60.41%), and in the direction of action of the muscle in 15/48 (31.2%). No definite influence was found of width of buckle or number of muscles involved with the buckle on incidence of strabismus. Strabismus was observed in 18.5% of patients with implants, compared to 11.3% of patients who received explants ($P=0.02$). Incidence of strabismus was higher after repeat scleral buckling surgery (4/9, 44.4%) compared to first scleral buckling surgery (44/335, 13.1%) ($P=0.02$).

The accuracy of the Edinburgh diplopia diagnostic algorithm
L Butler, T Yap and M Wright *Eye* June 2016; 30: 812-816; advance online publication, March 18, 2016; doi:10.1038/eye.2016.44

This is a paper that should be read by those who teach medical students/ general practitioners and emergency medicine residents. Evaluation of patients with diplopia is often a challenge for those who are triaging patients in emergency departments and in outpatient settings. To help in determining presumptive diagnosis and required work up, the authors developed an Algorithm to apply when patients present with the chief complaint of diplopia. To test the accuracy and utility of this algorithm the authors conducted a prospective study involving non ophthalmologists (general practitioners, optometrists and emergency department residents) who were treating patients with chief complaint of diplopia. 51 patients with diplopia were examined by the non ophthalmologists. The correct diagnosis was made 24% of the time. When the examiners followed the algorithm, the correct diagnosis was made in 82% of the patients. The authors conclude that the improvement in the diagnostic accuracy resulting from the use of the algorithm would, hopefully, result in more accurate triage of patients with diplopia that are referred to the hospital eye service.

Strabismus in patients with cortical visual impairment: outcomes of surgery and observations of spontaneous resolution
Binder NR, Kruglyakova and Borchert MS. *J AAPOS* April 2016;20:121-125.

This was a 10-year retrospective review of a cohort of patients with CVI. Of the
120 patients, 70 had strabismus. Of the 70, 11 had spontaneous resolution, 27 had persistence without surgery, 18 had strabismus surgery with a good motor surgical result and 14 had strabismus surgery with a poor motor result. Many of the poor result patients also had seizures. Older age was associated with not having undergone strabismus surgery. There were no differences in esotropia or exotropia prevalence or the underlying cause of the CVI between the groups. There was a trend towards better outcomes with better vision. The study methodology can be questioned, but the basic findings are strabismus can resolve spontaneously in CVI patients, and surgery can be considered as a treatment modality if they have a stable angle of strabismus and visual behavior.

Stability of human binocular alignment in the dark and under conditions of non fixation


The stability of human binocular alignment under conditions of altered fixation and luminance was evaluated in this interventional study in 8 healthy orthophoric subjects (one of them was a child). Horizontal binocular alignment was measured using infrared video-oculography (VOG) under conditions of binocular fixation and luminance change. Each testing condition was preceded by a binocular fixation period in room light (475 lux) to define the baseline binocular alignment. Binocular alignment was then measured in darkness without fixation, in room light through a semi-translucent filter that precluded fixation, and in darkness with a distant fixational target. We used the signed rank test to determine statistically whether these experimental conditions induced significant binocular alignment change from each baseline binocular alignment. The mean horizontal binocular alignment in the dark without fixation was similar to baseline binocular alignment (0.2 degrees ± 2.8 degrees; P = 0.4). The mean horizontal binocular alignment without fixation in room light was also similar to baseline binocular alignment (-1.4 degrees ± 1.6 degrees; P = 0.08). The mean horizontal binocular alignment in the dark when a fixational target was provided showed an exodrift compared to baseline alignment (2.3 degrees ± 1.0 degrees; P = 0.0004). The authors concluded that the human brain does not require visual input to maintain binocular alignment on a short-term basis. In this interesting study the authors discuss the possible mechanisms that maintain ocular alignment in these conditions. The authors postulate that the resilience of binocular alignment in non-strabismic healthy subjects probably reflects the presence of phoria adaptation and ocular proprioception. They also proposed that normal sources of retinal tonus (fixation, disparity, and luminance) are necessary to
calibrate stable binocular alignment, which then becomes stored by a process of phoria adaptation.

10. STRABISMUS SURGERY


The authors present three cases of ocular neuromyotonia in association with sixth nerve palsy. Two of the three cases developed ocular neuromyotonia after strabismus surgery for sixth nerve palsy (one spontaneously resolving), and one case demonstrated ocular neuromyotonia prior to strabismus surgery. All patients had a history of brain tumors treated with radiation therapy in addition to other modalities. All were successfully treated both for their sixth nerve palsy and/or associated oculoneuromyotonia. Prior reports have suggested that recession of the neuromyotonic muscle is the appropriate treatment. In the case of sixth nerve palsy this would only worsen the strabismus. The authors demonstrated several concepts: (1) strabismus surgery for 6th nerve palsy may unmask the ocular neuromyotonia likely by recession of the antagonist medial rectus; (2) spasm may also worsen if the neuromyotonic muscle (LR) is resected particularly if fixation duress is created (3) tightening of the neuromyotonic muscle by plication did not seem to worsen ocular neuromyotonia (in one case-one presumes fixation duress did not occur); (4) Faden on the involved lateral rectus muscle may reduce the undesired deviation (exotropia during an episode); (5) Faden on the contralateral yoke muscle did not worsen the spasm as might have been predicted by causing fixation duress and it helped manage the disorder and (6) exaggerated medial rectus recession that seemed to nearly extinguish abduction deficit seemed to help. The cases are beautifully presented and contribute to our varied experience on management of this rare but highly symptomatic disorder. They demonstrate the sometimes difficult-to-predict response to surgical intervention. The general take-home message was that you do not have to worsen the strabismus by recession of the neuromyotonic lateral rectus. You can effectively treat the 6th nerve palsy and then manage the oculoneuromyotonia by a combination of procedures that included further medial rectus recession eliminating abduction deficit, and consideration of faden procedures as noted above.

Evidence Basis for Surgical Correction of Intermittent Exotropia
Three common surgical approaches are used by most strabismus surgeons: Bilateral lateral rectus recessions, unilateral single muscle lateral rectus recession, and unilateral lateral rectus recession with medial rectus resection. There are many preoperative, intraoperative, and postoperative factors and variables that need to be taken into account when choosing the best surgical approach. There are very few randomized clinical studies comparing results between the different surgical approaches. A 20-year-old Level I trial comparing bilateral lateral rectus recessions to unilateral recess/resect showed that unilateral surgery (82% success rate, 12% under-correction rate) was significantly superior to bilateral (52% success rate, 37% under-correction rate). This study's findings have yet to be contraindicated or reproduced in the literature. PEDIG launched a randomized clinical trial in 2009 comparing the two surgical methods and the results are pending. In conclusion, evidence for intermittent exotropia management is limited, although alignment, control, and quality of life appear to be improved by surgery. Unilateral recess/resect is supported by the literature but bilateral lateral rectus recessions are favored by many surgeons.

**Effect of Limited Tenon Capsule and Intermuscular Membranes Dissection on the Outcome of Surgery in Patients with Horizontal Strabismus**


The authors evaluated the effect of limited dissection of Tenon capsule on the outcome of strabismus surgery. 54 patients of ages 2-50 years with horizontal strabismus were divided into two groups: case (n=27) and control (n=27) as a non-randomized study. The method of operation was similar in both groups except for the amount of Tenon sheath dissection. In the control group the intermuscular connections and Tenon capsule were cut as much as possible. In the study group, Tenon capsule, 3-4 mm posterior to the location of the sutures over the muscle (recessed or resected), were cut and intermuscular connections remained intact. The angle of strabismus was reduced after operation in both groups ($P<0.05$). For bi-medial recessions, the correction was $2.6 \pm 0.4$ prism dipters per mm (PD/mm) of muscle recession in the case group, and $2.2 \pm 0.9$ in the control group ($P=0.2$). For monocular recession and resection (R&R) for exotropia, the correction was $3.4 \pm 0.3$ PD/mm of muscle recession or resection in the case group, and $3.2 \pm 0.2$ in the control group ($P=0.05$). For bi-lateral recessions, the correction was $2.3 \pm 0.2$ PD/mm of muscle recession in the case group, and $2.2\pm0.2$ in the control group ($P=0.03$). For patients who had undergone R&R for exotropia, the correction was $3.1 \pm 0.5$ PD/mm of muscle recession or resection in the case group, and $2.7 \pm 0.3$ in the control group ($P=0.02$). The authors concluded that connective tissue ensheathments, whether disturbed or removed, do not affect the success of the strabismus surgery. Minimizing dissection of soft tissue around the extraocular muscles with less tissue damage at time of surgery may be advantageous, however, the authors did not evaluate variables such as bleeding during surgery, operating time, post-operative conjunctival
Hyperemia and scarring and rehabilitation time, to assess benefits. Additional limitations of the study include the lack of randomization and lack of a more detailed analysis comparing effect of limited dissection on smaller versus larger amounts of surgery.

**Evaluation of the Risk of Postoperative Infection in Adjustable Suture Strabismus Surgery**

In this invited commentary, Dr. Hunter notes that ocular infection after strabismus surgery is rare and so the current study uses suture colonization with bacteria as a surrogate for risk for infection. Despite the study’s failure to find a difference in bacterial colonization among the 3 groups of suture tested, he cautions the reader not to abandon the use of povidone-iodine solution at the beginning and end of a strabismus surgery case. He challenges the study’s assertion that longer time outside the eye increases the likelihood of suture colonization with bacteria and hence infection. If surgeons are concerned about the possibility of increased infection rate from sutures that are exteriorized to the skin for a long period of time, the surgeon might consider switching to a buried adjustable suture technique, such as the short-tag noose knot approach.

**Evaluation of Postoperative Povidone-Iodine in Adjustable Suture Strabismus Surgery to Reduce Suture Colonization A Randomized Clinical Trial**

Minimizing post-operative complications is a goal of all surgeons. Post-operative infection, such as orbital cellulitis or endophthalmitis, after strabismus surgery is rare. This study uses bacterial colonization of suture as a surrogate for risk for post-operative infection. This is a randomized clinical trial which studied 65 suture specimens from adult patients undergoing adjustable suture and 43 suture specimens from a control group of adult patients undergoing non-adjustable suture surgery. Adjustable sutures were randomized to application (Group 1) or no application (Group 2) of one drop of 5% povidone-iodine to the noose knot and control specimens were obtained if a non-adjustable technique was performed on another muscle in the same eye. There was no difference in the colonization rate between group 1 (57%) and group 2 (47%) (relative risk [RR], 1.1; 95% CI, 0.6-1.7; P = .80), group 1 and the control group (44%) (RR, 1.0; 95% CI, 0.5-1.8; P > .99), or group 2 and the control group (RR, 1.3; 95% CI, 0.8-2.1; P = .62). The predominant isolate was Staph epidermidis (71%). Although a longer interval between surgery and suture adjustment was associated with a higher likelihood of being bacteria positive (6.3 hours vs 4.4 hours in the bacteria positive and bacteria negative cultures respectively. P=0.001), there was no difference in bacterial growth between the 2 groups.
Conclusion: No difference in bacterial colonization rate was found in adjustable vs non-adjustable sutures, whether or not povidone-iodine solution was used.

**Suture Colonization Rate in Adjustable Strabismus Surgery**

In this prospective interventional case series, the author collected the sutures used for adjustable suture technique of eye muscle surgery in 59 consecutive patients. Bacterial colonization was found in 66% of the used sutures as compared to a lower rate that has been previously published for non-adjustable suture cases (28%). Despite this increased rate in bacterial colonization, no patient developed infection. *S epidermidis* (34 cases) and other *Staphylococcus* species were most frequently identified. Of the 34 *S epidermidis* cases, 7 (21%) were methicillin resistant and 4 (12%) were resistant to fluoroquinolones.

**Comment:** Given that many surgeons perform suture adjustment in a clean but not sterile surgical field, it may seem that contamination would be common. However it is interesting that in spite of the nonsterile surgical procedure, infections tend to be rare.

**Orbital cellulitis and multiple abscess formation after strabismus surgery.**

Orbital cellulitis is a well-established complication of strabismus surgery. This is a case report of a 3-year-old female, who underwent bilateral lateral rectus recessions of 7.0 mm for an intermittent exotropia of 35 prism diopters (PD) and developed multiple distinct orbital abscesses, dacryoadenitis, and small subperiosteal abscess in her left orbit. She was known for a history of bilateral mastoiditis and recurrent episodes of acute otitis media. But no upper respiratory infection was noted prior to surgery. Preoperatively, her face was prepped with 10% povidone solution, and 5% povidone drops were instilled in both eyes.

**Horizontal muscle surgeries**

**Comparison between medial rectus pulley fixation and augmented recession in children with convergence excess and variable-angle infantile esotropia**
The outcomes of medial rectus (MR) muscle pulley fixation and augmented recession in children with convergence excess esotropia and variable-angle infantile esotropia were compared in this prospective randomized interventional study. Children with convergence excess esotropia or variable-angle infantile esotropia were randomly allocated to either augmented MR muscle recession (augmented group) or MR muscle pulley posterior fixation (pulley group). In convergence excess, the MR recession was based on the average of distance and near angles of deviation with distance correction in the augmented group, and on the distance angle of deviation in the pulley group. In variable-angle infantile esotropia, the MR recession was based on the average of the largest and smallest angles in the augmented group and on the smallest angle in the pulley group. Pre- and postoperative ductions, versions, pattern strabismus, smallest and largest angles of deviation, and angle disparity were analyzed. Surgery was performed on 60 patients: 30 underwent bilateral augmented MR recession, and 30 underwent bilateral MR recession with pulley fixation. The success rate was statistically significantly higher (P = 0.037) in the pulley group (70%) than in the augmented group (40%). Patients were considered to have successful outcome if both the smallest and largest angles were within 8 PD of orthophoria in the infantile esotropia subgroup and if the distance and near angles with spectacles were <8D esotropia/phoria in the convergence excess subgroup. Patients with convergence excess who developed any exophoria/tropia or in whom hyperopic correction needed to be reduced for treatment of a consecutive exotropia were considered to be unsuccessful. Four patients (13%) in the augmented group and 5 patients (17%) in the pulley group had postoperative overcorrection (range, 0 PD-10 PD and 0 PD-25 PD, resp.). The postoperative smallest and largest angles and the angle disparity were statistically significantly lower in the pulley group than the augmented group (P < 0.01). The authors concluded that medial rectus muscle pulley fixation is a useful surgical step for addressing marked variability of the angle in variable angle esotropia and convergence excess esotropia. Even though, very rigid criteria were used to define success, the success rate in the pulley group was quite high. This interesting study is relatively well designed although the investigators were not masked at post-operative ophthalmic examination.

Patients with dysthyroid ophthalmopathy generally have been treated with recession only surgery for their strabismus correction due to concerns of worsening the restriction in eye motility with any muscle resections. However, some patients after recession continue to have residual strabismus. The purpose of this study was to describe one surgeons’ experience with bilateral lateral rectus resections for residual esotropia in patients with dysthyroid ophthalmopathy after medial rectus recessions. This was a retrospective study of 9 patients. Preoperative esotropia was 12-30 PD at distance and -2 to 40 PD esotropia at near. Seven of the nine patients had successful eye alignment (less than 8 PD at distance and phoria at near without diplopia) at the 3 month post op appointment after resections using the standard Parks table. No patients had exodeviations, one patient had asymptomatic exophoria and the two patients that were not successfully corrected had over 60 PD of esotropia before initial surgery. The author concluded that resections for residual esotropia were effective in patients with dysthyroid ophthalmopathy. The authors point out the limitations of small number of patients and the less than maximal recession technique with patients with large deviations was used. This study is important because it adds to the growing number of papers supporting the use of resection eye muscle surgery in patients with thyroid eye disease who have needed multiple recession surgeries without adequate alignment. Since these cases are very difficult, more options for the pediatric ophthalmologist are essential to maximize the potential of surgical success.

Long-term surgical outcomes and factors for recurrence after unilateral lateral rectus muscle recession


This is an observational study to evaluate long-term surgical outcomes and risk factors for recurrence after unilateral lateral rectus muscle recession (ULR) in children with small to moderate angle basic type of intermittent exotropia (IXT) defined as 15-24 PD. The main outcome measure was success rate at 2 years after surgery and at final follow-up. Postoperative alignment was considered satisfactory if the alignment was between 8 PD exophoria/tropia and 5 PD esophoria/tropia. Recurrence was defined as >8 PD of exophoria/tropia and overcorrection was defined as >5 PD of esophoria/tropia. The risk factors related to recurrence were evaluated using univariable and multivariable logistic regression analyses. The authors found that the success rate at postoperative 2 years was 92.5% and 83.2% at final examination after a mean follow-up of 3.9 years. No overcorrection was observed. Preoperative exodeviation of 20–24 PD was a significant risk factor for recurrence according to both univariable (OR=3.577, p=0.022) and multivariable analysis (OR=3.265, p=0.034). In conclusion, long-term success of ULR for 15-24 PD of IXT was good. However, recurrence risk of subjects with 20–24 PD of exotropia was about 3 times higher than among subjects with less than 19 PD of exodeviation.
Variability in response to Bilateral medial rectus recessions in Infantile Esotropia.

In this retrospective chart review, the authors attempt to evaluate the factors associated with surgical success in bilateral medial rectus recessions in infantile esotropia. Ninety-seven patients with infantile esotropia were included in the study and underwent bilateral medial rectus recession for the correction of infantile esotropia. Success was defined as a postoperative horizontal deviation of 10 PD or less after one procedure at the last follow-up. The overall success rate and factors correlated with success or failure, including age at surgery, magnitude of deviation, surgical dosage, presence of amblyopia, presence of inferior oblique overaction /DVD were analyzed. The surgical dose-response was also analyzed. The authors concluded that at the most recent follow-up (25 months post surgery), 59% of the patients achieved success with one procedure and that none of the potential associated factors influenced success. This is most likely secondary to the fact that there is high variability in the surgical dose-response.

The incidence of Reoperation and Related Risk Factors Among Patients With Infantile Exotropia.

This article studies the incidence and related risk factors for reoperation among patients with infantile exotropia. In this retrospective chart review, 82 children with infantile exotropia were divided into two groups three months after their first operation: children with horizontal deviation < 10 pd (n=64, success group), and children with horizontal deviation of >10 pd (n=18, failure group). Children with a deviation of 20 pd and more three months after their first operation were re-operated. Factors such as age at first operation, preoperative angle of deviation, inferior oblique overaction, A-V pattern, dissociated vertical deviation in relation to reoperation rates were also studied. The sensory status of patients age 5 years and older was also recorded. The authors reported that the initial angle of deviation (XT>30 PD) and the surgical approach(bilateral lateral rectus recession vs recess-resect procedures) were considered risk factors for reoperation. The majority of patients (71%) achieved fusion and gross stereopsis (<3000 seconds of arc) after surgery. In conclusion, 18.3% of patients with infantile exotropia need a second operation to achieve good alignment. Those with larger preoperative deviations had less favorable outcomes. Although the recess-resect method had better motor outcomes, it is not recommended as a first operation because it was performed on patients that had amblyopia and strong fixation preference. This is a study that is limited from the retrospective nature and the very short follow-up of its patients.
Comparison of Long-term Surgical Outcomes Between Unilateral Recession and Unilateral Recession-Resection in Small-Angle Exotropia.

There are multiple studies looking at outcomes of unilateral lateral rectus recession (ULR) for small angle exotropia, but many of them do not involve a comparison group. Additionally, surgical success from a unilateral rectus recession for intermittent exotropia has a wide range of success rates reported in the literature. The authors of this paper performed a retrospective review of 130 consecutive cases by one surgeon who had surgery for small angle (<20 PD) and who had results at 2 years of follow up. 61 of these patients had a recession/resection (RR) procedure and 69 patients had a unilateral lateral rectus recession to treat exotropia. Patients who had resection/recession procedures on one eye had more successful alignment after 2 years (60% vs. 52%) and lower recurrence (30% vs. 59%) when compared to patients who had unilateral rectus recession and the overcorrection rates were not significantly different. The authors point out that the study is limited by possible selection bias where the treatment was changed from R/R to ULR after reports were published demonstrating good surgical outcomes from these patients. Additionally, patients who had the ULR procedure all had a recession of 10mm and this was not titrated to the amount of deviation measured in the office.

Long-Term Surgical Outcomes of Augmented Bilateral Lateral Rectus Recession in Children With Intermittent Exotropia

Recurrent exotropia is common after surgery for strabismus surgery for exotropia and variable success rates are reported in the literature. Previous authors have suggested that increasing the amount of lateral rectus recession in order to minimize late undercorrections, but many have concerns of increased rates of over correction. This study was a large (447 patients) retrospective review of traditional (101) recessions vs. augmented (346 patients) recessions of the lateral rectus. The author augmented the surgery by 1 or 1.5mm. All surgeries were performed by the same surgeon. Patients under 3 years of age, severe amblyopia, neurologic compromise, and paralytic strabismus were excluded. The outcome was measured at 2 years of follow up and success was defined as less than 10 prism diopters of exotropia or exophoria and less than 5 prism diopters of esotropia or esophoria. Augmented surgery had higher long term successful alignment rates than the traditional recessions (59% vs. 48%, p= 0.047) without increased rates of over correction (3% vs. 4%, p=0.774). Patients with divergence excess type exotropia had the best results with the augmented procedure. The authors conclude that augmentation of lateral rectus recession table should be considered when planning surgery for exotropia.
Comparison of clinical features and Long-term Surgical Outcomes in Infantile Constant and intermittent exotropia.
March/April 216;53(2):99-104

This article studies the characteristics as well as the long-term surgical outcomes of infant-onset (before the age of 12 months) intermittent and constant exotropia. Sixty-seven patients were included in the study (n=37 in the X(T) and n=30 in the XT group). Both groups underwent bilateral lateral rectus recession and were followed for three years. The authors found that the patients with constant exotropia were associated with inferior oblique overaction, dissociated vertical deviation, poor stereopsis and distance suppression. They concluded that the presence of constant exotropia before the age of 12 months represents a reliable factor for predicting poor surgical outcomes in infantile exotropia at long-term follow-up. This study is limited by the fact that it is retrospective as well as by the small number of patients included.

Adjustable surgical treatment of adult exotropia: postoperative target angles and surgical success
Chalifoux E, Alkharashi M, Superstein R, Louis M, Claire Blais C et al

There is evidence that adjustable suture techniques have lowered the reoperation rate and improved the accuracy of alignment in adult exotropic patients. The authors claim that the target angle at the time of adjustment is controversial. Hence, one of the objectives of this retrospective observational cohort study was to correlate immediate postoperative target angles with successful long-term ocular alignment. They also compared the efficacy of two different suture adjustment techniques, group I using a limbal incision and an adjustable suture on both recessed and resected muscles and group II using a fornix incision and an adjustable suture with a noose on the recessed muscle only. Surgical success was defined as distance primary position alignment within 10 prism diopters (PD) of orthotropia 4–6 months postoperatively. A total of 133 adult exotropic patients treated surgically at three different centers were included in this study. Only 102 patients completed a follow-up of at least 4 months after their surgery. Overall success rates for ocular alignment at 4–6 months postoperatively were comparable with both surgical techniques (74.6% for group I and 74.3% for group II) for those 102 patients that completed follow-up. Patients with a preoperative deviation ≥ 40 PD had a lower surgical success rate (63.8%) than patients with a deviation <40 PD (80%). Patients presenting with a significant (-1 or worse) abduction deficit in the operated eye at their first visit after surgery had a better success rate at 4–6 months’ follow-up (83.3% vs 67.8%). The statistical significance of this difference is not shown in the results. The authors conclude that successful surgical outcomes can be achieved with different operative and adjustment techniques for adult exo-
tropia. Creation of an abduction deficit in the early postoperative period in this group of patients seems predictive of a better outcome. Larger preoperative angles (≥40 PD) were associated with more exotropic drift and a lower percentage of surgical success.

This study has several limitations: Short follow-up period, high dropout rate 3/133 patients, diverse group of patients with different surgeons with variations in surgical technique as well as unequal number of patients in the two study groups create inherent bias when assessing postoperative results.

Bilateral lateral rectus recession for the convergence insufficiency type of intermittent exotropia
Ma Ling, Yang L and Li N. J AAPOS June 2016;20:194-196.

This study evaluated the surgical results of lateral rectus recession OU (BLRR) in children with CI-type intermittent exotropia (with at least 15 PD of X(T) at distance). This was a 3-year retrospective chart review. Surgical dosing was based on the distance deviation. Twenty-five patients with a mean age at the time of surgery of 9 years met inclusion criteria. The mean exodeviation at distance was reduced from 32.5 PD to 3.5 PD. At near the deviation was reduced from 45 PD to 2.4 PD. Incomitance was also reduced from 16 PD to 2 PD postoperatively. Initial overcorrection occurred in 15 patients. However by the 2-week postoperative visit (with full daytime alternate patching) only 4 patients were overcorrected. By the one-year post-operative visit, only 2 patients remained overcorrected, but two patients developed a recurrent exodeviation. This study was not a comparative study but did show good success at 1-year using BLRR which usually causes less swelling and discomfort for the patient compared to a procedure involving rectus resection.

Effects of Bilateral Superior Oblique “Hang-Back” Recession in Treatment of A-pattern Strabismus with Superior Oblique Overaction

This study investigated the efficacy and safety of bilateral hang-back recession of superior oblique (SO) muscles in the treatment of A-pattern strabismus with superior oblique overaction (SOOA). 31 patients with A-pattern horizontal deviation and SOOA underwent hang-back recession of SO and horizontal rectus surgery. The average A-pattern was 27.58 ±11.47 prism diopters (PD) pre-operatively and 3.48 ± 3.70 PD after surgery (P<0.05). The mean A-pattern correction was 24.10 ± 10.32 PD. The average scale of SOOA on a scale of +1 to +4 was +3.05 ± 0.80 before surgery and +0.42 ± 0.50 after surgery (P<0.05). The mean corrected objective torsion was 4.91°± 4.53°. The surgical amount of SO hang-back recession ranged from 4 to 10 mm (mean: 7.62 ± 1.18 mm), which was related to the preoperative A-pattern and corrected A-pattern. There were no surgical complications. The authors conclude that SO hang-back recession is a safe and efficient option for A-pattern caused by SOOA. A limitation of the study is the short follow-
Vertical muscle surgeries

Partial tendon recession for small-angle vertical strabismus


In this retrospective case series effectiveness of the partial tendon recession procedure (one pole) in correcting small-angle vertical deviations is evaluated in a variety of clinical situations (patients with thyroid eye disease (TED) and those with muscles that had previous surgery). Orthophoria was the primary outcome success criterion; residual deviation, torsion, and the dose-response relationship were also evaluated. Surgery was performed under general anesthesia or local anesthesia with sedation. A total of 53 procedures in 44 patients (average age, 58 years; age range 8-88 years) were evaluated. The mean preoperative vertical deviation was 4.3 PD +/- 1.8 PD (range, 2 PD- 9 PD); the mean postoperative vertical deviation was 0 PD ± 2.3 PD. The mean response to surgery was 1.5 PD/mm. In the entire cohort, 62% of the procedures resulted in orthophoria, but 82% of patients had resolution of vertical diplopia with a single procedure. In TED patients, 60% of the procedures resulted in orthophoria, whereas only 29% of procedures on previously operated muscles resulted in orthophoria. Authors conclude that partial tendon recession of vertical rectus muscles reliably corrects small vertical deviations. This is equally true for patients with TED, but results are less predictable with re-operated muscles. Surgical technique is detailed with a good accompanying video as reference. Another possibility for the comprehensive strabismus surgeon inventory of treatments for small angle vertical deviations.

Surgical Management of Unilateral Superior Oblique Palsy: Thirty Years of Experience


The most common cause of vertical strabismus is superior oblique paresis and the etiology includes idiopathic, congenital, traumatic, vascular, and neoplastic. The superior oblique intorts, depresses, and abducts the eye. In patients with
unilateral fourth nerve palsies the hypertropia is the predominant deviation. Surgical treatment guidelines are based on Knapp’s classification. The author performed a retrospective chart review on 252 patients divided in 3 groups: Group 1 had inferior oblique weakening surgery, Group 2 had a contralateral inferior rectus recession, and Group 3 had a combination of the two procedures. Group 1 patients had a primary position hypertropia of <21Δ, +2 to +4 inferior oblique over-action, and -1 to -2 superior oblique under-action. Group 2 patients had a primary position hypertropia <21Δ, 0 to +1 inferior oblique over-action, and minimal superior oblique under-action. Group 3 patients had > 20Δ hypertropia, +2 to +4 inferior oblique over-action, and -2 to -4 superior oblique under-action. In Group 1 the surgical success was greater the smaller the pre-operative deviation was, 97.3% for deviations <12Δ and 84.6% for deviations >20Δ. And the reoperation rate was higher for the inferior oblique recession group (14.7%) versus the inferior oblique disinsertion-myectomy group (4.7%). Patients undergoing an isolated contralateral inferior rectus recession had a re-operation rate of 16% and patients undergoing a combined ipsilateral inferior oblique recession and contralateral inferior rectus recession had a 25.9% reoperation rate.

Graded vertical rectus tenotomy for small-angle cyclovertical strabismus in sagging eye syndrome


Graded vertical rectus tenotomy (GVRT) is postulated as effective for small-angle vertical heterotropia. This study’s aim was to determine the dosing recommendations for GVRT in sagging eye syndrome (SES). This was a retrospective, observational study of surgical outcomes for GVRT from 2009 to 2014 in a single surgeon’s academic practice. There were 37 patients (20 women) of average age 68±10 (SD) years with comitant or incomitant hypertropia ≤10Δ caused by SES. The main outcome measure was the dose–effect of GVRT required to correct intraoperative hypertropia. Preoperative average central gaze hypertropia measured 4.7±2.2Δ. Three patients underwent repeat GVRT for residual or consecutive hypertropia, one undergoing it twice. All surgeries were analyzed, increasing the total operations to 41. The inferior rectus tendon in the hypotropic eye was operated in 32 eyes, and the superior rectus tendon in the hypertropic eye in 9 eyes. Mean tenotomy was 68±19% of tendon width. Hypertropia was always eliminated intraoperatively by progressive GVRT. Mean hypertropia was 1.1±1.6Δ at average 93 days postoperatively. Linear regression demonstrated that 3–6Δ hypertropia correction requires 30%–90% graded tenotomy (R²=0.32, p<0.0001), but with substantial individual variability. Undercorrection necessitated reoperation in 10% of cases. GVRT precisely corrects hypertropia of up to 10Δ, but because of variable effect, it should be performed with intraoperative monitoring under topical anesthesia. The authors combined IR and SR GVRT in this series. Although authors set out to determine the dosing, effects of mini tenotomies, they found that the effects are highly variable. The data showed that 3–6Δ hypertropia correction requires 30%–90% graded tenotomy (R²=0.32).
Graded marginal recession: a surgical technique to correct small angle vertical deviations.  

Steven E. Brooks, Larissa Habib  

This study presents a novel surgical technique for recession of the extraocular muscles in order to correct for small angle vertical deviations in symptomatic adults with ability to fuse. Four patients were included in the study with hypertropia ranging from 1-5 PD. These patients had a graded recession of the medial and lateral pole of a vertical muscle along with a graded medial and lateral tenotomy of the muscle, and they were followed for three years. A surgical nomogram was developed. Three out of the four patients had resolution of their diplopia and no induced inomittance or torsion. One patient was initially orthotropic but one month later developed regression of his vertical deviation and required further surgical intervention in order to correct it. The authors conclude that a graded recession of the vertical muscles is a good surgical option in order to correct small angle vertical deviations in adults with fusion potential. This novel surgical approach has the advantage of leaving the muscle essentially intact, surgical revision is possible if necessary without leaving significant scarring. Also the fact that the tenotomies are being done on each pole of the muscle rather than on one side of the muscle reduced the chance of developing post-operative torsion or inomittance. A larger number of patients is needed however in order to validate the results of this study.

Inferior oblique botulinum toxin injection: A Postoperative Diplopia Test for secondary inferior oblique muscle overaction.  

Shveta Bansal, Ian B. Marsh  

This study evaluates the effect of botulinum toxin injection of the inferior oblique muscle for the treatment of secondary inferior oblique overaction in the setting of superior oblique palsy and orbital floor fractures. All patients (n=18) had an injection of 1.25 units of botulinum toxin A into the inferior oblique muscle through electromyographic guidance. Pre-injection deviation in primary position and contralateral side gaze, post-injection deviation in primary position and contralateral side gaze, and functional outcomes. Fourteen out of eighteen patients reported temporary improvement of their symptoms however eleven of those proceed with inferior oblique myectomy in order to achieve complete and permanent resolution of their symptoms. The authors concluded that this technique might be useful in order to evaluate the risk of overcorrection followed planned inferior oblique muscle weakening procedure, especially in cases where the deviation in primary gaze is small and diplopia exists on contralateral side gaze. This is a good study since it included a large number of patients with superior oblique palsy with and without previous surgery and the weakening of the muscle was confirmed with Hess chart.
Isolated inferior oblique myectomy for vertical deviations of at least 20 prism diopters in the primary position
Raoof N and Burke JP J AAPOS 2016;20:112-116

This study reports surgical outcomes of unilateral IO myectomy on patients with inferior oblique overaction and hyper deviations >=20 PD in primary position and on secondary positions of gaze. The study consisted of consecutive patients over a 15-year period reviewed retrospectively. Seventeen patients were included with a mean age of 40.8 years. Diplopia was present prior to surgery in 15/17. Mean follow-up was 17.3 months. There were no intraoperative complications. Two patients required a second surgery. In the early postoperative period the deviation decreased from 26.5 PD to 13.8 PD and at last follow-up the deviations improved to 4.1 PD on average. There were no post-operative overcorrections (one patient was lost to follow-up). All patients had a marked improvement in lateral incomitance postoperatively but this did not hold true for vertical incomitance. The degree of inferior oblique overaction did not correlate with residual hypertropia. Overcorrections do not seem to be a concern with this procedure but many patients had some degree of undercorrection.

Transposition surgeries

Comparison of augmented and non augmented modified Knapp procedure for the treatment of nonrestrictive double elevator palsies

In this retrospective case series the surgical results of augmented and nonaugmented modified Knapp procedure, for the treatment of non-restrictive double elevator palsies (DEP). Consecutive cases of unilateral congenital DEP from January 2007 to June 2015 were included. All patients had positive Bell’s phenomenon and the absence of inferior rectus restriction that was confirmed intraoperatively. Patients were divided into three treatment groups: standard transposition (group A), Foster transposition (group B), and resection transposition (group C). Pre- and postoperative vertical deviation in primary position, ocular motility, and binocular vision were compared. Thirty patients were enrolled. The pre- and postoperative deviations in group A were 34.7 PD ± 8.6 PD and 6.5 PD ± 6.5 PD; in group B, 38.6 PD ± 14.6 PD and 5.7 PD ± 9.3 PD; and in group C, 43.1 PD ± 10.3 PD and 8.5 PD ± 6.1 PD. The corrected vertical deviation of group B (32.9 PD ± 5.7 PD) and group C (34.6 PD ± 5.0 PD) were greater than that of group A (28.1 PD ± 3.6 PD; P = 0.03, 0.002). The pre- and postoperative measures
of upgaze in group A were -3.7 and -1.8; in group B, -4.0 and -1.3; and in group C, -3.6 and -2.0. The average improved upgaze in group B (2.6 ± 0.5) was statistically significantly better than that in group A (1.9 ± 0.6) and group C (1.5 ± 0.5; P = 0.03, 0.002). There was no significant difference in the surgical effect on downgaze in three groups (P > 0.05). The surgical outcome was satisfactory in 19 (63.3%) patients with preoperative vertical deviation of <35 PD. Surgical success was defined as residual vertical and horizontal deviations < 10 PD, AHP <50 and ocular motility improvement by at least 1 unit on the duction measurement (measured from -1 to -5). The authors concluded that all transpositions are reasonably effective in treating vertical deviations of <35 PD without obviously limiting downgaze in DEP. Augmented procedures could correct greater vertical deviation of 30 PD-40 PD. The Foster transposition demonstrates the strongest effect in improving upgaze. There are some obvious limitations to this study, mainly its retrospective nature and the possible selection bias. The statistical analysis is also not completely revealed.

Augmented superior rectus transposition with medial rectus recession in patients with abducens nerve palsy.
Patil-Chhablani, P., Kothamasu, K., Kekunnaya, R., Sachdeva, V., Warkad, V.

This retrospective study summarizes the experience of this group with augmented superior rectus transposition (SRT) and medial rectus recession (MRc) in patients with abducens nerve palsy. The medical records of consecutive patients with abducens nerve palsy who underwent unilateral or bilateral simultaneous SRT with MRc from January 2012 to December 2014 were analyzed. Patients with previous strabismus surgery or botulinum toxin injection were excluded. Primary outcome measures were esotropia in primary position and abduction deficit. Success was defined as postoperative alignment within 10 PD of orthotropia; failure, as residual esotropia of 20 PD or more. A total of 15 eyes of 13 patients were included. The most common cause of abducens nerve palsy was trauma (10 patients). The mean preoperative esotropia was 55.4 PD ± 24 PD, which improved postoperatively to 9.9 PD ± 10 PD (P = 0.0000). The mean preoperative abduction deficit was -5 units, decreasing postoperatively to -3.1 (P = 0.000). Mean follow-up period was 5.2 months (range, 1.5-12 months). Nine patients (69%) achieved success; 2 were classified as failures. Two other patients developed other postoperative complications; one developed hypotropia and another large intorsion; however, these were transient and did not require additional procedures. No patients developed anterior segment ischemia. The authors concluded that augmented SRT with MRc is effective in the management of abducens nerve palsy; however, its success in large
deviations remains variable. Of note, the MR recession was completed using a non-adjustable technique with fixed sutures. The authors acknowledge the short follow-up period in this study and state that long-term follow-up is essential to determine the incidence of vertical and torsional deviations. A table with surgical numbers is presented and can be used as a guideline.

Double Augmented Vertical Rectus Transposition for Large-angle Esotropia Due to Sixth Nerve Palsy.

In this prospective interventional study, fifteen patients with non-resolving sixth nerve palsy underwent surgical correction with double augmented Hummelsheim procedure. Fourteen of the fifteen patients also received a bilateral medial rectus recession. Two patients with an associated vertical deviation had also an augmentation of one of the vertical muscles with a complete resolution of the vertical deviation. Only three of the fifteen patients had a postoperative deviation greater than 10 pd of which only one was fitted with prism for residual diplopia. Induced vertical deviation was observed in two of the patients. The authors recommend this procedure in patients with a positive forced duction test in longstanding sixth nerve palsy. They also recommend a selective augmentation of one of the vertical muscles in cases with an associated vertical strabismus.

Medial transposition of split lateral rectus augmented with fixation sutures in cases of complete third nerve palsy

Surgical management of complete third nerve paralysis is a challenge. While several techniques have been described over the years, they result in less than satisfactory outcomes with residual deviations in primary gaze or postoperative drifts. One of the described techniques for management of oculomotor palsy has been medial transposition of the lateral rectus muscle, which provides a good surgical alternative but often can result in undercorrection. In this article, the authors describe a modification of the existing technique of medial transposition of the split lateral rectus by force augmentation through the use of equatorial fixation sutures (like Foster augmentation), resulting in an improved outcome in primary gaze alignment. The modified technique involves splitting the lateral rectus into two halves followed by transposing the superior half from below the superior oblique and superior rectus and inferior half from below the inferior oblique and inferior rectus to attach them at the superior and inferior edge of the medial rectus insertion, respectively. Posterior tenectomy of superior oblique helps in free movements of the transposed muscle under it, reduces the abduction effect, re-
sulting in greater correction. This is followed by placing non-absorbable sutures to fix each split belly of the transposed muscles to the sclera at the equator adjacent to the medial rectus such that the split muscles lie nearly parallel to the medial rectus till the equator before reflecting away. These sutures augment the force of the transposed muscles by redirecting the force vectors in the direction of action of the medial rectus. Satisfactory postoperative primary gaze alignment was achieved in three cases of complete third nerve paralysis. In the three cases described, all had residual exotropia and hypotropia. Duration of follow-up ranged from 3 to 10 months. There was no mention of whether surgery was able to achieve subjective diplopia-free zone even with a head posture.


This article describes a new surgical modified procedure in patients with chronic total oculomotor nerve palsy as well as the results of the procedure. Eight eyes of 6 consecutive patients who underwent strabismus surgery due to chronic total oculomotor nerve palsy were enrolled in the study. The lateral rectus muscle was split into two halves and disinserted from the sclera. The upper half of the muscle was passed under the superior rectus muscle and the inferior half of the muscle was passed under the inferior rectus muscle. The two halves of the muscle were moved to the medial rectus muscle insertion area and were sutured to sclera near the insertion. Additional medial rectus resections were made in the undercorrected patients. The mean age was 21.8 ± 12.1 years (range: 11 to 42 years). Postoperatively, 4 of 6 patients had stable horizontal deviations; 1 had orthophoria, 2 had 10 prism diopters (PD) of exotropia, and 1 had 10 PD of esotropia. However, 2 cases had 25 and 30 PD of undercorrection. Additional medial rectus resections were made in these undercorrected patients and horizontal deviations reduced to 15 and 20 PD of exotropia, respectively. The mean primary position horizontal deviation, which was 74.1 ± 10.2 PD before the surgeries, reduced to 10.8 ± 6.6 PD after the surgeries (P < .001). The authors concluded that this procedure might be an option in the treatment of chronic total third nerve palsy but that a larger sample is needed in order to reach safe conclusions.

Sutures

Nonabsorbable versus absorbable sutures in large hang-back medial rectus muscle resections
Awadein A, Marsh JD, and Guyton DL. J AAPOS June 2016;20:206-209
This study investigated the potential advantage of using a non absorbable suture on medial rectus muscles to reduce the risk of a consecutive exotropia. The concern is the possibility of inadequate muscle adherence with an absorbable suture. Enrolled patients had undergone a large recession of the medial rectus and were divided into two groups: absorbable 6-0 polyglactin suture versus non absorbable 6-0 polyester fiber suture. The groups were not divided randomly but were sequential based on the authors change in surgical technique. The absorbable group had 66 muscles in 44 patients with a mean age at surgery of 28.5 years. The non absorbable group consisted of 67 muscles in 50 patients with a mean age of 35.2 years. The mean medial rectus recessions were 7.2mm and 8.8 mm respectively. This difference was statistically significant. In the absorbable group at 3-month follow-up, 63% had satisfactory alignment and overcorrection occurred in 30%. Eleven patients required a second operation, and overall 11 of the 66 muscles were found to be 6-10mm posterior to the intended recession due to inadequate anchoring. In the non absorbable group satisfactory alignment at the 3-month mark occurred in 86% and there only was a 6% overcorrection rate. In the 2 patients who required a second operation the medial rectus muscle was found at the intended location. The results of this study need to be evaluated in the context that all surgeries were performed by hang-back technique and may not apply to directly sutured anchoring of the muscle.

**Strabismus surgery - Misc**

A modified technique for strabismus surgery in the presence of a scleral buckle.


A surgical technique to perform strabismus surgery in patients with a scleral buckle that allows for the use of adjustable sutures without removing or modifying the explant is described in this report. An accompanying video and detailed description of the technique is supplied.

Histopathological changes of fibrosis in human extra-ocular muscle caused by botulinum toxin A.


This report presents the histopathological findings of three patients where injections of botulinum toxin were used prior to strabismus.
surgery. In all cases, evidence of permanent extraocular muscle atrophy and fibrosis were demonstrated. One of the cases had prior strabismus surgery in the biopsied muscle. Hence, unclear if extent of fibrosis describe in this case is not related to prior surgery and scar formation.

**Strabismus surgery outcomes in the Infant Aphakia Treatment Study (IATS) at age 5 years.**


This is a publication from the Infant Aphakia Treatment Study (IATS) that reports on strabismus surgery frequency and outcomes following monocular infantile cataract surgery with or without IOL implantation. IATS is a well-known randomized, multicenter clinical trial comparing treatment of aphakia with a primary IOL or contact lens in 114 infants with a unilateral congenital cataract. Patients presented in this report had strabismus surgery prior to age 5 years. Strabismus surgery was performed in 45 (39%) patients (contact lens group [CL], 37%; IOL group, 42% [P = 0.70]). The indications for strabismus surgery were esotropia (62%), exotropia (33%), and hypertropia (4%). Infants who underwent cataract surgery at a younger age were less likely to undergo strabismus surgery (28-48 days, 12/50 [24%]; 49-210 days, 33/64 [52%]; P = 0.0037). Of the 42 patients who underwent strabismus surgery, 14 (33%) had a postoperative distance alignment within 8 PD of orthotropia at age 5 years. The 5-year visual acuity of children with strabismus was the same whether or not strabismus surgery had been performed (1.10 logMAR with surgery vs 1.00 without [P = 0.71]). The authors concluded that in their study cohort, cataract surgery performed in the first 6 weeks of life was associated with a reduced frequency of strabismus surgery. Strabismus surgery outcomes in this population were guarded. Surgical improvement of strabismus did not appear to influence long-term visual acuity. The timing and dosing of strabismus surgery were not part of the IATS protocol. Hence, strabismus surgery as an outcome was influenced by many factors that were at the discretion of the investigator and the family. It is not clear what conclusions can be drawn about case selection for strabismus surgery post infantile cataract surgery, when those factors are not revealed.

**Factors associated with surgical success in adult patients with exotropia**

This retrospective case series from Korea had looked into the clinical outcome of surgical treatment for intermittent or constant comitant exotropia in adults and examined the factors associated with the successful outcome. The medical records of consecutive patients older than 18 years of age at the time of surgery for intermittent or constant comitant exotropia and with at least 1 year's follow-up were retrospectively reviewed. Surgical success was defined as postoperative esodeviation of <5 PD, orthotropia, or exodeviation of <10 PD. Overcorrection (defined as esodeviation >5 PD) and recurrence (exodeviation of >10 PD) were considered surgical failure. Preoperative patient characteristics, surgical procedures performed, and early postoperative ocular alignment were evaluated as potential factors associated with the surgical outcome. A total of 39 patients were included, of whom 28 (72%) achieved surgical success, 7 (18%) showed overcorrection, and 4 (10%) had recurrence. The average postoperative follow-up was 1.9 ± 1.0 years (range, 1.0-6.3). Alignment at postoperative week 1 was the only significant factor correlated with surgical results. Surgical outcome was best with early postoperative alignment of <10 PD of esotropia. Other variables that were investigated (sex, time from deviation onset to surgery, age at surgery, best-corrected visual acuity, refraction, distant and near deviation angle, constancy of deviation, associated strabismus) were not found to be significantly associated with surgical outcome. The authors concluded that early postoperative overcorrection of <10 PD resulted in more favorable surgical outcomes in adults undergoing surgery to treat exotropia. Limitations of this study include its retrospective nature and small sample size, but it had a relatively long follow-up. A small overcorrection in the immediate post-operative period is a well-known favorable factor from better surgical outcome.

Planning Strabismus Surgery: How to Avoid Pitfalls and Complications

The purpose of the lecture is to emphasize the importance of preoperative planning and assessing all pertinent examination factors to obtain good surgical results following strabismus surgery. An outline of the surgical plan integrates a number of factors including diagnosis, visual acuity, refractive error, stereovision, risk of post-operative diplopia, fundus torsion, eye dominance, and most importantly orthoptic measurements. Minor complications from strabismus surgery include dellen formation, chronic red eye, ocular surface problem, pyogenic granuloma, Tenon’s fascia prolapse, epithelial inclusion cyst, mydriasis, reduced accommodation, stitch granuloma, chemosis, and hemorrhage. Severe compli-
cations include ocular perforation, orbital infection, endophthalmitis, surgical induced necrotizing scleritis, slipped muscle, lost muscle, retinal detachment, adherence syndrome, pulled-in-two syndrome and anterior segment ischemia. The most frequent complication of strabismus surgery is the need for additional surgery. The goals of strabismus surgery are: improved stereovision, increased binocular field, and improved cosmesis. The orthoptic evaluation is the most valuable tool preoperatively, it should include accounting for the refractive error, especially large hyperopic or myopic spectacles that under and over-measure the deviation respectively. The type of prisms used to measure, glass versus plastic, and the plane in which they are held also affects reliability of measurements. Other factors of the orthoptic evaluation that are important are distance-near disparity, AC/A ratio, patch test, prism adaptation, incomitance, presence of torsion, etc. The author also takes preoperative pictures of the ocular alignment in all fields of gaze to assist in surgical planning.

Myectomy of the extraocular muscles without reattachment as a surgical treatment for horizontal nystagmus.


This study compares the clinical findings for two nystagmus procedures in two consecutive case series: the Sinskey anterior extirpation procedure (SAEP) and a modification, myectomy without reattachment (MWR). In the SAEP procedure an enucleation snare is used to penetrate the dense capsuloseptal adhesion where the muscle emerges from the posterior Tenon’s fascia. In this newly described modification, myectomy without reattachment (MWR), the capsuloseptal adhesion is preserved without penetration in the posterior orbit. The purpose of this modification is to (a) reduce the risk of orbital bleeding by replacing snare excision with controlled clamp and cautery, (b) to reduce the risk for consecutive strabismus, and (c) to optimize preservation of versions by excising the capsuloseptal adhesion and not penetrating into the posterior orbit.

Twenty two patients underwent SAEP and nineteen underwent MWR. Videonystagmography was used preoperatively and postoperatively. The SAEP group experienced greater improvement in acuity and greater reduction in amplitude on average compared to the MWR group. Horizontal versions were more compromised in the SAEP group and one patient experienced intraoperative orbital bleeding. Patients requiring reoperation for strabismus numbered 5 of 20 (20%) in the SAEP and 3 of 19 (16%) in the MWR groups. In the authors opinion, the risks of SAEP for intraoperative bleeding, the greater reduction in versions, and the greater incidence of postoperative strabismus requiring reoperation do not justify recommending the SAEP technique over the MWR. In conclusion, MWR might present a promising approach to the treatment of most childhood onset, horizontal nystagmus, with or without a null point, and without the risks of the originally reported SAEP.
What do patients with strabismus expect post surgery? The development and validation of a questionnaire

Evidence, across a wide range of conditions, suggests that patients’ expectations about their health, disease course and treatment can influence a range of clinical outcomes and patient satisfaction. This study was aimed at development and validation of a short questionnaire to assess patients’ expectations about outcomes post strabismus surgery. Questionnaire items were extracted from previous literature and reviewed by a multidisciplinary team. A cross-sectional study was then undertaken with 220 adult patients due to undergo strabismus surgery. Participants completed the 17-item questionnaire. Scale structure was explored using principal component analysis (PCA), and the sub-scales analyzed in relation to demographic and clinical characteristics and psychosocial well-being in order to establish validity. PCA revealed a 3-factor solution for the Expectations of Strabismus Surgery Questionnaire (ESSQ): (a) intimacy and appearance-related issues, (b) visual functioning, (c) social relationships. This 3-factor solution explained 59.3% of the overall variance in the ESSQ. Internal consistency, content and nomological and concurrent validity were considered acceptable. Patients with strabismus have high expectations about their post-surgical outcomes. This questionnaire provides a useful tool to assess the expectations patients have about their surgery, whether these expectations change over time and how they impact on post-surgical outcomes. Although this study targeted only patients undergoing strabismus surgery, it would be interesting to see how these measures apply to those who declined surgery to determine the self-selecting bias of those who have already decided to undergo surgery.

Does strabismus surgery improve quality and mood, and what factors influence this?

This is an interesting paper with a surprising result. The authors investigate the change in quality of life and mood following strabismus surgery. Utilizing a previously validated tool – the AS-20, 335 adults undergoing strabismus surgery at Moorfields completed the questionnaire pre op and at 3 and 6 months post op. Results demonstrated that surgery lead to a significant improvement in the quality of life for most patients. Greater improvements in quality of life from pre- to post surgery was more likely in those who held more positive beliefs about their strabismus and treatment, experienced less social anxiety and social avoidance and had lower expectations about the outcome of their surgery pre-operatively. The biggest surprise in the results is that those patients who had partial clinical success experienced a deterioration in quality of life, more so than those whose surgery was considered a failure. The authors conclude that it is clear that not all
experience positive benefits despite successful clinical outcomes, therefore by intervening both psychologically and clinically the findings of this study may provide a unique mechanism via which the benefits of strabismus surgery can be optimized.

**Botulinum toxin injection for restrictive myopathy thyroid-associated orbitopathy: success rate and predictive factors**


This study evaluated the success rate of botulinum toxin injection in the treatment of restrictive myopathy thyroid-associated orbitopathy and the predictive factors for success. This was a prospective, interventional case series of consecutive patients over a 5-month period. Twenty patients were enrolled (esotropia n=10, hypotropia n=8, mixed n=2). Thirty-three extra ocular muscles were injected. Seven patients with esotropia and all of the patients in the other groups required more than one treatment. A total of 64 injections were performed and the mean interval between injections was 2.8 months. No complications occurred. Eight patients had initial overcorrections but none persisted at the 2-year follow-up. Overall there a success rate of 55%. Three factors were associated with success: type of deviation, smaller angle strabismus, and lower degrees of extorsion (although only smaller hypotropia remained significant after multivariate logistic regression). This study had a small sample, no control group, and absence of different dosages of the toxin.

**Pharmacologic injection treatment of combatant strabismus**

Debert I, Miller JM, Danh KK and Scott AB J AAPOS April 2016;20:106-111.

This was a prospective observational series with up to 5 years’ follow-up in 55 consecutive cases of combatant horizontal strabismus. Injections were performed with bupivicaine (BPX) (sometimes combined with epinephrine) to strengthen and shorten muscles and/or botulinum type A toxin (BTXA) to stretch the antagonist muscle. A minimum of six-months of follow-up was required. Eleven patients were lost to follow-up and removed. The 55 study patients had a mean final examination of 28 months. Initial misalignment was reduced from 23.8 PD to 9.1 PD with a successful outcome in 56%. Most patients required more than one treatment. Esodeviation patients and exodeviation patients had comparable results. Small deviations required fewer treatments but the difference was not statistically significant. Larger misalignments received combined BPX/BTXA treatments and had larger absolute corrections, although overall success rates were lower in this group. The authors discuss some clinical findings they observed regarding time course of effect and recovery, as well as treatment considerations. This paper would not be considered a well-designed study with valid statistical results; rather it is really a collection of findings and observations
of nonuniform pharmacologic treatment of a nonuniform collection of patients similar to publications of many decades ago.

**Superior rectus and lateral rectus muscle union surgery in the treatment of myopic strabismus fixes: three sutures versus a single suture**

Farid MF, Elbarky AM and Saeed AM J AAPOS April 2016;20:100-105.

This study compares two different surgical techniques for SR-LR union to treat myopic strabismus fixus. A single suture which can leave a gap versus a 3-suture technique was compared. Patients underwent surgery over a 2-year period and the results were evaluated retrospectively. A medial rectus recession was also performed. No information was provided as to how it was determined which patients would be in each group but the 3-suture group was significantly more myopic and had a greater average axial length. Twenty eyes of 10 patients were included (3-suture n=6, 1-suture n=4). Mean follow-up was 9 months versus 10.5 months in the respective groups. Esotropia improved from 93.3 PD preoperatively to 21.6 PD postoperatively and 102.5 PD preoperatively to 50 PD postoperatively in the 3-suture and 1-suture groups respectively. Mean hypotropia improvements were significant and similar between the two groups. The motility improvement in abduction was significantly better in the 3-suture group (-3.6 to -0.9) than the 1-suture group (-4.3 to -3.1). The difference in motility improvement in supraduction was also statistically significant between the two groups (-3.1 to -1.4 versus -3.7 to -2.8 respectively). There was only one surgical complication of an intraoperative muscle split in the 3-suture group. The 1-suture group had no complications reported. The authors feel the 3-suture technique is better because it can hold more muscle fibers, produces greater closure, and improves the muscle path compared to the 1-suture technique.

**Tendon elongation with bovine pericardium (Tutopatch(R)) when conventional strabismus surgery is not possible.**


Sometimes, a conventional recess-resect surgery may not be sufficient to obtain satisfactory ocular alignment. Patients who have previously undergone surgery and/or have a large difference in visual acuity between both eyes and do not wish to undergo surgery on the sound eye provide a surgical challenge. In these cases, tendon elongation with bovine pericardium may be an option. In this retrospective non-comparative case series the authors had reviewed the charts of 38 patients who underwent strabismus surgery with tendon elongation. Most of the patients (N=31) had exotropia (angle -21.8 +/- 5.7 degrees) and seven had esotropia (angle +19.1 +/- 5.4 degrees). Reasons for tendon elongation included the following: 15 pa-
tients refused surgery on their sound eye; in 15 patients, conventional re-
cess-resect was not possible; and in 7 patients, the elongation best fitted
the motility pattern, due to large mechanical or paretic duction deficits. In
one patient, tendon elongation was preferred over conventional recession
because of thin sclera. Surgery was planned according to Maddox cross at
2.5 m. Last follow-up visit was very variable, and ranged from 1 week to 4
years. Results are presented in degrees rather than PD. At last follow-up,
patients with previous exotropia, the angle was reduced to -3.3 +/- 5.9 de-
grees; in patients with previous esotropia it was +0.2 +/- 0.5 degrees. Most
had some duction limitation in the direction of the elongated muscle, which
was sustained at final follow-up 13/38 had at least a deficit of -2. In the pa-
tients with previous exotropia, there was a small but nonsignificant regres-
sion to recurrence of the exodeviation (on average 0.5 degree per year). In
one case that required reoperation, the pericardium had apparently disap-
peared and had been replaced by a small strand. The authors conclude that
tendon elongation is a valuable addition to our strabismus surgery reperto-
ire. However, because of duction limitations after surgery, it should be
reserved for those cases in which conventional surgery is not an option. It
is possible that similar limitations would have resulted from conventional
large recessions. Due to lack of a comparison group, no conclusions about
the efficacy can be drawn.

### Pulled-in-two syndrome: a multicenter survey of risk factors, management and outcomes


Pulled-in-two syndrome (PITS) is a serious complication of stra-
bismus surgery that occurs when an extraocular muscle ruptures
under tension. Marshall Parks and Mark Greenwald had coined the
term pulled-in-two syndrome in 1990. This multicenter survey was de-
signed to retrospectively evaluate the characteristics of patients
with PITS and identify risk factors, management, and outcomes. Stra-
bismus surgeons from around the world contributed cases of PITS
through an online survey. A total of 40 cases of PITS from 29 physicians
in 6 countries were collected. The most commonly involved muscles
were the medial rectus (18/40 [45%]) and the inferior rectus (17/40
[43%]). The most commonly identified risk factors were previous ocular
surgery (11/40 [28%]) and cranial nerve palsy (11/40 [28%]). Advanced
age was also a significant risk factor, with 28/40 (70%) of reported
patients being 50 years of age and above, but unlike previous reports, it
seems from this report that PITS can exist in a much younger age
with 4 patients [10%] presenting at an age <10 years. In most
cases the muscle was found and reattached to the globe (28/40
[70%]). The muscle was lost in 12 cases (30%). Half of these patients
received a transposition surgery; the other half were followed by observation. With some fancy calculations, the authors conclude that strabismus surgeons might encounter one case of PITS approximately every 10 years, with possible under-estimation. According to this survey, the preferred management for PITS is surgical recovery and reattachment of the muscle to the globe; however, if the muscle is lost, transposition surgery or observation are common forms of management. The authors acknowledge the study’s limitations as a case series and state that given the limited number of cases and lack of comparison or control groups, it was impossible to identify one best management.

Surgical planning and innervation in pontine gaze palsy with ipsilateral esotropia


Presented is a small case series of five consecutive patients with dorsal pontine lesions. Each patient had horizontal gaze palsy with symptomatic diplopia as a consequence of esotropia in primary gaze and an anomalous head turn to attain single binocular vision. Surgical intervention strategies are discussed. In the first two patients, complete loss of rectus muscle function from rectus muscle palsy was assumed. Based on this assumption, medial rectus recessions with simultaneous partial vertical muscle transposition (VRT) on the ipsilateral eye of the gaze palsy and recession-resection surgery on the contralateral eye were performed, resulting in significant motility limitation. Sequential recession-resection surgery without simultaneous VRT on the 3rd patient created an unexpected motility improvement to the side of gaze palsy. Recession combined with VRT approach in the esotropic eye was abandoned on subsequent patients. Simultaneous recession-resection surgery without VRT in the next 2 patients resulted in alleviation of head postures, resolution of esotropia, and also substantial motility improvements to the ipsilateral hemifield of gaze palsy without limitations in adduction and vertical deviations. Authors believe that ocular misalignment and abnormal head posture as a result of conjugate gaze palsy can be successfully treated by basic recession-resection surgery, with the advantage of increasing versions to the ipsilateral side of the gaze palsy. The group of patients that are presented here are variable in background diagnosis and age including both adults and children. Authors state that forced generation test and forced ductions were either
not reliable or difficult to perform. Not much data is available on this clinical situation and the cases that are presented in this report seem to support a simpler approach that includes recession-resection surgery over combined surgery with VRT.

Surgical correction of an inferiorly displaced lateral rectus with equatorial myopexy.

Clark, T. Y. and R. A. Clark J AAPOS 20(5): 446.e441-446.e443.

Orbital connective tissue normally loses strength and rigidity during aging. The lateral rectus pulley that surrounds and directs the lateral rectus path has the flimsiest support and can sag too far inferiorly, resulting in significantly reduced abducting force and secondary esotropia. This displacement is worsened by a weakened lateral rectus-superior rectus band from high myopia. Augmented medial rectus recessions can correct the esotropia, but long-term results may be less predictable because the underlying anatomic abnormality, the sagging lateral rectus muscle, has not been addressed. A video is presented demonstrating the proposed lateral rectus equatorial myopexy. A permanent scleral suture to fixate the posterior lateral rectus belly into its correct anatomic position is used. The authors claim that the response to surgery depends on the magnitude of lateral rectus sag and is somewhat self-titrating-more sag correlates with both larger distance esotropia and thus larger corrections from lateral rectus equatorial myopexy alone—but larger deviations often require repositioning of muscle insertions to compensate for secondary changes to muscle lengths and tension. This technique is one option in sagging eye with esotropia and distance-near disparity.

11. ANTERIOR SEGMENT

Tomographic indices as possible risk factors for progression in pediatric keratoconus.


The purpose of this retrospective case series from the UK was to determine whether corneal tomography can help predict the risk of progression of keratoconus in children. The medical records of pedi-
Pediatric patients with keratoconus presenting from 2009 to 2014 were reviewed retrospectively. Patients underwent serial clinical examination and corneal tomography. The minimum follow-up period was 5 months. Patients with a history of eye surgery including corneal crosslinking were excluded. The following tomographic parameters were analyzed: thinnest corneal thickness (TCT), average central corneal keratometry (Km), and maximum central posterior elevation (MCPE). The rate of progressive corneal thinning, in mum/month, was calculated as the difference between TCT on presentation and at the most recent visit divided by the time in months. A total of 36 eyes of 19 patients (10-16 years of age) were included. Mean follow-up was 19 months (range, 5-30 months). Six eyes (17%) developed corneal scarring and 1 eye (3%) developed acute hydrops. Of the 29 eyes that did not develop corneal scarring or hydrops, 24 (83%) demonstrated progressive corneal thinning over the period of the study. Eyes with TCT of <450 μm, Km above 50 D, and MCPE above 50 μm at presentation demonstrated the highest rates of progressive corneal thinning over the study period. The authors concluded that in pediatric keratoconus, lower TCT, higher Km, and higher MCPE on corneal tomography seem to be risk factors for faster rates of progressive corneal thinning. The study has several limitations due to its retrospective nature and the small sample, but it highlights the need to recognize risk factors for rapid progressive corneal thinning in pediatric keratoconus patients. In the era where crosslinking can be used to reduce progression, one must take into consideration that TCT of <400 mm is the accepted cut-off for safe corneal crosslinking and formulate the proper follow-up algorithm for at-risk patients.

Long-term Outcomes of Pediatric Penetrating Keratoplasty for Herpes Simplex Virus Keratitis.

There is little literature regarding the long-term survival and outcomes in pediatric patients who have a penetrating keratoplasty (PKP) secondary to HSV keratitis. This study was a retrospective consecutive case series looking at 9 eyes of 9 patients who received a PKP for HSV with the goal of understanding the characteristics and outcomes of these eyes. The median age at transplantation was 14 years. After a median follow up of 94 months, the patients had a statistically significant improvement in median visual acuity with an initial median vision of 20/400 and the median final visual acuity of 20/50. Complications included glaucoma, graft rejection, recurrence, and amblyopia. The authors did not have any graft failures. The one patient in this series with recurrence of HSV had discontinued their prophylactic acyclovir. The patients without significant improve-
ment in vision had amblyopia complicating their course. The authors point out that this is a small group of patients, even if it’s the largest cohort reported in the literature, continued prophylaxis in the pediatric population is especially important, and comorbid amblyopia is most likely to limit improvement in visual acuity. The key points of this paper is that without recurrence of disease and amblyopia that visual outcomes in this population have a potential to be excellent. The older age of these patients certainly could have decreased the potential impact of amblyopia on their results.

**Corneal Endothelial Cell Density in Children: Normative Data From Birth to 5 Years Old.**

There are no normative databases for endothelial cell density in children under the age of 5. Multiple congenital and pediatric diseases such as Peters anomaly, posterior polymorphous corneal dystrophy, congenital hereditary endothelial dystrophy, trauma and surgery can alter the number or function of the endothelial cells. It is hypothesized from previous, but very small studies, that there is a rapid decrease in endothelial cell density over the first years of life. That the corneal diameter growth in these first years of life can rapidly change, the endothelial cell density change in these first few years has also been explained by previous research. An understanding of the normal endothelial cell density in children can help guide the clinician to better understand disease. This was a cross sectional study evaluating 118 eyes of 118 patients using specular microscopy during a clinic visit in the standard upright position and in the lateral decubitus position in children under sedation for other unrelated surgeries. The corneal diameter was measured and stratified according to age. The mean age was 2.6 years (range 0.1-5 years). The authors found that in the first 2 years of life there is a rapid decline in endothelial cell density. They hypothesized that this is due to the growth in the corneal diameter and surface area. When the cornea reaches adult size then the endothelial cell density began to decrease in a rate similarly reported in adults. Linear regression demonstrated there was a different rate of endothelial cell density decline in relation to age before and after 2 years of age. There was a 4.4% per year decrease in cell density in the first 2 years and then a 1.3% decrease yearly after that. This paper is important for the pediatric ophthalmologist since understanding the normal change in endothelial cell density is essential for determining disease.

**Survival of Primary Penetrating Keratoplasty in Children.**

Pediatric penetrating keratoplasty is difficult because of additional challenges in the pediatric population such as abnormalities in the anterior segment in patients with congenital cornea opacities, complex postoperative course, and the need for
amblyopia and refractive management. The purpose of this study was to review the indications, outcomes and prognostic factors for corneal graft survival in a more contemporary pediatric population. This was a retrospective study at Wills Eye Hospital from 2007 to 2015 with 46 eyes of 35 children who had primary keratoplasty at a mean age of 24.6 months. There was a mean follow up of 36 months. The most common reason for the transplant was congenital opacity (Peters anomaly was the most common diagnosis) and the overall average graft survival time was 45 months. The authors found a graft survival rate of 75% at 1 year. The presence of glaucoma and concurrent surgeries during the keratoplasty were each associated with poor graft survival rate. The authors did not find an association between age and graft survival. Patients who had cataract extraction and intraocular lens placement at the same time had a 50% corneal graft failure rate. The authors point out the limitation of having few cases of complex pediatric corneal disorders such as sclerocornea, which could have skewed their results towards a better outcome. This paper is important to the pediatric ophthalmologist because it helps us communicate to our patients the rate of corneal failure in the pediatric population and explain to families the higher risk of failure in children with glaucoma or who require a triple procedure for complex anterior segment disorders. The authors’ recognition of the lack of sclerocornea and other difficult cases is an important one since it would be very difficult to generalize these results to many patients in the office, many of whom may be choosing no intervention over a pediatric penetrating keratoplasty.

Paediatric infectious keratitis at tertiary referral centres in Vancouver, Canada

This is an observational case series of pediatric patients with infectious keratitis in Vancouver, Canada. The authors reviewed the clinical and microbiological profiles of 17 eyes (16 children) with microbial keratitis in children aged 17 or younger. These patients had undergone corneal scraping between May 2006 and April 2011 at BC Children’s Hospital or Vancouver General Hospital Eye Care Centre in Vancouver, British Columbia, Canada. Demographic information, clinical features, predisposing factors, results of microbiology studies, antibiotic susceptibilities, treatment course and outcomes were analyzed. The mean age of patients was 11±5.7 years (range 1–17 years) and the male:female ratio was 1.4:1. Major predisposing factors were contact lens wear (6/17; 35%), and pre-existing ocular surface conditions including blepharitis (3/17; 18%) and Stevens–Johnson syndrome (3/17; 18%). Four patients had a previous corneal ulcer. The most commonly isolated microorganisms were Staphylococcus epidermidis and Acanthamoeba. Acanthamoeba was isolated in 67% of contact lens-related corneal ulcers, while the remaining 33% of contact lens-related corneal ulcers were associated with infection with Pseudomonas aeruginosa. Final visual acuity was better than 20/60 in 9 out of 16 patients (56%). Three patients subsequently required surgical management with either penetrating keratoplasty or deep anterior
lamellar keratoplasty for treatment of corneal scarring. Contact lens wear and pre-existing ocular surface conditions are significant risk factors for the development of infectious keratitis in this pediatric population. Knowledge of regional patterns of infection and susceptibility are essential in ensuring prompt treatment of this potentially sight-threatening condition.

Clinical and microbiological study of paediatric infectious keratitis in South India: a 3-year study (2011–2013)

This is a retrospective review describing clinical and microbiological profiles of infectious keratitis in pediatric patients aged 0 to 16 years who presented to Aravind Eye Hospital in Maurai, India from January 2011 and December 2013. In this time period, 240 eyes of 234 children had a diagnosis of infectious keratitis. One hundred and twenty-five (53.4%) children had a history of trauma. Smears were obtained in 220 eyes, while culture was performed in 191 eyes. The culture results were positive in 142 (74.3%) eyes. Fungi were the most common infectious agents isolated in culture (54.2%) followed by bacteria (40.8%) and acanthamoeba (2.1%). Successful healing of the keratitis with appropriate medical therapy occurred in 223 (92.9%) eyes, while 17 (7.1%) eyes required therapeutic keratoplasty. Of the 151 patients with preliminary and final visual acuity, vision improved by 2 lines in 68 eyes (45%), stayed the same in 75 eyes (49.6%) and worsened in 8 eyes (5.3%). The authors concluded that contrary to previous reports, fungi are the most common aetiological organism in the causation of infectious keratitis in children in this study population. Fusarium was the most common fungal species isolated. These data are similar to the data obtained from adult patients with infectious keratitis in this region. While microbiological investigations are important to initiate appropriate antimicrobial therapy, the findings from this study need to be kept in mind, especially while initiating empirical therapy in this population.

Anterior segment disorders - surgical procedures

Successful management of severe unilateral chemical burns in children using simple limbal epithelial transplantation (SLET)

Limbal stem cell deficiency (LSCD) can lead to loss of corneal clarity causing unilateral or bilateral corneal blindness. Severe ocular surface burns cause damage to limbal stem cells. This corneal blindness has extremely poor prognosis for corneal transplantation unless the ocular surface is reconstructed. The authors describe a retrospective outcome of simple limbal epithelial transplantation
(SLET) for treating these conditions amongst 4 children less than 15 years of age with minimum of 6 months follow-up. In brief, in SLET, a 3x2 mm limbal biopsy was extracted from the superior limbus of the fellow eye and then cut into 6-8 smaller pieces. The recipient eye was freed of vascularized pannus, Human amniotic membrane (hAM) graft was secured over bare sclera with fibrin glue. The transplants were then uniformly spread onto the hAM. A soft bandage contact lens was placed over the cornea. A symblepharon ring was placed in three cases. The mean age was 5.75 years (range 2-12) and three subjects were males. All eyes had grade 6 chemical injury based on Dua classification. The mean interval between initial injury and SLET was 6 months. One case achieved complete success and three cases achieved partial success. Cases with partial success underwent repeat SLET until all cases achieved complete success. The cases that had a focal recurrence underwent repeat SLET with conjunctival autograft. The overall follow-up was 12–60 months. Pre-SLET visual acuities were hand motions (one eye) and perception of light (three eyes). Post-SLET visual acuities were counting fingers close to face (one eye), 6/36 (two eyes) and 6/18 (one eye) at final follow-up. The authors have successfully managed children with these difficult conditions and are advocating for SLET.

Cataract surgery in patients with Alport Syndrome

In this case report the authors present their experience with cataract surgeries in two patients with Alport syndrome and anterior lenticonus. Of the four eyes they operated on, one had spontaneous anterior capsule rupture (ACR) prior to surgery. This report further support the building experience from previous reports that performing continuous curvilinear capsulorhexis (CCC) is difficult in patients with anterior lenticonus. The authors conclude that femtosecond laser-assisted cataract surgery (FLACS) can be a possible tool in order to achieve favorable results in this scenario, as suggested by a previous report. An author’s reply to Cataract surgery in patients with Alport syndrome is also published


Capsulorhexis tearing pattern during phacoemulsification in anterior lenticonus due to Alport syndrome


In this case report the authors describe an atypical cogwheel-like tearing pattern during continuous curvilinear capsulorhexis in a 37 year old patient with anterior lenticonus due to Alport syndrome. The authors propose that this tearing pattern likely correlates to the known ultrastructural characteristics of thinning and periodic dehiscence and breaks in the anterior cap-
sule. They conclude that knowing this tearing pattern preoperatively can help to prevent capsule runoff and capsule rupture.

**Anterior segment disorders – nonsurgical management**

The Frequency of Signs of Meibomian Gland Dysfunction in Children with Epidermolysis Bullosa


The authors prospectively evaluated 105 children with various type of epidermolysis bullosa (EB)(junctional 8.6%, simplex EB 34.3%, autosomal recessive dystrophic 34.3%, autosomal dominant dystrophic 22.9%). Mean age was 7.42 years. Ninety-two children (87.62%) demonstrated 1 or more features of MGD which may contribute to some of the ocular surface anomalies seen in children with EB. **Comment:** It is interesting that factors other than fragile epithelium and/or recurrent corneal erosion could contribute to chronic progressive corneal scarring.

**Anterior segment biometry and refraction**

Comparison of anterior segment parameters obtained by Dual-Scheimpflug analyzer before ad after cycloplegia in children.


This article describes the changes in anterior chamber parameters (anterior chamber depth, anterior chamber volume, anterior segment angle, and pupil diameter) after cycloplegia. Ninety-three patients were included in the study (43 males and 50 females, mean age 7.76+/-2.7 years) and anterior segment parameters were obtained by the Galilei Dual-Scheimpflug analyzer (Ziemer Group, Port, Switzerland) before and 40 minutes after the instillation of cyclopentolate 1% ophthalmic solution. There was a significant increase in anterior chamber depth, anterior chamber volume, and pupil diameter after the cycloplegia (P < .05). The anterior chamber angle increased after cycloplegia in the nasal, temporal, and inferior quadrants (P < .05), but not in the superior quadrant (P > .05). The mean values of anterior segment parameters were similar in both genders. This study presents the possibility of objective quantitative assessment of the anterior segment parameters using Galilei Dual-Scheimpflug analyzer which has multiple clinical applications such as in cataract surgery, glaucoma and refractive surgery.

12. **CATARACT**
Behaviors of children with unilateral vision impairment in the Infant Aphakia Treatment Study


The psychosocial effects of occlusion for amblyopia are debated. In this report from the Infant Aphakia Treatment Study (IATS) the investigators set to determine whether behavioral functioning of 4.5-year-olds differs between two treatments for unilateral cataract and whether behavioral functioning is predicted by visual acuity in the treated eye. The Infant Aphakia Treatment Study is a multicenter clinical trial in which 114 infants with unilateral congenital cataracts were randomized to undergo cataract extraction with contact lens correction or implantation of an intraocular lens. Patching data were collected during the year preceding a visit at age 4.5 years, when both visual acuity and caregiver-reported behavioral functioning were assessed for 109 participants. Caregiver stress was assessed with the Parenting Stress Index at 4.25 years. There were no treatment group differences in behavioral functioning as measured by the Child Behavior Checklist. Poorer visual acuity was associated with more externalizing behavior problems (attention problems and aggressive behavior) and total behavior problems in regression models that did not include caregiver stress. Both caregiver stress and dichotomized visual acuity significantly predicted externalizing problems. The authors concluded that treatment assignment did not affect caregiver-reported behavior. Poor visual acuity may confer risk for problems with attention and aggressive behavior in preschoolers treated for unilateral cataract.

Revisiting secondary capsulotomy for posterior capsule management in pediatric cataract surgery.


In this retrospective study, the development and treatment of visual axis opacification following pediatric cataract extraction with intraocular lens placement (IOL) without primary posterior capsulotomy and anterior vitrectomy (PPC+AV) were evaluated. The medical records of children who underwent cataract extraction and IOL by a single surgeon were reviewed retrospectively for development of posterior capsular opacification (PCO) to identify risk factors for development of treatment-requiring posterior capsular opacification. A total of 63 eyes of 47 children 7 months to 16 years of age were included. The rate of PCO formation following cataract extraction without PPC+AV was 90%. Of
those, 96% required a secondary capsular procedure to clear the visual axis; 55% had a clear visual axis after 1 procedure, almost exclusively with a YAG capsulotomy, and 3.5% did not require any secondary capsular procedure. Younger age was the only statistically significant characteristic associated with both PCO formation and need for more than one secondary capsular procedure. Children <3 years of age had an average of 2.1 capsular procedures. Cataract extraction and IOL without PPC+AV leads to an expected high rate of PCO formation, which can be effectively managed with a secondary capsular procedure in all age groups. The authors believe that leaving the posterior capsule intact is an acceptable option for handling this probable complication and that it should be discussed with parents to avoid a more complicated primary surgery. The study has several limitations apart from its retrospective nature. Visual acuity results are not presented and the development of amblyopia is not discussed.

Image features of lens opacity in pediatric cataracts using ultrasound biomicroscopy


This retrospective case series evaluated the lens opacity in pediatric cataract images captured using ultrasound biomicroscopy (UBM). The medical records of patients operated on from September 2012 to October 2013 were reviewed retrospectively. Prior to surgery, patients were placed in the supine position under sedation with oral chloral hydrate for UBM imaging. Lens morphology was evaluated by UBM examination with a 50 MHz probe that was equipped with a water bag instead of the standard plastic shell. UBM images were compared to images captured from intraoperative videos. UBM examination was performed in 50 patients (including 10 infants) aged 2 months to 6 years. The UBM echographic images showed features specific to pediatric cataract lenses. These features were used to define 2 types of anterior capsule of the lens, 4 types of cortex and nucleus of the lens, 3 types of posterior capsule of the lens, and membranous cataracts. The authors believe that UBM could provide useful preoperative information to surgeons. The data presented is not completely convincing regarding the relevance of this assessment to decision making. Slitlamp examination is probably superior to UBM in evaluating cataracts. UBM should be considered in situations, where the view is obscured and anterior segment dysgenesis is suspected.

ICO-OSCAR for pediatric cataract surgical skill assessment
Swaminathan, M., Ramasubramanian, S., Pilling, R., Li, J., Golnik, K. 

Pediatric cataract surgical skill assessment is important to ensure the competency of the trainees, especially pediatric ophthalmology fellows. Using a rubric would ensure objectivity in this process. The ICO-OSCAR pediatric cataract surgery rubric has been developed with global variations in techniques of pediatric cataract surgery in mind and is presented in this short report. Pediatric fellowship supervisors might find this tool useful in assessing and teaching trainees. The rubric is included in the supplement.

**Comparison of the rate of refractive growth in aphakic eyes versus pseudophakic eyes in the Infant Aphakia Treatment Study.**


The study purpose was to compare the rate of refractive growth between aphakic eyes and pseudophakic eyes in the Infant Aphakia Treatment Study (IATS). The IATS was a multicenter randomized clinical trial of patients undergoing unilateral cataract extraction with contact lens correction versus intraocular lens (IOL) implantation. The authors calculated a rate of refractive growth based on the change in refraction from the 1-month postoperative examination to age 5 years. Longitudinal refractive data were studied for 108 of 114 enrolled patients (contact lens group, n = 54; IOL group, n = 54). The mean rate of refractive growth was similar in the contact lens group (−18.0 diopter [D] ± 11.0 [SD]) and the IOL group (−19.0 ± 9.0 D) (P = .49). The rate of refractive growth value was not correlated with age at cataract surgery, glaucoma status, or visual outcome in the IOL group. In the aphakic group only, visual outcome was correlated with refractive growth (P = .01), with worse visual outcome having higher refractive growth. Data showing the wide range of refractions obtained in both the aphakic and pseudophakic groups are sobering. At age 5 years, the final refraction in the aphakic group ranged from -6.4 to +19.3 (mean 12.4+/-.5.3), and in the pseudophakic group, it ranged from -19.0 to +5.0 (mean -3.7 +/- 5.8).

**Quality of life and functional vision concerns of children with cataracts and their parents**

Y S Castañeda, C S Cheng-Patel, D A Leske, S M Wernimont, S R Hatt, L Liebermann, E E Birch and J M Holmes *Eye* September 2016; 30: 1251-1259; advance online publication, July 8, 2016; doi:10.1038/eye.2016.134

This is a MUST READ article that describes the authors efforts to develop and instrument that will measure Health related Quality of Life in both the children with cataracts and their parents. Using structured qualitative interviewing techniques at two different centers, the authors interviewed 16 children with history of
cataract and 31 parents of children with cataracts. 87% of the children had had surgery for their cataracts. The authors identified 6 themes shared by both the children and their parents: Visual Function (mentioned by 16 of 16 children (100%) and by 26 of 31 parents (84%), Social (94 and 65%), Treatment (81 and 90%), Worry (75 and 10%), Emotions (63 and 68%), and Physical Discomfort (63 and 26%). The biggest surprise is that the children were MORE WORRIED about their eyes (75% were worried) than what their parents perceived (only 6% of parents thought their children were worried.) This study will stimulate further discussion not only within our specialty, but in all pedi subspecialties and will help us determine value of our work value in the new emerging healthcare delivery paradigms.

Factors associated with stereopsis and a good visual acuity outcome among children in the Infant Aphakia Treatment Study

In this IATS study the authors examine the factors associated with the development of good acuity and stereopsis. 112 children with unilateral cataract had 5 year followup and patching compliance was measured using 7 day diaries and phone interviews. They found that 27% of the patients had 20/40 vision or better. Of these children 50% had stereopsis, and those with stereopsis they more more like to orthophoric and had LESS patching (3.4 hours/day in first year tapering to 1.8 hours by age 4). In contrast the group with no stereopsis showed an INCREASE in patching over 4 years (4.8 in first year increasing to 6.5 hours by age 3. There was no statistical difference in the IOL vs contact lens group. The authors conclude that the following patching regimen be applied to children who demonstrate good acuity and good compliance: year 1 - 4 hours/day, years 2-3 - 3 hours per day, year 4 -2 hours per day.

Strabismus developing after unilateral and bilateral cataract surgery in children

The authors conducted a retrospective study of patients treated at a single medical center for congenital cataracts over an 11 year period, specifically to determine the incidence of strabismus in these children with at least one year followup. 90 children (144 eyes) were included in the study 40% unilateral and 50% bilateral.83% had IOLO implantation. 46% of the children who were orthotropic pre cataract surgery subsequently developed strabismus, and 32% of the children who had strabismus prior to surgery become orthotropic after cataract surgery. In the entire cohort 14% required surgery for strabismus, with the expected finding that earlier cataract surgery, unilateral, PFV type cataract and poorer
acuity were associated with a higher prevalence of strabismus. Esotropia was more common than exotropia. A child with poor visual acuity is 9 times more likely to develop strabismus than a child with good visual acuity.

**Congenital cataract associated with persistent fetal vasculature: findings from IoLunder2**
A L Solebo, I Russell-Eggitt, P Cumberland and J S Rahi on behalf of the British Isles Congenital Cataract Interest Group *Eye* September 2016; 30: 1204-1209; advance online publication, July 29, 2016; doi:10.1038/eye.2016.159

This is an interesting article for 2 reasons: 1) the way they define PFV cataract and 2) the high incidence of PFV found in their cohort of congenital cataract. The IoLunder2 study was conducted in the UK and Ireland as a prospective study following the outcomes of children who received IOL implantation under the age of 2 years. In this paper they described the findings and outcomes of children who had PFV cataracts. They describe a classification scheme for PFV, that includes: 1) posterior plaque and persistent tunica, 2) anterior plaque and iris/pupillary membrane and 3) complex PFV involving retina and/or nerve. Using this classification scheme they found that in the 246 children enrolled in the study, 58 (24%) had PFV type cataracts – 47% of the unilateral cases and 8% of the bilateral cases. Followup was at least one year but length of fu was not reported for each group. The incidence of glaucoma during this one year time period was 4% for unilateral and 9% for bilateral cases. Not surprisingly the authors report that those with complex PFV had worse acuity outcomes than those with only anterior or posterior plaques. Using this liberal definition of PFV, the authors state that PFV is a more common association with congenital cataract than previously reported.

**Diagnosing the cause of bilateral paediatric cataracts: comparison of standard testing with a next-generation sequencing approach**

The authors describe the use of next generation sequencing technology to determine genetic conditions associated and causative in children with childhood cataracts. 27 children with bilateral cataracts were studied in Manchester Royal Eye Hospital UK using this methodology and identified a genetic cause in up to 80% in this research setting. Some of the causes would change ongoing treatment and prevent systemic morbidity in some of the children. In an excellent discussion, the authors propose modification of current recommendations when evaluating infants with bilateral cataracts, proposing greater use of rapid genetic sequencing and more targeted, selective screening for TORCH conditions.

**Associated systemic and ocular disorders in patients with con-**
genital unilateral cataracts: the Infant Aphakia Treatment Study experience
E I Traboulsi, D Vanderveen, D Morrison, C D Drews-Botsch, S R Lambert and The Infant Aphakia Treatment Study Group Eye September 2016; 30: 1170-1174; advance online publication, June 17, 2016; doi:10.1038/eye.2016.124

Analyzing patients recruited as a part of IATS, the authors investigate the association of systemic disorders in children with unilateral cataract. After excluding cases of persistent fetal vasculopathy with retinal involvement or stretching of the ciliary processes or medical conditions that would have precluded vision testing. 114 patients had 5 year followup and of these 4 had syndromes identified(Sticklers, autism, rubella, mitochondrial). None developed cataract in the fellow eye. The authors conclude that although there may be associated ocular conditions in the affected eye, systemic conditions are rare.

Global prevalence of childhood cataract: a systematic review
S Sheeladevi, J G Lawrenson, A R Fielder and C M Suttle Eye September 2016;30: 1160-1169; advance online publication, August 12, 2016; doi:10.1038/eye.2016.156

This article is must reading for anyone interested the epidemiology of Childhood cataracts, and the references alone will be invaluable. In a well designed literature review, the authors seek the true incidence and prevalence of congenital and childhood cataract and analyze the findings relative to economic and developmental status of the populations studied. The bottom line findings of the study are that averaged worldwide the incidence of childhood cataract is 1.69/10,000 births yielding 314,000 newly affected children per year. These data will inform policy concerning treatment of reversible blindness for NGOs and governments alike.

Outcomes of Pediatric Cataract Surgery in Copperbelt Province of Zambia.

This article studies the outcomes of pediatric cataract surgeries in children operated on in the Copperbelt Province of Zambia. The study included 102 eyes of 70 children with congenital, developmental and traumatic cataracts. In the congenital and developmental cataract group, the preoperative visual acuity (VA) was 6/60 or worse. Postoperatively, the visual acuity improved to better than 6/18 in 29.7% of the cases and between 6/24 and 6/60 in 35.9% of the cases. Older age \((P=.005)\), better preoperative visual acuity \((P=.045)\), unilaterality \((P=.012)\) and delay between presentation and surgery \((P=.025)\) were predictors of a better postoperative outcome. In the traumatic cataract group, 68% of the patients had VA
of 6/18 or better and 24% had BCVA between 6/24 and 6/60. The authors found that their visual outcomes after pediatric cataract surgery were comparable with those in India, China and Bangladesh. This article depicts that distance, cost and lack of awareness remain major barriers in accessing eye care for affected children.

**Diagnosing the cause of bilateral paediatric cataracts: comparison of standard testing with a next-generation sequencing approach.**

This study assesses the diagnostic outcomes of traditional routine investigations for childhood cataract (CC) and compares this with outcomes of next-generation sequencing (NGS) testing. A retrospective review of the medical records of 27 consecutive patients with bilateral CC presenting in 2010-2012 was undertaken. The outcomes of routine investigations in these patients, including TORCH screen, urinalysis, karyotyping, and urinary and plasma organic amino acids, were collated. The success of routine genetic investigations undertaken over 10 years (2000-2010) was also assessed. By April 2014, the underlying cause of bilateral CC had been identified in just one of 27 patients despite 44% (n=12) receiving a full 'standard' investigative work-up and 22% (n=6) investigations in addition to the standard work-up. Fifteen of these patients underwent NGS testing and nine (60%) of these received a diagnosis for their CC. NGS testing improved diagnostic rates and time to diagnosis, as well as changing clinical management.

**Association of Radiation Dose to the Eyes With the Risk for Cataract After Nonretinoblastoma Solid Cancers in Childhood**

This study mined the Euro2K database to determine the association of radiation treatment with cataract in solid nonretinoblastoma cancers. It included over 4000 5-year cancer survivors from 1945-1985. 1833 completed questionnaires and met inclusion criteria and were analyzed. Radiation doses to the eyes were estimated. Role of radiation in cataract risk was analyzed using Cox regression hazard analysis and relative risk and excess risk model. Multivariable Cox proportional hazard regression analysis suggests that patients who received radiation treatment had a 4.4-fold (95%CI, 1.5- to 13.0-fold) increased risk for cataract compared with patients who did not receive radiation treatment. Exposure to radiation doses of at least 10 Gy to the eyes increased the hazard ratio 39-fold (95%CI, 12.0- to 127.9-fold), relative to no radiation exposure. Although based on few patients, a strong increase in cataract risk (hazard ratio, 26.3; 95%CI, 7.1-96.6) was observed in patients treated with melphalan hydrochloride.

Importance: Parents want to know what to expect after treatment for their child’s
cancer. Therapies often include significant toxicities. This is a novel study which tries to answer the question of what is the risk for cataract formation after radiation treatment for nonretinoblastoma solid cancers in children.

**Gender Inequalities in Surgery for Bilateral Cataract among Children in Low-Income Countries a Systematic Review**
Gilbert CE, Lepvrier-Chomette N. Ophthalmology June 2016;123:1245-1251

In this systematic review article, the authors compiled 38 studies (6854 patients) with at least 20 patients each to evaluate for gender differences in for bilateral pediatric cataract surgery. The authors compared the proportion of children undergoing surgery for bilateral, nontraumatic cataract who were girls, using data from high-income, gender-neutral countries as the reference. Overall, 36.5% of children were girls. In gender-neutral countries, 47.5% of children (777/1636) were girls, being similar in the Middle East, North Africa, and Central Asia (48.6%; 87/179) and in Latin America and the Caribbean (43.7%; 188/430). Proportions were significantly lower in sub-Saharan Africa (41.1%; 225/547), East Asia and the Pacific (36.0%; 237/658), and South Asia (29.1%; 991/3404). Access to surgery by girls with bilateral cataract is lower in some regions than by boys. The authors discuss potential factors such as differences in access for boys and girls, gender bias among family members, X-linked inheritance in some countries, and fewer female children in some countries.

Comment: This study highlights potential cultural and societal differences that may result in reduced surgical treatment for pediatric cataracts for female patients.

**13. CATARACT SURGERY**

**Pediatric cataract surgery outcomes**

**Validation of Guidelines for Undercorrection of Intraocular Lens Power in Children.**

Myopic shift is seen in children as their eyes grow, thus many pediatric ophthalmologists initially under correct the intraocular lens power. However there is also concern about leaving the patient hyperopic since that can contribute further to amblyopia. Additionally some surgeons prefer to aim for emmetropia and plan for refractive surgery or lens exchange when older. Initial under correction of the power is the preferred approach, yet there are no studies comparing the outcomes for these two approaches. This was a retrospective observational study.
of 84 eyes of 56 children who had cataract surgery, primary IOL placement, and follow up to at least 7 years old with the goal of looking at the refractive status of children who were initially under corrected according to the paper by Enyedi and associates. Enyedi proposed a post op refractive goal using the rule of seven (+6 in a 1 year old, +5 in a 2 year old, etc). The surgeries were done at the LV Prasad Eye institute between January of 2005 and December of 2013. The authors only included patients who had an in the bag placement of the intraocular lens and surgery without complications. 7/84 children (8.3%) achieved emmetropia, with an equal proportion of the remaining children being either hyperopic or myopic. Almost half of children had a refraction +/- 1 diopter from emmetropia and 87% of children had refraction within 2 diopters. The children in the youngest age group had more residual hyperopia suggesting that the surgeon should consider less under correction in the 0-2 year group. The most important factor influencing the results was the age at surgery. The authors concluded that the guidelines suggested by Enyedi et al have an acceptable refractive error at the age of 7 in most children and that in children under 2 a decrease in under correction suggested may help decrease residual hyperopia at the age of 7. The key point of this paper is that the rule of seven’s for under correcting hyperopia in a child predicted an acceptable refractive outcome in 87% of patients.

**Capsular bag stabilization during lens extraction and intraocular lens implantation in cases of Marfan syndrome with ectopia lentis using ultra-high-viscosity ophthalmic viscosurgical devices.**


The authors present three patients with Marfan’s syndrome who underwent lensectomies with use of Healon 5 (an ultra-high viscosity viscoelastic) to maintain the capsular bag. The technique obviates the use of capsular hooks that have been conventionally used to stabilize the capsular bag. One of the three cases was an eleven year old boy with bilaterally subluxed lenses. During his lensectomies, Healon 5 was injected into the capsular bag used to support the area of zonular weakness. An IOL was placed in the bag. A capsular tension segment was also placed in the bag and sutured to the sclera. After two years, the IOLs remained centered and he retained visual acuity of 20/20 OD and OS with mild hyperopic astigmatism OU.

**Secondary intraocular lens implantation following infantile cataract surgery: intraoperative indications, postoperative outcomes**

K S Wood, D Tadros, R H Trivedi and M E Wilson

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In this single surgeon study, Dr Wilson reports his outcomes following secondary lens implantation in 37 eyes of children with monocular and bilateral surgical aphakia. The average age at time of secondary IOL was 55 +/- 21 months and followup was at least one year. 69% were implanted in the bag and 29% in the sulcus. He does not compare the outcomes in these two groups. Of note Glaucoma occurred in 30% of the eyes with 16% occurring after implantation of the IOL. Visual acuity was excellent with median acuity of 20/40, 20/60 for unilateral and 20/30 for bilateral.

**Outcome of primary intraocular lens implantation in infants: Complications and rates of additional surgery.**


This prospective observational case series from India studied primary intraocular lens (IOL) implantation with unilateral congenital cataract surgery. Infants who had phacoaspiration, primary posterior capsulotomy, anterior vitrectomy, and primary intraocular lens implantation were evaluated for complications and the need for additional surgery over a 3-year period. The main outcome measures were the rate of complications, adverse events, and need for additional surgery. Sixty infants (100 eyes) with a mean age of 7.13 months ± 2.32 (SD) (range 3 to 12 months) were studied. The mean follow-up was 41.2 ± 3.5 months. Indication of additional surgery included visual axis opacification in 13 eyes, pupillary membrane/IOL decentration in 4 eyes, and iris prolapse in 4 eyes. Adverse events included pigment on the IOL in 14 eyes and iridolenticular adhesions in 9 eyes. Ocular hypertension was observed in only 2 eyes. All surgeries were done by a single surgeon.

This study reports a low incidence of adverse events and additional surgery in infants who had cataract surgery with primary IOL implantation, and stands in contrast to the results of the North American Infant Aphakia Treatment Study (IATS). The study authors speculate that their more frequent use of steroid eye drops, compared to the IATS protocol, may have been responsible for better outcomes. The authors also describe the challenges of treating aphakia with contact lenses in developing countries.

**Congenital cataract surgery without intraocular lens implantation in persistent fetal vasculature syndrome: Long-term clinical and functional results**


In this retrospective study from a German University, the authors looked at outcomes after congenital cataract surgery in eyes with persistent fetal vasculature (PFV). 19 eyes of 19 children were included, age 18 months and younger. These patients were compared to children treated for unilateral (11 eyes) or bi-
lateral (58 eyes) congenital cataracts without PFV. Follow up ranged from 6 months to 13.5 years, with a mean follow up of 4 years 5 months in the PFV group and 4 years 10 months in the comparison group. Visual acuity better than finger counting was achieved in 7 of 19 (37%) PFV eyes compared to 10 of 11 (91%) unilateral congenital cataract eyes. As expected, visual outcomes were best in the bilateral congenital cataract eyes, with 100% having visual acuity better than finger counting, and 23 of 58 eyes (40%) having mildly decreased to normal acuity. Vitreous hemorrhage took place in 10 of 19 (53%) PFV eyes and was severe enough to require ultrasound examination of the retina in 8 of the 19 eyes (42%). Only one of 69 eyes (1%) in the comparison group developed vitreous hemorrhage. Retinal detachment was also more common in the PFV group (3 of 19 eyes; 16%) versus the comparison group (0 of 69 eyes; 0%). This study’s main findings are that (1) congenital cataract surgery in PFV eyes has a high risk of postoperative vitreous hemorrhage and retinal detachment, and (2) most patients have a poor visual outcome.

Association Between Occlusion Therapy and Optotype Visual Acuity in Children Using Data From the Infant Aphakia Treatment Study A Secondary Analysis of a Randomized Clinical Trial

Removal of a visually significant cataract and aphakic rehabilitation in an infant are just the first steps in an often arduous process of restoring visual acuity. Patching, or occlusion therapy, of the dominant eye is a mainstay of helping achieve the best possible vision in an infant who is surgically rendered aphakic. The authors study the efficacy of patching in achieving optotype visual acuity in children from the infant aphakia treatment study. The authors hypothesized that primary IOL implantation would not be associated with adherence to occlusion therapy but that reported hours of patching would be associated with visual acuity. The study design included a secondary analysis of children who were enrolled in the infant aphakia treatment study, which comprised 114 children who had unilateral congenital cataract diagnosed between August 2004 and December 2008 and who were randomized to receive an intraocular lens or contact lens as the means of aphakic rehabilitation after cataract surgery. Caregivers reported patching in the previous 48 hours in quarterly semistructured interviews. The mean number of hours of patching per day was calculated from surgery to the first birthday (n = 92) and between 12 and 48 months of age (n = 102). Monocular optotype acuity was assessed at 4 years of age by a traveling examiner using the Infant Aphakia Treatment Study HOTV protocol. Caregivers reported patching their children a mean (SD) of 3.73 (1.47) hours per day in the first year of life and 3.43 (2.04) hours per day thereafter. Visual acuity outcome did not vary by treatment group. Visual acuity was associated with reported hours of patching in the first year of life (r = −0.32; 95%CI, −0.49 to −0.13) and between 12 and 48 months of age (r = −0.36; 95%CI, −0.52 to −0.18). Importance: There were a few surprising findings in this study. Similar visual out-
comes were achieved with various levels of patching. Considerable variation in visual outcome is seen for a given level of patching. In fact, patching accounted for less than 15% of the variance in logMAR acuity at 4 years of age. The authors note that the association between adherence and visual acuity is bidirectional. Children with the best vision may less resistant to prescribed patching and therefore may wear patches more than children with poorer vision. Also, the implantation of an IOL does not appear to affect adherence with patching.

Outcomes after lensectomy for children with Marfan syndrome

This study assessed risk factors for postoperative retinal detachment in Marfan syndrome patients who underwent lensectomy. The authors also report the rate of endothelial cell loss. The medical records over a 21-year period were retrospectively reviewed. A total of 30 eyes of 15 patients were included. The average age at lensectomy was 4.6 years. Sixteen eyes of 8 patients subsequently underwent Artisan implantation at an average age of 12.7 years. Prior to lensectomy, the mean best-corrected visual acuity was 0.66 logMAR and 0.11 logMAR after lensectomy. This difference was statistically significant. However mean-best corrected visual acuity before Artisan implantation and after was essentially unchanged and there was no difference in visual acuity between the pseudophakic and aphasic groups. There were no cases of retinal detachment in either group. One eye required a posterior capsulotomy 2 years following lensectomy. One eye in the pseudophakic group required a repeat peripheral iridectomy for pseudophakic pupil block. One eye had a dislocated Artisan haptic 7 years after surgery and underwent two additional surgeries. In the pseudophakic group the mean endothelial cell count was 3109 cells/mm2 preoperatively and 2632 cells/mm2 postoperatively. Overall cell loss was 15.4% over a mean follow-up of 4.1 years. The authors feel the lack of retinal detachments in this study might be attributable to the young age at lensectomy and therefore milder octopi and absence of lattice degeneration. Genetic data was not obtained and it is possible that this cohort’s genetic make-up placed them at a lower risk of retinal detachment. Surgeons also need to be aware of the moderate but significant rate of endothelial cell loss found in this study.

Ocular axial growth in pseudophakic eyes of patients operated for monocular infantile cataract: a comparison of operated and fellow eyes measured at surgery and 5 or more years later

The authors report axial length (AL) changes with >=5 years of follow-up after unilateral infantile cataract surgery. They compared AL growth in operated eyes and percentage of AL growth in pseudophakic eyes to AL
changes in the unoperated fellow eyes. This was a 14-year retrospective review. A total of 72 pseudophakic patients operated on before 7 months of age were reviewed but only 24 met inclusion criteria. Thirteen patients received a primary IOL implant and 11 received a secondary implant at a mean age of 4.3 years. Overall duration of follow-up was 8.2 years and follow-up after secondary IOL implantation was 3.6 years. Operated eyes were significantly shorter than unoperated eyes, both preoperatively and at final follow-up. However, AL growth and percentage of AL growth were not significantly different between operated and unoperated eyes. Also AL growth of primary IOL implanted eyes was not significantly different than that of fellow eyes (this was true for single IOL as well as piggyback IOL implanted eyes). These results contradict other studies such as IATS. This study was retrospective and had a small sample size. However, the study is strengthened by length of follow-up, uniformity of surgical technique by a single surgeon, and the use of immersion A-scan ultrasound to measure axial length.

Pediatric cataract surgery complications

Incidence, management, and visual outcomes in pediatric endophthalmitis following cataract surgery by a single surgeon


This retrospective case series from Chennai, India describes the incidence of endophthalmitis following pediatric cataract surgery by a single surgeon between January 2000 and December 2012. The authors also describe its microbiological profile, management, and visual outcomes. The medical records of patients who underwent cataract surgery were reviewed and those with postoperative endophthalmitis were identified. A total of 2,390 cataract surgeries were performed during the study period. The overall endophthalmitis rate during the study period was 0.376% (95% CI, 0.357-0.395). The incidence is comparable to previous reports. Of the 9 cases of postoperative endophthalmitis identified, 8 had a median duration of 2.5 days between time of surgery and diagnosis. The common presenting symptoms were pain and redness. Of the 5 cases in which early vitrectomy was performed, 4 showed good visual recovery at final follow-up visit. Follow up period ranged from 1 month-14 years. At final follow-up, 6 of 9 patients had best-corrected visual acuity of 6/12 or better. Both Gram-positive and Gram-negative organisms were seen equally. Culture-positive results were seen in 4 patients; two cases of Acinetobacter calcoaceticus, one case of methicillin-resistant
Staphylococcus aureus (MRSA) and one case of Pseudomonas stutzeri. Three of the four cultured organisms were resistant to ceftazidime. This study has many limitations, but it highlights the importance of early recognition and treatment in salvaging the vision, in cases that develop endophthalmitis following pediatric cataract surgery.

Effect of intracameral triamcinolone acetonide on postoperative intraocular inflammation in pediatric traumatic cataract.


Some children develop fibrinous uveitis following cataract surgery. The risk of inflammation is even higher in traumatic cataract cases. The purpose of this prospective interventional study was to study the effect of a single intracameral injection of preservative-free triamcinolone acetonide (2 mg) given at the end of pediatric traumatic cataract surgery on postoperative inflammation. They recruited 40 children with unilateral traumatic cataract and divided them into two groups: the study group, in which intraoperative intracameral triamcinolone acetonide (2 mg) was used at the end of surgery; and a control group, which did not receive intracameral triamcinolone acetonide.

Their results show that none of the study group eyes developed fibrinous anterior chamber reaction in the immediate postoperative period, whereas 3 eyes of the control group (15.0%) did. There were no cases of endophthalmitis. In addition, 3 eyes (15%) in the control group had obscuration of the visual axis at the last follow-up. This complication was not encountered in the study group. No serious intraoperative complications were reported. In this study no adverse events were reported with the use of triamcinolone, such as increased post-operative intraocular pressure. The mean postoperative IOP was 13.65 ± 1.52 in the study group and 13.30 ± 1.65 in the control group at 1 month follow-up. Their conclusion was that the use of intracameral triamcinolone decreased anterior segment inflammation postoperatively in children who had surgery for traumatic cataract. They point out that the adventitious effect of triamcinolone is not only related to its anti-inflammatory effect, but also to the ability to visualize the vitreous and ensure thorough and complete anterior vitrectomy and the reduced need for topical steroid use in non-compliant kids. The limitations of this study are that it was non-randomized and non-masked.

Pediatric cataract surgery – other topics

Trypan blue as a surgical adjunct in pediatric cataract surgery.
The authors studied the effects of trypan blue on performing a continuous curvilinear capsulorhexis (CCC) in a sheep lens model and subsequently in 3 pediatric patients. In the animal model portion of the study, the authors immersed 24 ex vivo fresh sheep lenses in trypan blue or in balanced salt solution. Ease of capsulorhexis was graded on a 4 point scale, with 0 being a failed capsulorhexis and 4 being the easiest-to-perform capsulorhexis. Lenses immersed in trypan blue had a mean score of 2.6 for ease of completion of capsulorhexis compared with the control group score of 1.5 (P=0.03). Capsulorhexis was successfully completed in 92% of trypan blue cases compared with 58% of controls. Immersion in trypan blue decreased the intralenticular pressure by a mean of 4.5 mm Hg (P = .025). In the three pediatric cataract surgery cases, trypan blue was injected into the anterior chamber and left in place for 90 seconds. In two cases, a CCC was created with a cystotome and Utrata forceps. In one case, an anterior capsulotomy was created with a vitrector. Immersion in trypan blue facilitated the completion of the capsulorhexis in sheep eyes by decreasing the elasticity of the lens capsule. Immersion in trypan blue decreased intralenticular pressure, possibly by the dye’s osmotic effect on the lens. The effect of trypan blue dye might reduce the elasticity of the pediatric lens capsule, which could be beneficial if attempting to create a pediatric CCC.

Is an iris claw IOL a good option for correcting surgically induced aphakia in children? A review of the literature and illustrative case study
R Barbara, S R Rufai, N Tan and J E Self Eye September 2016: 30: 1155-1159; advance online publication, July 8, 2016; doi:10.1038/eye.2016.140

The authors review the literature concerning the use of iris claw lenses in the treatment of aphakia in children and they report one case involving a complication of this type of lens. They raise concern about the possibility of continuing endothelial cell loss when these lenses are used and also describe a case of deenclavation of the implant. They recommend that further long term follow-up is needed before the use of this lens can be universal recommended, but do state that the lens can lead to significant improvement in the quality of vision in aphakic children,

Cataract Surgery in Children from Birth to Less than 13 Years of Age Baseline Characteristics of the Cohort

The authors describe baseline characteristics, initial postoperative refractive errors, operative complications, and magnitude of the intraocular lens (IOL) prediction error for refractive outcome in children undergoing lensectomy and entered into a prospective registry study. 1266 eyes of 994 children were studied. Mean
age at first lens surgery was 4.2 years; 337 (34%) were <1 year of age. Unilateral surgery was performed in 584 children (59%). Additional ocular abnormalities were noted in 301 eyes (24%). An IOL was placed in 35 of 460 eyes (8%) when surgery was performed before 1 year of age, in 70 of 90 eyes (78%) from 1 to <2 years of age, and in 645 of 716 eyes (90%) from 2 to <13 years of age. Intraoperative complications were reported for 69 eyes (5%), with the most common being unplanned posterior capsule rupture in 14 eyes, 10 of which had an IOL placed. Prediction error of the implanted IOL was <1.00 diopter in 54% of eyes, but >2.00 diopters in 15% of eyes.

Comment: While we await PEDIG’s future 5-year follow-up data on this cohort, these initial figures on surgical complications do provide the individual surgeon a reference point for studying one’s own frequency and spectrum of surgical complications.

Use of the Delphi process in pediatric cataract management


The Delphi technique is a widely used and accepted method to achieve consensus among experts in controversial areas. This research tool provides a flexible and adaptable method to gather and analyze data regarding practice patterns using a panel of experts. Unlike unstructured group discussions, the Delphi technique allows for equal input from each participant and avoids undue influence from any one individual. An expert group is asked to answer questionnaires anonymously in two or more rounds. Questions that do not result in consensus, are then reviewed during a face-to-face discussion meeting with the assistance of a facilitator. Experts are encouraged to revise answers to earlier questions after hearing the questionnaire responses to parse out those areas where consensus can or cannot be achieved. By using this process, the range of answers decreases, and the group converges towards a consensus. The addition of this face-to-face group discussion meeting is referred to as a modified Delphi approach. In this article, a group of international pediatric cataract experts who had a publishing record in pediatric cataract management, identified areas of consensus and disagreement in the management of pediatric cataract using a modified Delphi approach. The process consisted of three rounds of anonymous electronic questionnaires followed by a face-to-face meeting, followed by a fourth anonymous electronic questionnaire. The executive committee created questions to be used for the electronic questionnaires. Questions were designed to have unit-based, multiple choice or true–false answers. The questionnaire included issues related to the preoperative, intraoperative and postoperative management of pediatric cataract. Sixteen of 22 invited pediatric cataract surgeons agreed to participate. They arrived at consensus or near consensus for 85/108 (78.7%) questions and non-consensus for the remaining 23 (21.3%) questions. Those questions where consensus was not reached highlight areas of either poor evidence or contradicting evidence, and may help investigators identify possible research questions. The authors identified top five questions in the no consensus areas
that need further research: (1) suggested minimum age for bilateral primary IOL implantation, (2) IOL power calculation formula, (3) IOL type for in-the-bag IOL implantation, (4) medications on the table at the end of surgery and (5) upper age limit for performing posterior capsulectomy and anterior vitrectomy.

Retinal Nerve Fiber Layer and Macular Thickness Measurements in Children After Cataract Surgery Compared With Age-Matched Controls.

There are multiple studies using OCT to look at the retinal nerve fiber layer thickness (RNFL) and macular thickness (CMT) in patients with amblyopia. Many of these studies are small with heterogeneous causes of amblyopia and arrive at conflicting conclusions. This study focuses on RNFL and CMT thicknesses in pediatric patients who had had bilateral cataract surgery, unilateral cataract surgery, and in controls, with the goal of understanding structural changes in eyes with deprivation amblyopia from cataract. The patients with unilateral cataracts had significantly thinner RNFL in the affected eyes compared to the fellow eye (85.5um vs. 93.9um) and were also thinner in the superior, nasal and temporal quadrants. Additionally the CMT in the eyes of unilateral cataract was less when compared to normal controls (221 vs. 245um). The authors conclude that eyes with unilateral cataract had thinner RNFL compared to the fellow eye and age matched controls. Additionally, CMT is thinner in eyes with deprivation amblyopia than age matched controls but not compared to the fellow normal eyes. The authors point out that the strength of this study that all of the patients have deprivation amblyopia and that they included controls. However the study is small and only included 15 patients in each group and cannot make any conclusions about causation of their findings.

Comparison of transcorneal and pars plana routes in pediatric cataract surgery in infants using a 25-gauge vitrectomy system.

The purpose of this study is to compare the performance of the 25 gauge transconjunctival sutureless vitrectomy via anterior (transcorneal) and posterior (pars plana) routes in congenital cataracts in infants. Twelve eyes of patients younger than 1 year of age with bilateral cataracts underwent cataract surgery. For each patient one eye was randomized to be operated via the transcorneal route and the other one via the pars plana route. All eyes were left aphakic. All surgeries were performed by one surgeon. Intraoperative complications and postoperative parameters such visual axis opacification and astigmatism were compared between the two groups. All patients had excellent intraoperative and postoperative results. All eyes had a clear visual axis 12 months after surgery.
Mean spherical equivalent was 15.50 ± 2.28 diopters (D) and mean astigmatism was 0.25 ± 0.45 D in the transcorneal group, whereas in the pars plana group it was 15.46 ± 2.45 D and 0.16 ± 0.39 D, respectively, at 12 months, the difference being statistically insignificant ($P > .05$).

The authors concluded that the 25-gauge vitrectomy system allows sutureless surgery with excellent intraoperative control and minimal postoperative inflammation and astigmatism with clear visual axis by both the transcorneal and pars plana routes. Nevertheless increased surgical time, inability to deal with thick fibrous membranes, the potential for wound leaks and postoperative hypotony and endophthalmitis as well as the high cost of the disposable trocars should be considered when planning surgery.

**Lens regeneration using endogenous stem cells with gain of visual function.**

The repair and regeneration of tissues using endogenous stem cells represents an ultimate goal in regenerative medicine. This is the first study demonstrating the regeneration of a human lens. The authors isolate lens epithelial stem/progenitor cells (LECs) in mammals and show that Pax6 and Bmi1 are required for LEC renewal. They design a surgical method of cataract removal that preserves endogenous LECs and achieves functional lens regeneration in rabbits and macaques. They then perform this technique in 12 infants (24 eyes) ages <24 months with bilateral congenital cataracts. The control group was 25 infants (50 eyes) who underwent standard cataract surgery with either intraocular lens implantation or aphakia. In the new technique, the authors perform a 1.0-1.5 mm peripheral anterior capsulorrhexis and remove the cataractous lens through this small opening, leaving most of the anterior capsule and posterior capsule intact, and leaving most of the LECs. Then, over the next three to six months, they observe the LECs recreate a lens with refractive power and some accommodating ability. The small peripheral anterior capsular opening heals, leaving a peripheral scar in the lens. They use Teller acuity cards to measure postoperative visual acuity, showing approximately 20/200 average acuity six months later. They show slit lamp photographs and clear fundus photographs through the regenerated lenses, proving relatively normal lens shape and clarity.

The authors harness what we previously deemed a complication of infantile cataract surgery: Soemmering’s ring formation and visual axis opacification, and use the ability of LECs to proliferate to an advantage. This approach demonstrates a novel treatment strategy for infantile cataracts, and it’s exciting to envision whether this approach could even be utilized in adult eyes. This study is a breakthrough for medicine in general, showing functional tissue regeneration using endogenous stem cells. Finally, the study is an exceptional example of translational research, truly taking what is learned from the laboratory bench to the bedside!

Critiques of this study: The control group did not undergo standard of care as practiced in the United States (undergoing YAG laser to the posterior capsule three months postoperatively rather than a primary posterior capsulectomy / an-
terior vitrectomy). The control group eyes were not directly compared to the study group eyes in terms of visual acuity outcomes. The main statistical comparison was preoperative versus postoperative visual acuity in the experimental group, rather than postoperative visual acuity in the experimental group vs postoperative visual acuity in the control group, and that set the bar low for showing a successful treatment effect. Those measuring visual acuity with Teller cards could not truly be masked to experimental vs. control treatment group owing to the need for aphakic correction in the control group. Refractive correction is not discussed in this paper. Amblyopia is also not discussed; what impact will that 3-6 month delay in waiting for a lens to grow back play on final visual outcome? Many of these questions pertinent to the pediatric ophthalmologist will hopefully be addressed in a subsequent paper giving more details.

14.GLUCOMA

Pediatric glaucoma - surgical management

Outcomes of surgical interventions for primary childhood glaucoma in Northern Tanzania

This is a study on outcome of surgical interventions for primary childhood glaucoma at the Kilimanjaro Christian Medical Center in Tanzania. The authors provide descriptive statistics of their retrospective analysis of outcome after goniomotomy, trabeculotomy, transscleral cyclophotocoagulation (TSCPC) and trabeculectomy (with 5FU or MMC) as initial procedures in children with primary childhood glaucoma from 2000 to 2013. The first two interventions were predominantly used in children below 2 years of age, and the latter procedures in older children. Success was defined as postoperative intraocular pressure (IOP) below 22 mmHg. Success rates, IOP, visual acuity (VA), subsequent interventions and potential risk factors for failure were reported for the respective interventions. Visual function was tested in all infants over 6 months of age using fixation, Cardiff cards, Lea symbols or Snellen charts. If both eyes needed surgery, the second eye was usually operated on 2–3 weeks later. IOP was assessed either with Schiotz, Icare or applanation tonometry. If necessary, children were sedated for the measurement of IOP. The study included 116 eyes of 70 children (age 4.6±5.9 years) with primary childhood glaucoma. The preoperative IOP was 33.1±10.2 mmHg, the preoperative cup/disc (CD) ratio 0.71±0.3 and the corneal diameter 13.3±1.4 mm. As a primary intervention, 61 (52.6%) eyes underwent goniomotomy, 10 (8.6%) eyes trabeculotomy, 12 (10.3%) TSCPC and 33 (28.4%) trabeculectomy. Follow-up data after 12 months were available for 63 (54.3%) eyes. Success rates at 12 months were 38% (goniometomy), 30% (trabeculotomy), 17% (TSCPC) and 64% (trabeculectomy). Goniometomy and trabeculotomy achieved a statistically significant IOP reduction at 3, 6 and 12 months. Tra-
beculectomy achieved this after 6 months. TSCPC did not show significant IOP reduction. Postoperative endophthalmitis occurred in one child treated with trabeculectomy. Visual acuity was maintained or had improved in 82% of all eyes after 12 months. Based on the outcome, the authors recommended goniotomy or trabeculotomy for younger and trabeculectomy for older children. Late presentation in combination with advanced glaucomatous damage as well as erratic postoperative follow-up and treatment were likely factors that compromised overall success rates. More efforts are necessary to detect the blinding disease earlier and improve adherence to follow-up.

Comparison of 360 degrees circumferential trabeculotomy and conventional trabeculotomy in Primary Pediatric Glaucoma surgery: Part 1

Christiana Celea, Serban Dragosloveanu, Mihai Pop, Christian Celea.

In this retrospective chart review, 79 eyes were operated and thirty-eight (n1=38) received traditional trabeculotomy (conventional group) whereas the other forty-one (n2=41) received a 360 degrees circumferential trabeculotomy with a 40-gauge red-light-guided catheter (circumferential group). The post-operative exams were performed under sedation at 10 days, 1 month, 6 months and 2 year post-operatively and included intraocular pressures (IOP), corneal diameter, axial length and posterior and anterior segment exams. At 2 years postoperatively, the IOPs tended to slowly elevate in both groups with values in the circumferential group being statistically significantly lower than the conventional group. In terms of corneal diameters, there were statistically significant differences between the two groups and greater decrease in the circumferential group. Axial lengths were not influenced in either group. In the circumferential group, the surgery could not be completed in 7.1% of the case due to anatomic difficulties, and these cases were considered as procedure failures, which means that a conversion to tradition trabeculotomy can be indicated sometimes. The authors conclude that conventional trabeculotomy should be the first choice procedure in the surgical management of pediatric glaucoma.

Management of pediatric aphakic glaucoma with vitrectomy and tube shunts.


The purpose of this study is to investigate the impact of vitrectomy and tube shunts on mean intraocular pressure (IOP) and number of glaucoma medications in pediatric aphakic glaucoma. In this retrospective chart review, a total of 14 eyes underwent concomitant vitrectomy (traditional pars plana or limbal-based) and posterior glaucoma shunt tube placement (Amhed or Baerveldt) for uncontrolled aphakic glaucoma. Data recorded were: age at the time of surgery, gender,
laterality, preoperative IOP and number of glaucoma medication, pre and post operative BCVA. The mean IOP post-operatively was checked at day 1, and months 3, 6, 9, and 12. The authors found that the mean IOP at 12 months post-operatively was 16.6 mmHg with a mean of 2.3 glaucoma medications.

In conclusion, although this study included a small number of subjects, it supports the contention that glaucoma tube shunts with concomitant vitrectomy can successfully control IOP in the majority of patients. Although many of the patients required concomitant medical therapy with topical ocular hypotensive agents, the average preoperative IOP decreased by 51% with fewer topical medications.

**Boston type 1 keratoprosthesis for primary congenital glaucoma**


The authors described their experience in using Boston type 1 keratoprosthesis (KPro-1) in the treatment of eyes with primary congenital glaucoma (PCG). A retrospective review was performed of every eye with PCG that was treated with a KPro-1 at a tertiary eye care centre between January 2008 and July 2014. They excluded cases of juvenile glaucoma or childhood-onset glaucoma secondary to disorders such as anterior segment dysgenesis or aniridia. The main outcome measures were visual outcome, prosthesis retention and postoperative complications. They found six eyes of six patients. Age range varied widely: two pediatric patients were aged 6 months and 6 years, and four adults who were 27–33 years of age. Preoperatively, the best corrected visual acuity (BCVA) was worse than 20/400 in every eye. Three eyes had hand motions and one eye had light perception vision. After a mean follow-up period of 31 months (range 16–51 months), three eyes (50.0%) had a BCVA that was ≥20/400. Overall, the BCVA improved in four eyes (66.7%), and remained the same in two eyes (33.3%). The device was retained in six eyes (83.3%). One or more complications occurred in five eyes (83.3%) and included sterile corneal ulceration (three eyes), retroprosthetic membrane formation (three eyes), progressive glaucomatous optic neuropathy (two eyes), device extrusion (one eye) and an epiretinal membrane (one eye). The authors concluded that the Boston KPro-1 has an “excellent” prognosis for retention in eyes with congenital glaucoma. The visual prognosis remains guarded due to the high prevalence of pre-existing ocular comorbidity and the common occurrence of sight-threatening postoperative complications. However, there was no improvement in vision in the 50 months of follow-up in the two pediatric cases. There is also a significant degree of morbidity associated with maintenance therapy after K-Pro.

**Pediatric glaucoma – corneal biometry, OCT and visual field**
The macula in pediatric glaucoma: quantifying the inner and outer layers via optical coherence tomography automatic segmentation


Recent Spectralis (Heidelberg, Germany) spectral domain optical coherence tomography (SD-OCT) research software can automatically quantify the thickness of each individual retinal layer. The macular ganglion cell layer (GCL) and ganglion cell complex may be more sensitive for detecting glaucoma than the peripapillary retinal nerve fiber layer (pRNFL). The aim of this retrospective study was to characterize and compare the volume of each macular layer in the eyes of children with glaucoma versus those of normal controls. The medical records of children with primary glaucoma and physiologic cupping who had undergone Spectralis SD-OCT imaging of the macula and pRNFL were reviewed. Controls were recruited from a separate prospective study. Children with refractive error of >5 D myopia or hyperopia, retinal abnormalities or neurologic abnormalities were excluded. The average volume of each of the 8 retinal layers in the macula (central 6 mm) and pRNFL were compared among diagnostic groups. A total of 80 eyes of 80 children were included: 37 glaucoma eyes (25 with primary congenital and 12 with juvenile open-angle glaucoma) and 43 nonglaucoma eyes (28 with physiologic cupping). Eyes with glaucoma had significantly thinner mean macular nerve fiber layers, ganglion cell layers, inner plexiform layers, and pRNFLs than nonglaucomatous eyes: 0.82 ± 0.24 μm versus 1.00 ± 0.12 μm; 0.93 ± 0.22 μm versus 1.13 ± 0.10 μm; 0.80 ± 0.14 μm versus 0.91 ± 0.07 μm; 81.6 ± 26.5 μm versus 102.7 ± 10.0 μm, respectively (P < 0.05 for all); whereas the inner nuclear layer was minimally thicker compared to nonglaucomatous eyes 1.04 ± 0.09 μm versus 0.98 ±0.07 μm. Eyes without cupping and those with physiologic cupping were equivalent for all variables tested. The authors concluded that children with glaucoma have thinning of the three innermost retinal macular layers. Apart from the RNFL, GCL and IPL, the clinical relevance of other retinal layers thickness within the macula to glaucoma is not completely clear. The authors acknowledge some of the limitations of this study including its retrospective nature and small sample size. The population of PCG children was skewed toward eyes with relatively better vision, because some eyes with severe PCG were excluded due to high refractive errors, media opacities and poor vision.
Diurnal fluctuation of intraocular pressure (IOP), implicated in progression of adult glaucoma, has been reported in children only in the context of office and short-term home monitoring. The purpose of this prospective study was to evaluate long-term patterns of IOP fluctuation and changes resulting from outflow-enhancing intervention in pediatric glaucoma. Parent-measured home-based rebound tonometry (Icare, Finland Oy) in pediatric glaucoma patients was used to monitor IOP for more than 1 month, with requested measurements at least 3 times daily. IOP was recorded at home on electronic data sheets. It was then evaluated for trends including mean overall IOP, IOP pre- and post-planned IOP-lowering interventions, and IOP spikes over determined time intervals. IOP was measured in 14 eyes of 7 children (mean age, 9.3 +/- 2.4 years) over a mean of 164.3 days (range, 75-341), with a mean of 2.46 readings daily. Six eyes of 5 children underwent attempted outflow improvement, with improved mean IOP before versus after intervention (26.6 vs 15.5 mm Hg, P < 0.0001) and decreased mean daily IOP fluctuation (8.4 vs 4.6 mm Hg, P < 0.001) for each. The likelihood of measuring an IOP spike (20% greater than mean for an individual eye over the entire period) was found to be 19.3 ± 6.7% over 1 day, 62.9 ± 18.0% over 3 days, 80.8 ±12.2% over 7 days, and 92.9 ± 9.4% over 14 days. The authors concluded that long-term home monitoring in pediatric glaucoma proved feasible in this study population and often demonstrated large IOP fluctuations. A 14-day period of home monitoring provided >90% chance of identifying an IOP spike. Successful outflow improvement lowered both mean IOP and mean daily IOP fluctuations. This study was intended to be a pilot on long-term home tonometry and was limited to motivated families of cooperative children with glaucoma. Included patients had post cataract surgery glaucoma and juvenile open-angle glaucoma; other types of pediatric glaucoma were not included. The cost-effectiveness of this type of home-monitoring of intra-ocular pressure in pediatric glaucoma has yet to be established. Yet this interesting and well-designed study gives us some insight into the IOP fluctuations in pediatric glaucoma.
Primary Congenital Glaucoma Versus Glaucoma Following Congenital Cataract Surgery: Comparative Clinical Features and Long-term Outcomes.

Primary congenital glaucoma (PCG) and glaucoma following congenital cataract surgery (GFCS) are both rare eye disorders, but are two of the most important causes of glaucoma in the pediatric population. Both types of glaucoma (PCG and GFCS) can lead to impaired vision and other complications. The purpose of this study was to compare outcomes of patients with primary congenital glaucoma (PCG) to those who have glaucoma following congenital cataract surgery (GFCS). This was a retrospective review of 72 PCG and 56 GFCS patients at Emory eye center over a 32-year period. Patients were included if they had more than a 2 year follow up. The vision in the better seeing eye of the bilaterally affected children was 20/30 in the PCG groups vs. 20/70 in the GFCS patients. Median IOP was lower on average in the eyes with PCG (15.5 vs. 17.5 mmHg). The patients with PCG were also on fewer medications to control IOP (1.49 vs. 2.54) and had fewer surgeries (1.0 vs. 1.25). Additionally patients with PCG were less likely to have a devastating complication (endophthalmitis, retinal detachment, hypotony). In sum, the children with PCG had an earlier presentation overall, required fewer medications and had lower eye pressure and better vision than their counterparts with GFCS. The authors point out the limitations of being at a tertiary care center where many patients receive care prior to presentation and the retrospective nature of the study. Additionally, the aphakic status of the GFCS patients might confound the visual acuity data in this study. This study is important to our field because it highlights how complex GFCS is and how different it is than PCG in the setting of outcomes. This large retrospective study is helpful for the pediatric ophthalmologist when we counsel patients with pediatric glaucoma in understanding their prognosis and natural disease course.

Impact of Surgery on the Quality of Life of Caregivers of Children with Congenital Glaucoma

In this prospective cohort study, the authors surveyed 111 caregivers of children with congenital glaucoma using the 20-item Caregiver's Congenital Glaucoma Quality of Life (CarCGQoL) survey before and after glaucoma surgery. On average, patients experienced a significant reduction in IOP (mean change -13.6 mmHg) post-operatively. There was a significant improvement in caregivers' CarCGQoL score from 0.84 pre-operatively and 2.18 postoperatively. According to survey results, caregivers reported an improvement in depression, anxiety, lack of self-confidence, poor appetite, insomnia, anger and irritability.

Comment: It is interesting to see the improvement in quality of life after surgery but it is not stated whether there was any correlation in improved
CarCGQoL and success of surgery. Anxiety and other negative symptoms may be increased above baseline pre-operatively by awareness of upcoming surgery. This theoretical escalation of caregivers’ negative emotions could confound whether surgery actually produces an overall reduction in negative symptoms and improvement in quality of life.

Rapidly growing iris melanocytoma with secondary glaucoma in a 6-year-old child.

In this case report the authors describe an unusual case of a 6-year-old Asian girl with pediatric iris melanocytoma with secondary pigment dispersion glaucoma that resolved after resection of the primary tumor. She was initially treated with topical anti-glaucoma medication and observation. Rapid growth prompted biopsy, revealing melanocytoma. As the tumor continued to grow, excision of the primary tumor was performed. Surgery proved curative in that the pigment dispersion slowly reabsorbed and her glaucoma resolved. In this case, rapid growth did not indicate malignant transformation. The authors conclude that initial observation for growth and judiciously timed surgical intervention prevented progression, loss of vision, and potentially the loss of the eye.

Rebound tonometry over an air-filled anterior chamber in the supine child after intraocular surgery

This study compared the new position-independent Icare PRO with a handheld applanation tonometer, the Tono-Pen XL after placement of intracameral air during anterior chamber intraocular surgery. This was a 9-month prospective study of consecutive children. Thirty children were included (3 had bilateral surgery and 5 had more than one procedure). One eye was excluded and 42 eyes were included. Preoperatively the mean IOP with the Tono-Pen XL and the Icare PRO were 23.52 mm Hg and 20.94mm Hg respectively. Immediately after surgery, the IOP over intracameral air was 12.66mm Hg and 12.96mm Hg respectively. It was noted that the Icare Pro was better at obtaining results in cases of low IOP. There was much greater similarity of IOP measurements (ie. <5mm Hg difference) with postoperative measurements (92.7%) than preoperative measurements (64.3%). Eyes with corneal edema had higher IOP measurements pre- and postoperatively than those without corneal edema. The Icare PRO offers the advantage of horizontal or vertical measurements and may reduce the need for examinations under anesthesia.
15. REFRACTIVE SURGERY

Changes in stereopsis after photorefractive keratectomy.

Photorefractive keratectomy (PRK) could improve stereoacuity by correcting anisometropia or eliminating the magnification or minification and prismatic effects of glasses. Alternatively, it could reduce stereoacuity by decreasing contrast sensitivity, changing the location of the nodal point, or increasing optical aberrations, especially in a decentered ablation. The purpose of this prospective cohort study was to evaluate the effects of photorefractive keratectomy (PRK) on the stereopsis of myopic and hyperopic patients. Recruited patients were adults age 18 to 36 years, who had hyperopia less than 4.0 D, myopia less than 9.0 D, corrected distance visual acuity better than 5/10, and no strabismus (no distance or near phoria or tropia >5PD horizontally or >1PD vertically). Near stereoacuity was measured using the Randot test using corrective glasses preoperatively and without corrective glasses at 1, 3, and 12 months postoperatively. The study included 180 patients. The mean preoperative stereoacuity was 121 seconds of arc (arcsec) ± 150 (SD), improving to 84 ± 76 arcsec 1 month postoperatively and 81 ± 64 arcsec at 3 months (both P < 0.001). Stereoacuity remained unchanged (83 ± 75 arcsec) at 12 months (P = 0.6). Patients with high myopia (6.0 to 9.0 D myopia) had the greatest improvement in stereopsis after PRK compared with low myopic and hyperopic patients (P < 0.001). The improvement in stereocuity was significantly higher in the severely anisometropic group; the lowest improvement was in the group without anisometropia. The authors conclude that PRK can improve stereopsis, especially among high myopes and those with severe anisometropia. It is unlikely that the neural basis for stereopsis improved in these adult patients. The optical effects of viewing through high minus lenses, and aniseikonia, likely limited stereopsis, and these optical effects were eliminated with corneal refractive surgery. Improvement in stereopsis could also have been due to a learning effect.

16. GENETICS

The genetics of nonsyndromic bilateral Duane retraction syndrome

In this consecutive case series from Saudi Arabi, 12 patients with (bilateral nsDRS) were tested for various monogenic mutations and
chromosomal copy number variants (CNVs). None of the patients in the series had dysmorphism or other obvious congenital ophthalmologic, neurologic, auditory, facial, musculoskeletal, or general medical abnormalities. Genes associated with DRS and associated congenital cranial dysinnervation disorders (SALL4, CHN1, HOXA1, TUBB3, and KIF21A) were sequenced in the standard fashion in each patient. Array comparative genomic hybridization (array CGH) was performed using Affymetrix Cytogenetics Whole-Genome 2.7M array, and the results were analyzed using Affymetrix Chromosome Analysis Suite v1.2. CNVs were assessed as unlikely to be pathologic if they were also present in the Database of Genomic Variants (DGV) or in the local database of array CGH results in 150 normal individuals of Middle Eastern ethnicity. No patient had a sequence mutation in SALL4, CHN1, HOXA1, TUBB3, or KIF21A. These 12 patients each had 36-42 chromosomal deletions and/or duplications (mean with standard deviation, 26.25 +/- 6.77), but all of these CNVs were present either in the DGV or in our local database of normal individuals of similar ethnicity and, therefore, were considered non-pathogenic. The authors concluded that their results suggest that bilateral non-syndromic bilateral Duane retraction syndrome is not usually associated with mutations in these genes or with chromosomal CNVs, and that other factors, epigenetic and/or teratogenic abnormalities, may be a potential cause of bilateral nsDRS. One might not be able to generalize these conclusions to other ethnic groups. Authors also suggest the following algorithm, when assessing a patient with either unilateral or bilateral DRS. First, rule out syndromic features. If present, consider evaluation of genes associated with DRS, or array CGH, or both. Lack of syndromic features, should warrant an assessment of family members for nsDRS or syndromic features with or without DRS. Family history can give an indication for a possible monogenic or chromosomal etiology. A patient with no family history of dysmorphism or other anomaly, probably does not require genetic evaluation.


Typical Duane retraction syndrome, a common form of congenital cranial dysinnervation disorder (CCDD), is rarely due to a monogenic mutation. However, the unusual form of exotropic Duane syndrome with synergistic divergence was recently associated with bi-allelic mutations in the gene COL25A1, raising the possibility that this particular Duane syndrome phenotype could be a monogenic recessive CCDD. To explore this possibility, the authors tested 4 consecutive unrelated subjects with the diagnosis for COL25A1 mutations. None har-
bored pathogenic variants, evidence that exotropic Duane syndrome with synergistic divergence is not specifically caused by mutations in the gene.

**Large Deletions of TSPAN12 Cause Familial Exudative Vitreoretinopathy (FEVR).**

Familial exudative vitreoretinopathy (FEVR) is a rare, hereditary visual disorder. The gene TSPAN12 is associated with autosomal dominant inheritance of FEVR. The prevalence and impact of large deletions/duplications of TSPAN12 on FEVR patients is unknown. Thirty-three Korean FEVR patients, who previously screened negative for TSPAN12 mutations, mutations in other FEVR-associated genes such as NDP, FZD4, LRP5, and large deletions and duplications of NDP, FZD4, and LRP5, were selected for TSPAN12 large deletion and duplication analyses. Semiquantitative multiplex PCR for TSPAN12 gene dosage analyses were performed, followed by droplet digital PCR (ddPCR) for validation. Three patients were confirmed to carry large TSPAN12 deletions. Two of them had whole-gene deletions of TSPAN12, and the other patient possessed a deletion of TSPAN12 in exon 4. FEVR severity detected in these patients was not more severe than in a patient with TSPAN12 point mutation. Patients with TSPAN12 large deletions were more common than patients with single nucleotide variants in TSPAN12. Evaluating TSPAN12 large deletions and duplications should be considered in FEVR screening and diagnosis as well as in routine genetic workups for FEVR patients.

**Novel PEX11B Mutations Extend the Peroxisome Biogenesis Disorder 14B Phenotypic Spectrum and Underscore Congenital Cataract as an Early Feature.**

Peroxisomes perform complex metabolic and catabolic functions essential for normal growth and development. Mutations in 14 genes cause a spectrum of peroxisomal disease in humans. Most recently, PEX11B was associated with an atypical peroxisome biogenesis disorder (PBD) in a single individual. In this study, the authors identify further PEX11B cases and delineate associated phenotypes. Probands from three families underwent next generation sequencing (NGS) for diagnosis of a multisystem developmental disorder. Autozygosity mapping was conducted in one affected sibling pair. ExomeDepth was used to identify copy number variants from NGS data and confirmed by dosage analysis. Biochemical profiling was used to investigate the metabolic signature of the condition. All patients presented with bilateral cataract at birth but the systemic phenotype was variable, including short stature, skeletal abnormalities, and dysmorphism-features not described in the original case. Next generation sequenc-
ing identified biallelic loss-of-function mutations in PEX11B as the underlying cause of disease in each case (PEX11B c.235C>T p.(Arg79Ter) homozygous; PEX11B c.136C>T p.(Arg46Ter) homozygous; PEX11B c.595C>T p.(Arg199Ter) heterozygous, PEX11B ex1-3 del heterozygous). Biochemical studies identified very low plasmalogens in one patient, whilst a mildly deranged very long chain fatty acid profile was found in another. The findings expand the phenotypic spectrum of the condition and underscore congenital cataract as the consistent primary presenting feature. Biochemical measurements of peroxisome function may be disturbed in some cases. Furthermore, diagnosis by NGS is proficient and may circumvent the requirement for an invasive skin biopsy for disease identification from fibroblast cells.


The authors evaluate consanguineous pedigrees from Pakistan with a clinical diagnosis of nonsyndromic congenital retinal nonattachment (NCRNA) and identify genes responsible for the disease as currently only one NCRNA gene is known (atonic basic helix-loop-helix transcription factor 7: ATOH7). A three-step genotyping platform was implemented: single nucleotide polymorphism genotyping to identify loss of heterozygosity regions in patients, Retinal Information Network panel screening for mutations in currently known retinal genes. Negative patients were then subjected to whole exome sequencing. Twenty-one consanguineous NCRNA pedigrees and identified the causal mutations in known retinal genes in 13 out of our 21 families. ATOH7 mutations were found in three families. Surprisingly, the authors then found mutations in familial exudative vitreoretinopathy (FEVR) genes; low-density lipoprotein receptor-related protein 5 mutations (six families), tetraspanin 12 mutations (two families), and NDP mutations (two families). Thus, 62% of the patients were successfully genotyped in the study with seven novel and six previously reported mutations in known retinal genes. Because severe congenital retinal detachment has not been previously associated with all the FEVR genes, the authors have thus expanded the phenotypic spectrum of FEVR, a highly variable retinal detachment phenotype that has clinical overlap with NCRNA. Seven novel mutations were identified. Eight NCRNA families did not harbor mutations in any known retinal genes, suggesting novel causal genes in these families.

Characterization of CDH3-Related Congenital Hypotrichosis With Juvenile Macular Dystrophy.
Congenital hypotrichosis with juvenile macular dystrophy (HJMD) is a rare disorder presenting in childhood and adolescence with central visual disturbance and sparse scalp hair. Reported retinal imaging is lacking, and whether the condition is progressive remains unclear. The authors investigate a series of patients with HJMD due to balletic mutations in CDH3 and thereby characterize the disorder. Ten patients from 10 families underwent detailed clinical assessment, including serial retinal imaging and electrophysiologic evaluation, at Moorfields Eye Hospital, St James's University Hospital, and Calderdale Royal Infirmary. Patients ranged in age from 3 to 17 years at onset and 5 to 57 years at last assessment. The molecular genetic investigation included bidirectional Sanger sequencing of all exons and intron-exon boundaries of CDH3 and whole-exome sequencing in 2 patients. The study was conducted from June 5, 2013, to January 15, 2016, with final follow-up completed on December 15, 2015. All 10 patients (7 male and 3 female) presented with central visual disturbance in childhood and had lifelong sparse scalp hair with normal facial hair. Fundus examination revealed chorioretinal atrophy of the posterior pole contiguous with the disc in all but 1 patient that was associated with marked loss of autofluorescence on fundus autofluorescence imaging. Optical coherence tomography (OCT) demonstrated variable degrees of atrophy of the outer retina, retinal pigment epithelium, and choroid, with outer retinal tubulations frequently observed. One patient had mild disruption of the inner segment ellipsoid band on OCT and additional mild digit abnormalities. Electrophysiologic evaluation in 5 patients demonstrated macular dysfunction with additional mild, generalized retinal dysfunction in 2 patients. Eight patients had more than 1 evaluation; of these, 5 patients showed deterioration of visual acuity over time, 1 patient remained stable, and 2 patients had severe visual loss at presentation that precluded assessment of visual deterioration. The area of atrophy did not progress with time, but retinal thickness decreased on OCT. Electrophysiologic evaluation in 1 patient found deterioration of macular function after 13 years of follow-up, but the mild, generalized photoreceptor dysfunction remained stable. Biallelic mutations were identified in all patients, including 6 novel mutations. The disease is readily distinguished from other juvenile macular dystrophies by the universally thin and sparse scalp hair. Patients may have additional limb abnormalities.

**Expanding the Phenotype of TRNT1-Related Immunodeficiency to Include Childhood Cataract and Inner Retinal Dysfunction.**

*TRNT1* causes a multiorgan syndromic disorder characterized by sideroblastic anemia, immunodeficiency, periodic fever, and developmental delay with an uncharacterized retinal dystrophy. This report of a family with a homozygous mutation in *TRNT1* expands the ocular phenotype to include cataract and inner retinal dysfunction and details a mild systemic phenotype. A consanguineous family with 3 affected children was investigated. Key clinical features comprised hypogammaglobulinemia, short stature with microcephaly, cataract, and inner reti-
nal dysfunction without sideroblastic anemia or developmental delay. Two sib-
lings had poor balance and 1 sibling had sensorineural hearing loss. The oldest
sibling had primary ovarian failure diagnosed at age 14.5 years. Exome sequenc-
ing identified a homozygous missense variant in \textit{TRNT1}, c.295C>T (p.Arg99Trp)
in all 3 patients. The sibling with hearing loss also harbored a homozygous muta-
tion in \textit{GJB2}, c.71G>A (p.Trp24*), which is an established cause of sensorineural
hearing loss. This family expands the ocular and systemic phenotypes associat-
ed with mutations in \textit{TRNT1}, demonstrating phenotypic variability and highlight-
ing the need for ophthalmic review of these patients.

\textbf{Characterization of Chorioretinopathy Associated with Mitoch-
ondrial Trifunctional Protein Disorders: Long-Term Follow-up of 21 Cases.}


Authors aim to assess, through a retrospective case series, the long-term effects
of genotype on chorioretinopathy severity in patients with mitochondrial trifunc-
tional protein (MTP) disorders. Participants are consecutive patients with MTP
disorders evaluated at a single center from 1994 through 2015, including 18 pa-
tients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
and 3 patients with trifunctional protein deficiency (TFPD). Local records from all
visits were reviewed. Every participant underwent a complete ophthalmic exami-
nation and was evaluated by a metabolic physician and dietitian. Nine patients
underwent ancillary funduscopic imaging including optical coherence tomography
(OCT) and OCT angiography. The primary outcome measure was best-corrected
visual acuity at the final visit. Secondary outcome measures included spherical
equivalent refraction, visual fields, electroretinography B-wave amplitudes, and
qualitative imaging findings. Participants were followed up for a median of 5.6
years (range 0.3-20.2 years). The median age of LCHADD participants at initial
and final visits was 2.3 and 11.9 years, whereas that for TFPD participants at ini-
tial and final visits was 4.7 and 15.5 years, respectively. Four long-term survivors
older than 16 years were included (3 with LCHADD and 1 with TFPD). The
LCHADD participants demonstrated a steady decline in visual acuity from an av-
erage of 0.23 logarithm of the minimum angle of resolution (logMAR; Snellen
equivalent, 20/34) at baseline to 0.42 logMAR (Snellen equivalent, 20/53) at the
final visit, whereas TFPD patients maintained excellent acuity throughout follow-
up. Participants with LCHADD, but not TFPD, showed an increasing myopia with
a mean decrease in spherical equivalent refraction of 0.24 diopters per year. Vis-
ual fields showed sensitivity losses centrally associated with defects on OCT.
Multimodal imaging demonstrated progressive atrophy of the outer retina in
LCHADD, often preceded by the formation of outer retinal tubulations and cho-
riocapillaris dropout. Electroretinography findings support the more severe clini-
cal profile of LCHADD patients compared with TFPD patients; the function of
both rods and cones are attenuated diffusely in LCHADD patients, but are within
normal limits for TFPD patients. Authors conclude that Multimodal imaging is most consistent with choriocapillaris loss exceeding photoreceptor loss.

**Characterization of CDH3-Related Congenital Hypotrichosis With Juvenile Macular Dystrophy**

This study examined 10 patients with congenital hypotrichosis with juvenile macular dystrophy with detailed phenotyping, including serial imaging and electrophysiologic evaluation with genetic confirmation of biallelic CDH3 mutations and describes 6 novel mutations. The disease is caused by biallelic loss of function mutations in the CDH3 gene (OMIM 114021), which encodes P cadherin, a regulator of hair, retinal pigment epithelium (RPE), and limb development. 8 families were consanguineous. Most children presented with early central vision loss in the first decade of life. The vision loss was progressive in 5 of the patients. The mean age at last exam was 27.2 years, with visual acuity ranging from 0.18 logMAR (Snellen, 20/30) to hand motion. This correlated with atrophy of the posterior pole of the retina, choroid and RPE. Serial imaging confirmed increasing hyperpigmentation around areas of atrophy and autofluorescence. ERG revealed absent pattern ERG in 3/5 patients tested consistent with severe macular dysfunction. All patients had sparse, thin hair.

Conclusion: CDH3-related disease appears to be centrally progressive with preserved peripheral function. Consider the diagnosis when a child presents with marked macular dysfunction and has thin, sparse hair.

**Expanding the Phenotype of TRNT1-Related Immunodeficiency to Include Childhood Cataract and Inner Retinal Dysfunction**

This study delineates the ocular phenotype and ERG characteristics of 3 siblings with TRNT 1 – related immunodeficiency. Congenital sideroblastic anemia with immunodeficiency, fever, and developmental delay (SIFD) is a recessively inherited disorder due to mutations in tRNA nucleotidyltransferase CCA-adding, 1(TRNT1, OMIM 61290712,13). The patients had acquired bilateral posterior subcapsular opacities noted between age 3 and 5 years. All were successfully operated, No mutation was reported in recessive cataract genes using whole-exome sequencing. Inner retinal dysfunction has not previously been reported for this disease and resembles congenital stationary night blindness with normal fundus appearance, moderately reduced vision and nystagmus. Genetic mutations known to cause congenital stationary night blindness were not found in these patients. Conclusion: All patients with TRNT-1 mutations should have eye exams.
Axenfeld–Rieger Syndrome and Leukoencephalopathy Caused by a Mutation in \textit{FOXC1}
Manish Kumar, Chelsea Chambers, Radhika Dhamij. p113–114. Published online: September 9, 2016

Next-generation sequencing testing identified a pathogenic variant in the \textit{FOXC1} (c.477C>G, p.Tyr159*), predicted to result in premature protein truncation in a patient with Axenfeld-Rieger and leukoencephalopathy. In this case, the authors note the importance of MRI imaging in patients with neurologic disease and features of Axenfeld-Rieger Syndrome and highlight this mutation found via NGS.

Next-Generation Sequencing in the Diagnosis of Juvenile Neuronal Ceroid Lipofuscinosis.
Brita S. Deacon, Jane M. Charles, Edward W. Cheeseman, Sara S. Cathey p71–72. Published online: April 18, 2016

Next-generation sequencing (NGS) technology detected the deletion of exons 7 and 8 (c.461-280_677þ382del), the most frequent mutation in CLN3 disease in this case report of a nine-year old child who presented with optic atrophy and decreased visual acuity in the setting of developmental regression, gait abnormality, and autism spectrum disorder. Her symptoms evolved to include a cherry-red foveal spot, vascular attenuation in both eyes and a bull's eye maculopathy. Through NGS and allele specific PCR, they were able to successfully diagnose the patient with juvenile neuronal ceroid lipofuscinosis and confirm the presence of the deletion in CLN3.

Correlation between \textit{PABPN1} genotype and disease severity in oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant disease characterized by dysphagia and ptosis with onset in the fourth to sixth decade of life. The genetic abnormality which causes OPMD is a triplet repeat expansion on the \textit{PABPN1} gene. Wild type \textit{PABPN1} contains 10 triplet repeats, while OPMD patients have between 11-18 repeats. Previous studies have shown no correlation with the size of the expansion and severity of the phenotype, with sample sizes ranging from 17-86 patients. This study evaluated 354 patients with OPMD. There was a strong negative correlation of number of triplet repeats with age at diagnosis. Patients who were homozygous for \textit{PABPN1} expansion were also found to have a negative correlation between age at diagnosis and number of repeats. Homozygous patients had the worse phenotype compared to heterozygous patients. Patients with larger expansions also had worse clinical symptoms, including ptosis, dysphagia, and proximal weakness. Analysis of the
number of triplet repeats in PABPN1 expansion in OPMD patients may predict the course and severity of disease.

**Dysregulated mitophagy and mitochondrial organization in optic atrophy due to OPA1 mutations**  
Chunyan Liao, Neil Ashley, Alan Diot, Karl Morten, et al.  

Mitophagy (recycling of mitochondria by autophagosomes) has been found to be increased in patients with Leber hereditary optic neuropathy. Fibroblasts from 5 patients who had dominant optic atrophy plus (DOA plus) were evaluated. Mitochondria were found to be more fragmented in these fibroblasts compared to controls. There were more cells that were depleted of mitochondrial DNA in biallelic DOA plus patients compared to controls. *OPA1* knockdown cells had significant loss of mitochondrial DNA. Autophagosomes colocalized with mitochondria, indicating that mitophagy, and not decreased mitochondrial DNA synthesis, was the cause for decreased mitochondrial DNA in these fibroblasts from DOA plus patients. Dysregulation of mitophagy may be important in the pathogenesis of mitochondrial optic neuropathies, and may be a useful target for therapies for these disorders.

**Three-Dimensional Characteristics of Four Macular Intraretinal Layer Thicknesses in Symptomatic and Asymptomatic Carriers of G11778A Mutation with Leber’s Hereditary Optic Neuropathy**  
Huang S, Chen Q, Ma Q, Liu X, et al.  
*Retina* 2016 December; 36:2409-2418.

25 eyes (7 symptomatic and 18 asymptomatic) of patients with Leber’s hereditary optic neuropathy (G11778A homoplasmic mutations) from one Chinese family and 16 normal eyes underwent macular radial scans by SD-OCT. Custom software produced 3D thickness maps. The macula was divided into 9 regions, and each region included 4 intraretinal layers: nerve fiber layer, ganglion cell layer and inner plexiform layer, inner nuclear layer and outer plexiform layer, and outer retinal layer. Nerve fiber layer in the symptomatic eyes was significantly thinner than in normal eyes for most of the macular regions, though in the asymptomatic eyes it was thicker in 3 regions. Ganglion cell layer and inner plexiform layers in all regions of symptomatic eyes were thinner than in asymptomatic eyes and controls. Inner nuclear layer and outer plexiform layers in 6 regions of symptomatic and asymptomatic eyes were significantly thicker than in controls, and the outer retinal layer of asymptomatic eyes was thicker than in most control regions.

This study was limited by its small sample size and cross-sectional design. However, all enrolled patients came from one Han Chinese family with the same mutation who lived in close proximity to one another, thus minimizing any effect of
differing environmental conditions on disease development. Objective evaluation of macular changes in symptomatic and asymptomatic carriers of LHON gene mutations may aid in understanding the natural history of the disease and may become a useful tool for the early identification of patients with LHON.

**Single-Exome sequencing identified a novel RP2 mutation in a child with X-linked retinitis pigmentosa.**

This study presents a case of novel RP2 mutation in a child with X-linked retinitis pigmentosa (RP) using a single-exome sequencing. Current strategy for molecular diagnosis of X-linked RP involves mutation screening of the RPGR and RP2 genes by conventional Sanger sequencing or arrayed primer extension (APEX) chips. Sanger sequencing is time consuming, costly, and labor intensive, especially when screening multiple genes or regions in genetically heterogeneous diseases such as RP. On the other hand, the APEX method cannot offer a chance to identify novel genes or mutations because the array is designed to detect only known mutations in known genes. An 8-year-old proband and his family underwent comprehensive ophthalmologic examinations. Exome sequencing undertaken in the proband used Agilent SureSelect Human All Exon Kit and Illumina HiSeq 2000 platform. Bioinformatic analysis used Illumina pipeline with Burrows-Wheeler Aligner-Genome Analysis Toolkit (BWA-GATK), followed by ANNOVAR to perform variant functional annotation. All variants passing filter criteria were validated by Sanger sequencing to confirm familial segregation. Analysis of exome sequence data identified a novel frameshift mutation in RP2 gene resulting in a premature stop codon (c.665delC, p.Pro222fsTer237). Sanger sequencing revealed this mutation co-segregated with the disease phenotype in the child's family. The authors identified a novel causative mutation in RP2 from a single proband's exome sequence data analysis. This study highlights the effectiveness of the whole-exome sequencing in the genetic diagnosis of X-linked retinitis pigmentosa, over the conventional sequencing methods. Even using a single exome, exome sequencing technology would be able to pinpoint pathogenic variant(s) for X-linked retinitis pigmentosa, when properly applied with aid of adequate variant filtering strategy.

**Preserved visual function in retinal dystrophy due to hypomorphic RPE65 mutations**

In this report, Dr. Moore and his co-authors describe detailed phenotypic and molecular findings in four patients from four families with atypical, mild, recessive RPE65-related retinal dystrophy. The authors discuss potential implications for
gene replacement therapy. These patients with early onset retinal dystrophy underwent clinical examination, retinal imaging and electrophysiological testing. Bidirectional Sanger sequencing of all exons and intron–exon boundaries of RPE65 was performed. All patients presented with nyctalopia in early childhood but demonstrated a mild phenotype with good visual acuity until at least 19 years of age. All had generalized retinal dysfunction on electroretinography. Central macular thickness on optical coherence tomography was preserved in those patients with good visual acuity. One patient had extensive white dots throughout the retina reminiscent of fundus albipunctatus with electrophysiological evidence of partial recovery of rod function after prolonged dark adaptation. Sanger sequencing identified RPE65 mutations in all patients including three missense variants likely to represent hypomorphic alleles. Hypomorphic mutations of RPE65 are associated with mild disease in childhood with preservation of good visual acuity into adulthood; they may in rare cases be associated with a flecked retina appearance similar to fundus albipunctatus. The presence of normal visual acuity in patients with hypomorphic mutations in RPE65 suggests that efficiency of transduction may not be the limiting factor in improving visual acuity in trials of gene replacement therapy. Rather, it suggests that for optimal recovery of visual acuity gene replacement therapy may need to be provided much earlier in childhood.

**WFS1 in Optic Neuropathies: Mutation Findings in Nonsyndromic Optic Atrophy and Assessment of Clinical Severity**

In this retrospective observational study, genetic and clinical database was sampled to identify *WFS1* mutations in patients with optic atrophy (OA) and assess visual impairment. Biallelic *WFS1* mutations were found in 3 of 24 unrelated patients (15%) with autosomal recessive nonsyndromic optic atrophy (arNSOA) and in 8 patients with autosomal recessive Wolfram syndrome (arWS) associated with diabetes mellitus and OA. Heterozygous mutations were found in 4 of 20 unrelated patients (20%) with autosomal dominant OA. The 4 *WFS1*-mutated patients of this latter group with hearing loss were diagnosed with autosomal dominant Wolfram-like syndrome (adWLS). Most patients had VA decrease, with logMAR values lower in arWS than in arNSOA (1.530 vs. 0.440; *P*=0.026) or adWLS (0.240; *P*=0.006) but not differing between arNSOA and adWLS (*P*=0.879). All patients had decreased RNFL thickness that was worse in arWS than in arNSOA (SD OCT, 35.50 vs. 53.80 mm; *P*=0.018) or adWLS (TDOCT, 45.84 vs. 59.33 mm; *P*=0.049). Visual acuity was negatively correlated with RNFL thickness (*r*=0.89; *P*=0.003 in SD OCT and *r*=0.75; *P*=0.01 in TD-OCT). The authors concluded that *WFS1* is a gene causing arNSOA and that patients with this condition had significantly less visual impairment than those with arWS.

Comment: The key point of the paper is that a clinically available genetic test for mutations of *WFS1* performed in isolated, sporadic, or familial optic atrophies may elucidate a systemic diagnosis of Wolfram syndrome which significant sys-
temic implications such as pituitary dysfunction (diabetes insipidus), sensorineural deafness, urinary tract dysfunction, male hypogonadism, neurological and psychiatric disorders

**Bull’s Eye and Pigment Maculopathy are Further Retinal Manifestations of an Abnormal Bruch’s Membrane in Alport Syndrome.**

Alport syndrome is an inherited form of progressive renal failure, associated with hearing loss, lenticular and central perimacular and peripheral fleck retinopathies. Inheritance is X-linked with mutations in the *COL4A5* gene, or autosomal recessive with mutations in the *COL4A3* or *COL4A4* genes. Previously described retinal features of Alport syndrome include a central and peripheral fleck retinopathy, temporal retinal thinning, and a macular hole. Vision is normal or nearly normal with both the central and peripheral retinopathies. There are two previous reports of a “bull’s eye” maculopathy in patients with Alport syndrome. This paper describes two unrelated but affected individuals with a florid bull’s eye maculopathy, and also a subtler maculopathy with hyper- and hypopigmentation at the foveola in a cohort of Alport patients. The authors reviewed archived retinal images from a cohort of X-linked (28 males, 28 females) or autosomal recessive (n = 13) Alport syndrome. All individuals had Alport syndrome confirmed on genetic testing or renal biopsy, were examined by an ophthalmologist, and underwent retinal imaging. In the index female patient with bull’s eye maculopathy, optical coherence tomography (Heidelberg Spectralis) demonstrated a disrupted retinal pigment epithelium and retinal atrophy. Upon review of the cohort, another female patient with an early bull’s eye maculopathy was identified (1/69, 1.4%). The authors noted a subtle pigment maculopathy associated with an abnormal retinal pigment epithelium in 27 (27/69, 39%) subjects with Alport syndrome, in both males (8/28, 29%) and females (13/28, 46%) with X-linked disease, and in autosomal recessive disease (6/13, 38%). The bull’s eye and pigment maculopathies in Alport syndrome result mainly from the damaged Bruch’s membrane and overlying retinal pigment epithelium. The association of bull’s eye maculopathy with Alport syndrome is unlikely to be coincidental since both conditions are rare, and there are two previous case reports. The authors recommend that Alport patients undergo regular monitoring for retinal complications considering bull’s eye maculopathy affects vision

**Mutations in CPAMD8 Cause a Unique Form of Autosomal-Recessive Anterior Segment Dysgenesis.**
Anterior segment dysgeneses (ASDs) comprise a heterogeneous spectrum of developmental disorders affecting the anterior segment of the eye. Here, the authors describe three unrelated families affected by a previously unclassified form of ASD. Shared ocular manifestations include bilateral iris hypoplasia, ectopia lentis, corectopia, ectropion uveae, and cataracts. Whole-exome sequencing and targeted Sanger sequencing identified mutations in CPAMD8 (C3 and PZP-like alpha-2-macroglobulin domain-containing protein 8) as the cause of recessive ASD in all three families. A homozygous missense mutation in the evolutionarily conserved alpha-2-macroglobulin (A2M) domain of CPAMD8, c.4351T>C (p. Ser1451Pro), was identified in family 1. In family 2, compound heterozygous frameshift, c.2352_2353insC (p.Arg785Glnfs*23), and splice-site, c.4549-1G>A, mutations were identified. Two affected siblings in the third family were compound heterozygous for splice-site mutations c.700fl1G>T and c.4002fl1G>A. CPAMD8 splice-site mutations caused aberrant pre-mRNA splicing in vivo or in vitro. Intriguingly, the phylogenetic analysis revealed rodent lineage-specific CPAMD8 deletion, precluding a developmental expression study in mice. The authors therefore investigated the spatiotemporal expression of CPAMD8 in the developing human eye. RT-PCR and in situ hybridization revealed CPAMD8 expression in the lens, iris, cornea, and retina early in development, including strong expression in the distal tips of the retinal neuroepithelium that form the iris and ciliary body, thus correlating CPAMD8 expression with the affected tissues. This study delineates a unique form of recessive ASD, characterized by predominant iris and lens anomalies that don’t affect the cornea or posterior segment. It also defines a role for CPAMD8, a protein of unknown function, in anterior segment development, implying another pathway for the pathogenicity of ASD. The findings of this study suggest that mutations in CPAMD8 might cause ASD in genetically unresolved individuals.

Unilateral BEST1-Associated Retinopathy.


Best disease (vitelliform macular dystrophy) is an early-onset macular dystrophy typically characterized by bilateral accumulation of subretinal deposit resulting from heterozygous mutations in the BEST1 gene (OMIM 153700). It is a slowly progressive macular dystrophy with usual onset in childhood but sometimes in later teenage years. The retinal changes are typically bilateral and relatively symmetrical, but rarely, inherited BEST1 mutations may be associated with unilateral maculopathy, with only 3 cases reported in the literature to date. The authors describe five patients with molecularly confirmed mutation in BEST1 causing Best disease but with apparent unilateral clinical manifestation. Patients had full ophthalmologic examination, color fundus photography, fundus autofluorescence imaging, spectral-domain optical coherence tomography, and detailed electrophysiologic assessment. The authors claim that all cases had a clinical appearance typical of and consistent with Best disease at various stages, except that the presentation was unilateral. The reduced electrooculogram light rise was
bilateral and in the context of normal electroretinograms indicated generalized dysfunction at the level of the retinal pigment epithelium. The unilateral nature of four out of the five cases, however, is disputable. A letter to the editor (Unilateral BEST1-Associated Retinopathy. Cicinelli MV, Sacconi R, Querques G. Am J Ophthalmol. 2017 Jan;173:148-149), noted that all cases, except Case 1, contain a thickening at the IS/OS interface on SD-OCT scan. This indicates that the fellow eyes of Cases 2-5 should be classified as previtelliform phenotypes, rather than normal. Irregardless, this paper demonstrates the variable expressivity of Best disease. Furthermore, it reveals that Best disease

**Ocular Morphology and Function in Juvenile Neuronal Ceroid Lipofuscinosis (CLN3) in the First Decade of Life.**


Neuronal Ceroid-Lipofuscinosis (CLN, OMIM 256730) comprises a group of lysosomal storage disorders. Common to all forms of CLN is accumulation of lipofuscin-like autofluorescent deposits in all cells of the body examined so far. Currently 13 genes and one locus have been identified to underlie one autosomal dominant and 13 autosomal recessive traits of the disease. Most patients show infantile or juvenile onset of the disease caused by mutations in three genes *PPT1* (CLN1), *TPP1* (CLN2) and *CLN3* (CLN3). The majority of the patients with CLN3 suffer from neurological degeneration in the first decade of life leading to death in the second or third decade. One of the first symptoms is a rapid visual decline from retinal degeneration. The aim of this study was to correlate the retinal changes in CLN3 as seen with spectral domain optical coherence tomography (SD-OCT) with functional data in patients in the first years after the subjective onset of ocular symptoms. Three unrelated children aged from 5.6 to 8.8 years, and with molecularly confirmed CLN3, underwent a comprehensive ophthalmological examination including visual acuity, fundus photography, fundus autofluorescence (FAF), electrophysiology (multifocal ERG), Goldmann visual fields, and SD-OCT. A predominant loss of the first and second neuron retinal layers progressing from the macula to the periphery was identified. The retinal nerve fibre layer (RNFL) displayed gliosis and an irregular lining of the inner limiting membrane. Compared to the preferential reduction of photoreceptor layer thickness in other maculopathies with pan-retinal involvement, the thickness of the first and second neuron layers was reduced simultaneously in CLN3. Functional testing by multifocal ERG reflected the degenerative progress. Semiquantitative evaluation revealed a generally reduced FAF. This is the first detailed morphological evaluation of CLN3 patients in the first years after the subjective onset of ocular symptoms. The authors revealed CLN3 is characterized by an early degeneration predominant of the first and second neuron compared to other macular and generalized retinal dystrophies. Simultaneous loss of the first and second neuronal layer distinguishes CLN3 from other early onset cone-rod-dystrophies. This proves that imaging is instrumental for early diagnosis and gene-directed molecular analysis of this fatal disorder.
Cystinosis is a rare autosomal recessive disorder that results in intracellular accumulation of cystine in several organs and tissues including the eye. The implicated gene is *CTNS*. The most commonly encountered ocular symptoms of corneal cystinosis include photophobia, foreign body sensation and pain. Corneal cystine crystals begin in infancy and can be identified on slit-lamp examination in all nephropathic cystinosis patients by 16 months of age. The mainstay of treatment of cystinosis is oral cysteamine, however the effect of oral medication in dissolving corneal crystals is poor. The aim of this study is to evaluate the efficacy of topical cysteamine 0.55% eye drops in the treatment of corneal cystine crystal deposits in patients with nephropathic cystinosis. Thirty-two patients with nephropathic cystinosis were prospectively included in the study. Patients with corneal cystinosis were treated with topical cysteamine 0.55% eye drops every 2 hours while awake in both eyes. They were examined before treatment, on each monthly visit and after treatment at the last follow-up. Photophobia was classified as grade 0 (none) for no photophobia, grade 1 (mild) for photophobia in bright light, grade 2 (moderate) for photophobia in room light and grade 3 (severe) for photophobia in dim light. Corneal cystine crystals were graded as grade 0=none, grade 1=1-10 crystals/mm², grade 2=11-50 crystals/mm², grade 3=more than 50 crystals/mm². The main outcome measure was evaluation of photophobia and resolution of corneal cystine crystals. The mean age was 8 years with an age range of 8 months to 19 years. The mean follow-up period was 4.1 years. In this study, 18 (56%) patients had photophobia at presentation. Corneal cystine crystals were found in all patients in the study group at the time of presentation. Improvement of photophobia was not clinically significant in symptomatic patients. Patients displayed statistically significant worsening of corneal cystine deposits during the follow-up period. This study has shown that topical 0.55% cysteamine eye drops may have limited effects in decreasing the corneal cystine deposits in patients with severe forms of nephropathic cystinosis. This is in contrast to several previous reports that have shown the efficacy of topical cysteamine in relieving both signs and symptoms of corneal cystinosis. The authors speculate that genetic variations and poor tissue absorption of cysteamine eye drops may have predisposed to poor outcome following treatment.

**The Ophthalmic Presentation of Hermansky–Pudlak Syndrome 6.**

Hermansky-Pudlak syndrome (HPS) may present to the ophthalmologist with signs suggestive of oculocutaneous albinism (OCA). Consideration of HPS as a differential diagnosis is important due to its potential systemic complications including bleeding diathesis, pulmonary fibrosis, and granulomatous colitis. HPS is an inherited disorder of lysosomal organelle biogenesis most prevalent in Puerto
Rico at a rate of 1 in 1800 due to founder mutations in HPS1 and HPS3. HPS6 is a rarely reported subtype. To date, six families have been reported with HPS6-related disease characterised by OCA with bleeding diatheses. In this report, the initial isolated ophthalmic presentation of HPS6-related disease in three patients from two families is described and the utility of exome sequencing is demonstrated. The patients underwent clinical examination, imaging and targeted systemic investigations. Electrophysiology with visual-evoked potentials (VEPs) was performed in both children of family 1. Whole exome sequencing (WES) was performed on the proband of family 1. Bidirectional Sanger sequencing of the single exon and intron-exon boundaries of HPS6 was performed on all affected patients and segregation confirmed in available relatives. Two siblings, from distantly consanguineous parents of Punjabi Afghan descent, presented in infancy with nystagmus and reduced vision. They were initially diagnosed with isolated foveal hypoplasia with no aberrant chiasmal misrouting on VEPs. WES performed in the proband when 10 years of age identified a novel homozygous missense variant in HPS6 and further questioning elicited a history of nose bleeds and mild bruising. Segregation supported causality of this variant in the affected younger sibling. In the third unrelated patient, of parents of Russian-Palestinian origin, an initial diagnosis of ocular albinism was made at 3 months with HPS only diagnosed at 26 years. Biallelic, truncating mutations in HPS6 were identified by candidate Sanger sequencing and included a novel variant. Abnormal platelet function consistent with HPS was confirmed in all patients. The diagnosis of HPS in all patients was delayed due to a mild systemic phenotype. This study demonstrates that HPS6 can be associated with mild and late systemic manifestations and a diagnosis of HPS should therefore be considered in any patient presenting with foveal hypoplasia, ocular albinism or OCA. An accurate diagnosis will ensure appropriate precautions during surgical or dental procedures. Furthermore, next-generation sequencing can aid diagnosis of syndromic conditions with important consequences for preventing morbidity.


Leber’s hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial genetic disease that causes bilateral acute or subacute, painless, loss of central vision in otherwise healthy young adults, especially in men. More than 95% of LHON cases are caused by three point mutations in the mitochondrial DNA (mtDNA): G11778A, T14484C, and G3460A. LHON-associated vision loss is due mainly to apoptotic degeneration of retinal ganglion cells (RGCs) and their axons, sparing the photoreceptors and retinal pigment epithelium (RPE), as clearly documented by histological studies. Histological examinations have also revealed RGC loss, especially in the macular area and in the papillomacular bundle. The aim of this study is to characterize by spectral domain optical coherence tomography (SD-OCT) the three-dimensional (3D) thicknesses of four mac-
ular intraretinal layers in symptomatic and in asymptomatic carriers of G11778A mutation with LHON. Twenty-five eyes (7 symptomatic eyes and 18 asymptomatic eyes) of patients with LHON from one Chinese family and 16 normal eyes were enrolled. Macular radial scans by SD-OCT and custom software produced intraretinal 3D thickness maps. The macula was divided into nine regions, and each included four intraretinal layers: nerve fiber layer, ganglion cell layer and inner plexiform layer, inner nuclear layer and outer plexiform layer, and the outer retinal layer. Nerve fiber layer in the symptomatic eyes was significantly thinner than in normal eyes for most of the macular regions; however in the asymptomatic eyes, it was increased in three regions. Ganglion cell layer and inner plexiform layers in all regions of symptomatic eyes were significantly thinner than in asymptomatic eyes and controls. Inner nuclear layer and outer plexiform layers in six regions of symptomatic and asymptomatic eyes were significantly thicker than in controls. The outer retinal layer of asymptomatic eyes was thicker than in most control regions. In conclusion, intraretinal thickness changes in asymptomatic patients could be prodromal events that indicate the imminent conversion to symptomatic patients with LHON. SD-OCT with 3D thickness mapping may provide useful information for the early identification of patients with LHON before genetic analysis confirmation. Additionally, SD-OCT can provide an essential tool for monitoring the possible effects of future treatments, such as gene therapy.

**MECR Mutations Cause Childhood-Onset Dystonia and Optic Atrophy, a Mitochondrial Fatty Acid Synthesis Disorder.**


Mitochondrial fatty acid synthesis (mtFAS) is an evolutionarily conserved pathway essential for the function of the respiratory chain and several mitochondrial enzyme complexes. The authors report here a unique neurometabolic human disorder caused by defective mtFAS. Seven individuals from five unrelated families presented with childhood-onset dystonia, optic atrophy, and basal ganglia signal abnormalities on MRI. All affected individuals were found to harbor recessive mutations in *MECR* encoding the mitochondrial trans-2-enoyl-coenzyme A-reductase involved in human mtFAS. All six mutations are extremely rare in the general population, segregate with the disease in the families, and are predicted to be deleterious. The nonsense c.855T>G (p.Tyr285*), c.247_250del (p.Asn83Hisfs*4), and splice site c.830+2_830+3insT mutations lead to C-terminal truncation variants of MECR. The missense c.695G>A (p.Gly232Glu), c.854A>G (p.Tyr285Cys), and c.772C>T (p.Arg258Trp) mutations involve conserved amino acid residues, are located within the cofactor binding domain, and are predicted by structural analysis to have a destabilizing effect. Yeast modeling and complementation studies validated the pathogenicity of the *MECR* mutations. Fibroblast cell lines from affected individuals displayed reduced levels of both MECR and lipoylated proteins as
well as defective respiration. These results suggest that mutations in MECR cause a distinct human disorder of the mtFAS pathway. The mtFAS pathway has not been implicated up to now in human disorders. This inborn error of metabolism resembles typical mitochondrial disorders by the involvement of organs with high energy demands and susceptibility to oxidative stress such as basal ganglia and optic nerve. However, it differs by the relative sparing of cognition and absence of additional organ involvement and typical mitochondrial biomarkers. The observation of decreased lipoylation raises the possibility of a potential therapeutic strategy. The authors propose a name for this disorder, MEPAN (mitochondrial enoyl CoA reductase protein-associated neurodegeneration).

**Autosomal-Recessive Mutations in AP3B2, Adaptor-Related Protein Complex 3 Beta 2 Subunit, Cause an Early-Onset Epileptic Encephalopathy with Optic Atrophy.**

Early-onset epileptic encephalopathy (EOEE) represents a heterogeneous group of severe disorders characterized by seizures, interictal epileptiform activity with a disorganized electroencephalography background, developmental regression or retardation, and onset before 1 year of age. Approximately 100 single-gene disorders with EOEEs have been identified, and each disorder has considerable clinical and genetic heterogeneity. Among a cohort of 57 individuals with epileptic encephalopathy, the authors ascertained two unrelated affected individuals with EOEE associated with developmental impairment and autosomal-recessive variants in AP3B2 by means of whole-exome sequencing. The targeted sequencing of AP3B2 in 86 unrelated individuals with EOEE led to the identification of an additional family. The authors gathered five additional families with eight affected individuals through the Matchmaker Exchange initiative by matching autosomal-recessive mutations in AP3B2. Reverse phenotyping of 12 affected individuals from eight families revealed a homogeneous EOEE phenotype characterized by severe developmental delay, poor visual contact with optic atrophy, and postnatal microcephaly. No spasticity, albinism, or hematological symptoms were reported. AP3B2 encodes the neuron-specific subunit of the AP-3 complex. Autosomal-recessive variations of AP3B1, the ubiquitous isoform, cause Hermansky-Pudlak syndrome type 2. The only isoform for the d subunit of the AP-3 complex is encoded by AP3D1. Autosomal-recessive mutations in AP3D1 cause a severe disorder cumulating the symptoms of the AP3B1 and AP3B2 defects.

**Optical Coherence Tomography Angiography of Choroidal Neovascularization in Four Inherited Retinal Dystrophies.**
Choroidal neovascularization (CNV) is a common complication of multiple inherited chorioretinal dystrophies (IRDs), including vitelliform dystrophies, Sorsby macular dystrophy, pattern dystrophy, choroideremia, and EFEMP1-related retinopathy. Fluorescein angiography (FA) is the current gold standard for diagnosis and classification of new-onset CNV, whereas spectral domain optical coherence tomography (OCT) is routinely used to monitor fibrovascular morphology and fluid accumulation. Patients with retinal degenerative diseases often have distorted retinal architecture, which may complicate the interpretation of both FA and OCT. Optical coherence tomography angiography (OCT-A) is a noninvasive, functional extension of OCT for visualizing retinal and choroidal microvasculature. Unlike the two-dimensional view provided by FA, OCT-A permits topographic isolation of vascular flow by the retinal layer. The authors sought to demonstrate the clinical utility of OCT-A in inherited retinal dystrophies complicated by CNV. OCT-A and structural OCT were performed using a 70-kHz spectral domain OCT system using the split-spectrum amplitude-decorrelation angiography algorithm. Semiautomated image processing software was used to segment and measure the CNV. Four participants were enrolled to study the following inherited retinal dystrophies complicated by CNV: choroideremia, EFEMP1-related retinopathy, Best vitelliform dystrophy, and adult-onset vitelliform dystrophy. Interpretation of FA was difficult because of abnormal retinal architecture but suggested the presence of CNV. Structural OCT revealed subretinal or subretinal pigment epithelium fibrovascular tissue, within which flow signal was observed on OCT-A. The CNV morphology varied from dense capillary networks in active lesions to asymptomatic large caliber loops. Baseline CNV vessel areas ranged from 0.07 mm² to 0.98 mm². After treatment with intravitreous bevacizumab, the CNV in choroideremia decreased in the vessel area then rebounded, whereas the one in EFEMP1-related retinopathy remained largely unchanged. OCT-A enables morphologic characterization and quantification of CNV in patients with retinal dystrophies despite distorted retinal architecture, can assess response to treatment, and may facilitate differentiation between active and regressed lesions.

**Mutations in REEP6 Cause Autosomal-Recessive Retinitis Pigmentosa.**

Retinitis pigmentosa (RP) is the most frequent form of inherited retinal dystrophy. RP is genetically heterogeneous and the genes identified to date encode proteins involved in a wide range of functional pathways, including photoreceptor development, phototransduction, the retinoid cycle, cilia, and outer segment development. Despite the development of targeted next-generation sequencing screening strategies for identifying pathogenic variants in genes already associated with RP, an estimated 40% of cases remain without a molecular diagnosis, suggesting that mutations may exist in genes not previously associated with Mendelian disease. The authors report the identification of biallelic mutations in Receptor Expression Enhancer Protein 6 (REEP6) in seven individuals with autosomal-
recessive RP from five unrelated families. REEP6 is a member of the REEP/Yop1 family of proteins that influence the structure of the endoplasmic reticulum but is relatively unstudied. The six variants identified include three frameshift variants, two missense variants, and a genomic rearrangement that disrupts exon 1. Human 3D organoid optic cups were used to investigate REEP6 expression and confirmed the expression of a retina-specific isoform REEP6.1, which is specifically affected by one of the frameshift mutations. Expression of the two missense variants (c.383C>T [p.Pro128Leu] and c.404T>C [p.Leu135Pro]) and the REEP6.1 frameshift mutant in cultured cells suggest that these changes destabilize the protein. Furthermore, CRISPR-Cas9-mediated gene editing was used to produce Reep6 knock-in mice with the p.Leu135Pro RP-associated variant identified in one RP-affected individual. The homozygous knock-in mice mimic the clinical phenotypes of RP, including progressive photoreceptor degeneration and dysfunction of the rod photoreceptors. Therefore, this study implicates REEP6 in retinal homeostasis and highlights a pathway previously uncharacterized in retinal dystrophy.

Retinitis Pigmentosa-Associated Cystoid Macular Oedema: Pathogenesis and Avenues of Intervention.

Hereditary retinal diseases are now the leading cause of blindness certification in the working age population (age 16–64 years) in England and Wales, of which retinitis pigmentosa (RP) is the most common disorder. RP may be complicated by cystoid macular oedema (CMO) in 10%-50% of patients, causing a reduction of central vision. The underlying pathogenesis of RP-associated CMO (RPCMO) remains uncertain, however, several mechanisms have been proposed, including: (1) breakdown of the blood-retinal barrier, (2) failure (or dysfunction) of the pumping mechanism in the retinal pigment epithelial, (3) Müller cell oedema and dysfunction, (4) antiretinal antibodies and (5) vitreous traction. There are limited data on efficacy of treatments for RP-CMO. Treatments attempted to date include oral and topical carbonic anhydrase inhibitors, oral, topical, intravitreal and periocular steroids, topical non-steroidal anti-inflammatory medications, photo-coagulation, vitrectomy with internal limiting membrane peel, oral lutein and intravitreal antivascular endothelial growth factor injections. This review summarises the evidence supporting these treatment modalities and discusses the pathogenesis of RP-CMO. It highlights the lack of high-quality evidence for RP-CMO treatments. While concrete conclusions cannot be drawn, the evidence currently available suggests that topical CAIs may be used as a first-line approach. Consideration should be given to the possibility of side effects and potential for rebound CMO. Oral CAIs may be a second-line agent, but there is the risk of more side effects. Setting up clinical trials for RP-CMO, however, remains a challenge due to its low prevalence, the highly variable course of disease progression, significant genetic and allelic heterogeneity and very slow progression to visual loss.
Fundus autofluorescence (FAF) imaging is an emerging technology that allows the functional evaluation of photoreceptors and retinal pigment epithelium (RPE). The green light (532nm) widefield autofluorescence imaging modality records signal mainly from RPE lipofuscin but also other fluorophores in the macula and periphery. Reduced FAF is thought to result from photoreceptor loss in early life and is absent with RPE loss. Increased recorded autofluorescence occurs with increased lipofuscin in the RPE or loss of rod outer segments. Ultra-widefield FAF (UW-FAF) allows the characterization of the peripheral retinal features of vitreoretinal diseases. The purpose of this study was to examine possible genotypic/phenotypic correlations of UW-FAF patterns in patients with a variety of retinal dystrophies and retinitis pigmentosa (RP). An IRB-approved retrospective consecutive case series study was performed of genetically characterized retinal dystrophy or RP patients who underwent UW-FAF imaging. UW-FAF was performed with the Optos 200Tx system. Clinical variables, genotypic analysis, and phenotypic characteristics were reviewed. Seventeen patients were identified who had identified mutations in retinal dystrophy or RP genes and who also had undergone UW-FAF. Three patients had X-linked RP with RPGR mutations. Six patients had autosomal dominant RP (four with RHO mutations and one with a PRPF31 mutation, and one with RDS/PRPH2 mutation). Four patients had autosomal recessive RP (four with USH2A mutations). Three patients had Leber Congenital Amaurosis (LCA) with mutations including CRB1, CEP290, and RPGRIP1. Macular hyperautofluorescence was noted in all patients. A ring of hyperautofluorescence was clear in patients with RHO and USH2A mutations, and patients with USH2A mutations demonstrated a second ring of hyperautofluorescence. In the periphery, patients with RHO or RPGR mutations exhibited hyperautofluorescence with patchy areas of hypoautofluorescence. Patients with USH2A mutations had a distinctive pattern of diffuse and homogeneous peripheral hypoautofluorescence. This study suggests the UW-FAF findings in patients with retinal dystrophies is heterogeneous and may have distinctive features in different genetic types of inherited retinal diseases. A prospective large-scale assessment of longitudinal changes on UW-FAF is needed to better characterize UW-FAF as a potential imaging biomarker for inherited retinal diseases with different underlying genetic alterations.

Long-term Follow-up of Patients With Retinitis Pigmentosa Receiving Intraocular Ciliary Neurotrophic Factor Implants.

Ciliary neurotrophic factor receptor alpha is located on Muller glial membranes and on rod and cone photoreceptors. Ciliary neurotrophic factor has been shown
to rescue photoreceptors after a single intraocular injection in a variety of animal models of RP and with maintained exposure through gene therapy in mouse models. However, retinal degeneration models treated with ciliary neurotrophic factor may also show suppression of retinal function as measured with the electroretinogram, suggesting that dosage and duration of exposure can be critical. A therapeutic approach to treatment with ciliary neurotrophic factor in patients with RP was established through sustained-release delivery with intraocular encapsulated cell technology implants. As reported previously, no significant changes in visual acuity were observed in ciliary neurotrophic factor or sham-treated eyes, effectively ruling out any short-term benefit to visual acuity from the ciliary neurotrophic factor implants. In the current study, the authors evaluated the long-term efficacy of ciliary neurotrophic factor delivered via an intraocular encapsulated cell implant for the treatment of retinitis pigmentosa. Thirty-six patients at 3 CNTF4 sites were randomly assigned to receive a high- or low-dose implant in 1 eye and sham surgery in the fellow eye. The primary endpoint (change in visual field sensitivity at 12 months) had been reported previously. Here we measure long-term visual acuity, visual field, and optical coherence tomography (OCT) outcomes in 24 patients either retaining or explanting the device at 24 months relative to sham-treated eyes. Eyes retaining the implant showed significantly greater visual field loss from baseline than either explanted eyes or sham eyes through 42 months. By 60 months and continuing through 96 months, visual field loss was comparable among sham-treated eyes, eyes retaining the implant, and explanted eyes, as was visual acuity and OCT macular volume. Over the short term, ciliary neurotrophic factor released continuously from an intravitreal implant led to loss of total visual field sensitivity that was greater than the natural progression in the sham-treated eye. This additional loss of sensitivity related to the active implant was reversible when the implant was removed. Over the long term (60–96 months), there was no evidence of efficacy for visual acuity, visual field sensitivity, or OCT measures of retinal structure.

Preserved Visual Function in Retinal Dystrophy due to Hypomorphic RPE65 Mutations.

RPE65 (retinal pigment epithelium-specific protein, MIM# 180069) encodes a 65 kD visual cycle protein, retinoid isomerohydrolase, a vital component of the visual cycle. Recessive mutations in RPE65 are associated with severe early onset retinal dystrophy including Leber congenital amaurosis (LCA) and account for approximately 11% of early onset rod–cone dystrophy (RCD). Previous reports of atypical recessive RPE65-related disease have described mild phenotypes due to presumed hypomorphic alleles; a single patient with a fundus albipunctatus phenotype has also been reported. The authors present detailed phenotypic and molecular findings in four patients from four families with atypical, mild, recessive RPE65-related retinal dystrophy and discuss potential implications for gene replacement therapy. All patients underwent clinical examination, retinal imaging
and electrophysiological testing. Bidirectional Sanger sequencing of all exons and intron-exon boundaries of RPE65 was performed. The patients presented with nyctalopia in early childhood but demonstrated a mild phenotype with good visual acuity until at least 19 years of age. All had generalised retinal dysfunction on electroretinography (ERG). Central macular thickness on optical coherence tomography was preserved in those patients with good visual acuity. One patient had extensive white dots throughout the retina reminiscent of fundus albipunctatus with electrophysiological evidence of partial recovery of rod function after prolonged dark adaptation. Sanger sequencing identified RPE65 mutations in all patients including three missense variants likely to represent hypomorphic alleles.

In the patients described here, low level of RPE65 activity from birth is associated with normal VA but markedly reduced rod and cone function (as seen on ERG). In summary, hypomorphic mutations of RPE65 are associated with mild disease in childhood with preservation of good visual acuity into adulthood; they may in rare cases be associated with a flecked retina appearance similar to fundus albipunctatus. The presence of normal visual acuity in patients with hypomorphic mutations in RPE65 suggests that efficiency of transduction may not be the limiting factor in improving visual acuity in trials of gene replacement therapy. Rather, it suggests that for optimal recovery of visual acuity gene replacement therapy may need to be given much earlier in childhood.

Two Missense Mutations in SALL4 in a Patient with Microphthalmia, Coloboma, and Optic Nerve Hypoplasia.

The human Spalt family members, Sal-like proteins 1 to 4 (SALL1, SALL2, SALL3, and SALL4), are transcription factors containing C2H2 double zinc fingers that have been implicated in developmental eye defects. The authors investigate the genetic etiology of anophthalmia and microphthalmia, using exome sequencing in a Caucasian female with unilateral microphthalmia and coloboma, bilateral optic nerve hypoplasia, ventricular and atrial septal defects, and growth delays. They found two sequence variants in SALL4 - c.[575C>A], predicting p.(Ala192Glu), that was paternally inherited, and c.[2053G>C], predicting p.(Asp685His), that was maternally inherited. Haploinsufficiency for SALL4 due to nonsense or frameshift mutations has been associated with acro-renal ocular syndrome that is characterized by eye defects including Duane anomaly and coloboma, in addition to radial ray malformations and renal abnormalities. This report is the first description of structural eye defects associated with two missense variants in SALL4 inherited in trans; the absence of reported findings in both parents suggests that both sequence variants are hypomorphic mutations and that both are needed for the ocular phenotype. SALL4 is expressed in the developing lens and regulates BMP4, leading us to speculate that altered BMP4 expression was responsible for the eye defects, but we could not demonstrate altered BMP4 expression in vitro after using small interfering RNAs (siRNAs) to reduce SALL4
expression. The authors conclude that $SALL4$ hypomorphic variants may influence eye development.

**Ocular and Electrophysiological Findings in a Patient with Sly Syndrome.**

Sly syndrome (Mucopolysaccharidosis Type VII) is an autosomal recessive metabolic storage disorder due to mutations in the $GUSB$ gene encoding the enzyme beta-glucuronidase. Deficiency of this lysosomal enzyme impairs the body’s ability to break down the glycosaminoglycans - dermatan, heparan and chondroitin sulphate. Coarse facial features and macrocephaly are typically seen along with bony and skeletal abnormalities, including joint contractures and short stature. Widespread involvement occurs in many other tissues including cardiopulmonary, gastrointestinal, and neurological systems. In view of the rarity of Sly syndrome the ophthalmic features have not been well described. This is a case report of a 16-year-old boy with Sly syndrome with serial OCT, ocular ultrasound, and electroretinogram (ERG). Corneal clouding was present but there was no evidence of glaucoma or optic neuropathy. Despite no clinical evidence of retinopathy, electrophysiology showed reduced photopic and scotopic responses, particularly involving the b-wave which appears progressive. OCT showed normal foveal architecture and normal retinal nerve fiber thickness. Although retinopathy has not been previously described in Sly syndrome, the ERG changes in this patient suggest that a rod-cone dystrophy, as seen in other MPS disorders, may be a feature of MPS VII. To our knowledge, this is the first description of a retinopathy detected on electrophysiology in a patient with Sly syndrome.

**Stargardt Disease: Clinical Features, Molecular Genetics, Animal Models and Therapeutic Options.**

Stargardt disease (STGD1; MIM 248200) is the most prevalent inherited macular dystrophy and is associated with disease-causing sequence variants in the gene $ABCA4$. The characteristics of STGD1 vary widely due to the marked phenotypic heterogeneity associated with the large number (>900) of disease-causing sequence variants identified in $ABCA4$. Significant advances have been made over the last 10 years in our understanding of both the clinical and molecular features of STGD1, and also the underlying pathophysiology, which has culminated in ongoing and planned human clinical trials of novel therapies. The aims of this review are to describe the detailed phenotypic and genotypic characteristics of the disease, conventional and novel imaging findings, current knowledge of animal models and pathogenesis, and the multiple avenues of intervention being explored. This review concluded that further robust longitudinal prospective natural
history studies, probing genotype-phenotype and structure-function associations, are crucial in order to provide improved prognostication and genetic counseling, as well as optimization of clinical trial design, including identifying suitable participants, windows of opportunity and the most sensitive and reliable outcome metrics.

**Association of Single-Nucleotide Polymorphisms in Non-Coding Regions of the TLR4 Gene with Primary Open Angle glaucoma in a Mexican Population.**

In the last few years, six primary open angle glaucoma genes (MYOC, OPTN, WDR36, NTF4, TBK1, and ASB10) have been reported to cause Mendelian forms of glaucoma. Mutations in the MYOC gene are the most commonly known cause of glaucoma cases worldwide (~1 in 25 cases) and are associated with glaucoma that has high eye pressure. Toll-like receptor 4 (TLR4) non-coding polymorphisms have been reported to be associated with primary open angle glaucoma (POAG), normal tension glaucoma, and pseudoexfoliation glaucoma in the Japanese and Chinese populations. This study was performed to determine whether non-coding single nucleotide polymorphisms (SNPs) in the TLR4 gene contribute to POAG in a Mexican population. A total of 187 unrelated Mexican patients with POAG and 109 control subjects were included. Allelic, genotypic, and haplotypic diversity was assessed for the non-coding polymorphisms rs11536889, rs1927911, rs12377632, and rs2149356 of the TLR4 gene. Genotyping of target SNPs was performed by 5′ exonuclease allelic discrimination assays. Strong linkage disequilibrium was observed among the SNPs (D' > 0.818), which were located in one haplotype block. The rs11536889 polymorphism was not associated with POAG in any case. The frequency of the minor allele of rs2149356 was significantly higher in the glaucoma group, conferring an increased risk of POAG (p = 0.0018, OR = 1.803, 95% CI 1.2556–2.5890) whereas minor allele of rs12377632 was significantly lower, attributing a protective effect (p = 0.0001, OR = 0.6662, 95% CI 0.4753–0.9339). Subjects with genotypes carrying the minor allele of rs1927911 and rs2149356 showed an increased risk for POAG (p = 0.03, OR = 1.78, 95% CI 1.10–2.87, and p < 0.0004, OR =2.62, 95%CI 1.61–4.27 respectively). Finally, the authors found significant risk haplotypes. The GTT haplotype (constituted by rs1927911, rs12377632, and rs2149356) reached the higher OR (p = 0.0026, OR = 4.70, 95% CI 1.73–12.77). In conclusion, the authors have identified intronic TLR4 SNPs as genetic susceptibility alleles for POAG in a Mexican population. These findings support the association of the TLR4 gene with POAG. Additional studies are needed to clarify the role of the TLR4 gene in POAG prognosis, and to elucidate the TLR4 pathways associated with glaucoma.

**Vitamin A Deficiency Due to Bi-Allelic Mutation of RBP4: There’s More To It Than Meets the Eye.**
Vitamin A deficiency is the leading cause of preventable blindness in children worldwide and results in a well-recognized ocular phenotype. Herein we describe a patient presenting to the eye clinic with a retinal dystrophy and ocular colobomata. The patient did not show any features typical of vitamin A deficiency on the eye exam. She also had malar skin pustules. This combination of clinical signs and consanguineous pedigree structure suggested a genetic basis for the disease, a hypothesis that was tested using whole genome sequencing. Bi-allelic mutations in RBP4 were identified (c.248+1G>A), consistent with a diagnosis of inherited vitamin A deficiency. Bi-allelic mutations in RBP4 have only been reported twice before and are thus a poorly recognized cause of disease. This patient and the published cases appear to share a distinctive phenotype comprising of a severe rod-cone dystrophy with ocular colobomata. In summary, the authors describe a constellation of signs that appear to be characteristic for this disease, increasing clinical awareness of this rare condition.

A Family Harboring Homozygous FZD4 Deletion Supports the Existence of Recessive FZD4-Related Familial Exudative Vitreoretinopathy.


Familial exudative vitreoretinopathy (FEVR) is a disease of retinal vascular developmental that primarily affects the peripheral retina and shows marked variable expressivity. FEVR is classically autosomal dominant and is genetically heterogeneous, associated with heterozygous mutations in frizzled-4 (FZD4), low-density lipoprotein receptor-related protein 5 (LRP5), tetraspanin-12 (TSPAN12), zinc finger protein 408 (ZNF408), and, most recently, kinesin family member 11 (KIF11). FEVR can also be X-linked, from hemizygous mutations in norrin (NDP). Recessive FEVR, first described for LRP5, is less common and has been recognized for multiple families with bi-allelic mutations in LRP5 or TSPAN12. There has been only one patient reported with recessive FEVR from FZD4 mutations, a single Japanese girl. The authors document recessive FZD4-related familial exudative vitreoretinopathy in one family. Two brothers, the only two males among five siblings, were found to have bilateral infantile retinal detachments and were referred for genetic counseling. Next-generation sequencing uncovered a homozygous FZD4 frameshift deletion in both affected brothers (c.40_49delCCCGGGGCG; p.Pro14Serfs*44). None of the other immediate family members had clinical evidence for retinal disease, including the three family members who underwent confirmatory genetic testing and were found to be heterozygous for the mutation (both parents and one sister). Interestingly, the FEVR deletion that segregated as a recessive disease-causing allele in this family was previously reported as a cause for dominant FEVR in an
outbred Chinese family. The findings in this family support the concept that some mutated \textit{FZD4} alleles can be associated with recessive rather than dominant disease. In this family, a severe FEVR phenotype segregated with a biallelic deletion in \textit{FZD4}. Heterozygotes were asymptomatic and without retinal findings; however, because fluorescein angiography was not performed the presence of a subtle phenotype cannot be ruled out.


This study aims to expand on current clinical, electrophysiologic, and molecular genetic findings in Knobloch syndrome. Knobloch syndrome is a rare, recessively inherited disorder classically characterized by high myopia, retinal detachment, and occipital encephalocele, but it is now known to have an increasingly variable phenotype. Twelve patients from 7 families underwent full ophthalmic examination and retinal imaging. Further investigations included electroretinography and neuroradiologic imaging. Bidirectional Sanger sequencing of \textit{COL18A1} was performed with segregation on available relatives. The study was conducted from July 4, 2013, to October 5, 2015. Data analysis was performed from May 20, 2014, to November 3, 2015.

Of the 12 patients (6 males; mean age at last review, 16 years [range, 2-38 years]), all had high myopia in at least 1 eye and severely reduced vision. A sibling pair had unilateral high myopia in their right eyes and near emmetropia in their left eyes from infancy. Anterior segment abnormalities included absent iris crypts, iris transillumination, lens subluxation, and cataract. Two patients with iris transillumination had glaucoma. Fundus characteristics included abnormal collapsed vitreous, macular atrophy, and a tesselated fundus. Five patients had previous retinal detachment. Electroretinography revealed a cone-rod pattern of dysfunction in 8 patients, was severely reduced or undetectable in 2 patients, and demonstrated cone-rod dysfunction in 1 eye with undetectable responses in the other eye in 2 patients. Radiologic imaging demonstrated occipital encephalocele or meningocele in 3 patients, occipital skull defects in 4 patients, minor occipital changes in 2 patients, and no abnormalities in 2 patients. Cutaneous scalp changes were present in 5 patients. Systemic associations were identified in 8 patients, including learning difficulties, epilepsy, and congenital renal abnormalities. Biallelic mutations including 2 likely novel mutations in \textit{COL18A1}, were identified in 6 families that were consistent with autosomal recessive inheritance; a single mutation identified in a family with 2 affected children. Two patients had normal neuroradiologic findings, emphasizing that some affected individuals have isolated ocular disease. Awareness of the ocular phenotype may aid early diagnosis, appropriate genetic counseling, and monitoring for potential complications.

This report describes the ocular features of the chromosome 22q11.2 duplication syndrome and provides ophthalmologic examination recommendations for affected patients. The medical records of 19 children with chromosome 22q11.2 duplication who had undergone complete ophthalmological examination, including dilated fundus examination and cycloplegic refraction, were studied retrospectively. Over half of the children with 22q11.2 duplication syndrome were found to have visually significant ocular abnormalities, including 6 with strabismus, 2 with moderately high astigmatism requiring glasses, 1 with unilateral congenital cataract requiring surgery, 1 with optic disk drusen, 1 with bilateral megalocornea with normal eye pressures, 1 with nystagmus that resolved spontaneously, and 1 with delayed visual maturation. Because of the high incidence of conditions that could affect visual development, the authors recommend that children with 22q11.2 duplication syndrome have a complete ophthalmological examination on diagnosis and regular vision screenings by their primary care physician thereafter.


A summary of 70 years of data collected on patients with Leber hereditary optic neuropathy (LHON) in Denmark. Affected individuals were identified from a national register of hereditary eye diseases at the National Eye Clinic (NEC), a tertiary low vision rehabilitation center for the entire Danish population. The assembling of LHON pedigrees was based on the reconstruction of published families and newly diagnosed cases from 1980 to 2012 identified in the files of NEC. Genealogic follow-up on the maternal ancestry of all affected individuals was performed to identify a possible relation to an already known maternal line. A full genotypic characterization of the nation-based LHON cohort is provided by the authors. In this study, forty different lines were identified. The number of live affected individuals with a verified mitochondrial DNA mutation was 104 on January 1, 2013, which translates to a prevalence rate of 1:54,000 in the Danish population. Haplogroup distribution as well as mutational spectrum of the Danish LHON cohort do not deviate from those of other European populations. The genealogic follow-up reveals a relatively high turnover among families with approximately 15 newly affected families per century and the dying out of earlier maternal lines.

Biallelic Mutations in CRB1 Underlie Autosomal Recessive Familial Foveal Retinoschisis.
The authors of this study identify changes in CRB1 as the genetic cause of autosomal recessive familial foveal retinoschisis (FFR).

A female sibship with FFR was identified (Family-A; 17 and 16 years, respectively); panel based genetic sequencing (132 genes) and comparative genome hybridization (142 genes) were performed. Whole-exome sequencing (WES) was performed on both siblings using the Illumina-HiSeq-2500 platform. A sporadic male (Family-B; 35 years) with FFR underwent WES using Illumina NextSeq500. All three affected subjects underwent detailed ophthalmologic evaluation including fundus photography, autofluorescence imaging, spectral-domain optical coherence tomography (SD-OCT), and full-field electroretinogram (ERG). Panel-based genetic testing identified two presumed disease causing variants in CRB1 (p.Gly123Cys and p.Cys948Tyr) in Family-A sibship; no deletion or duplication was detected. WES analysis in the sibship identified nine genes with two or more shared nonsynonymous rare coding sequence variants; CRB1 remained a strong candidate gene, and CRB1 variants segregated with the disease. WES in Family-B identified two presumed disease causing variants in CRB1 (p.Ile167_Gly169del and p.Arg764Cys) that segregated with the disease phenotype. Distance visual acuity was 20/40 or better in all three affected except for the left eye of the older subject (Family-B), which showed macular atrophy. Fundus evaluation showed spoke-wheel appearance at the macula in five eyes. The SD-OCT showed macular schitic changes in inner and outer nuclear layers in all cases. The ERG responses were normal in all subjects.

Expanding the clinical, allelic, and locus heterogeneity of retinal dystrophies.

This study investigates a next-generation sequencing assay that allows known (Retinal dystrophies) RD genes to be sequenced simultaneously. The authors also performed mapping studies and exome sequencing on familial and syndromic RD patients who tested negative on the panel. Panel testing identified the likely causal mutation in >60% of the 292 RD families tested. Mapping studies on all 162 familial RD patients who tested negative on the panel identified two novel disease loci on Chr2:25,550,180-28,794,007 and Chr16:59,225,000-72,511,000. Whole-exome sequencing revealed the likely candidate as AGBL5 and CDH16, respectively. Exome sequencing was also performed on negative syndromic RD cases and identified a novel homozygous truncating mutation in GNS in a family with the novel combination of mucopolysaccharidosis and RD. Moreover, a homozygous truncating mutation in DNAJC17 was identified in a family with apparently novel syndrome of retinitis pigmentosa and hypogammaglobulinemia. The study expands the clinical and allelic spectrum of known RD genes, and reveals AGBL5, CDH16, and DNAJC17 as novel disease candidates.

In this prospective open-label trial (NCT02161380), the study drug (self-complementary AAV [scAAV]2(Y444,500,730F)-P1ND4v2) was intravitreally injected unilaterally into the eyes of 5 blind participants with G11778A LHON. Four participants with visual loss for more than 12 months were treated. The fifth participant had visual loss for less than 12 months. The first 3 participants were treated at the low dose of vector (5 × 10^9 vg), and the fourth participant was treated at the medium dose (2.46 × 10^10 vg). The fifth participant with visual loss for less than 12 months received the low dose. Treated participants were followed for 90 to 180 days and underwent ocular and systemic safety assessments along with visual structure and function examinations. Visual acuity as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart remained unchanged from baseline to 3 months in the first 3 participants. For 2 participants with 90-day follow-up, acuity increased from hand movements to 7 letters in 1 and by 15 letters in 1, representing an improvement equivalent to 3 lines. No one lost vision, and no serious adverse events were observed. Minor adverse events included a transient increase of intraocular pressure (IOP), exposure keratitis, subconjunctival hemorrhage, a sore throat, and a transient increase in neutralizing antibodies (NAbs) against AAV2 in 1 participant. All blood samples were negative for vector DNA. The investigators conclude that no serious safety problems were observed in the first 5 participants enrolled in this phase I trial of virus-based gene transfer in this mitochondrial disorder. Additional study follow-up of these and additional participants are planned for the next 4 years.


A retrospective, observational case series exploring the ocular manifestations of cobalamin C (cblC) deficiency, an inborn error of intracellular vitamin B12 metabolism. Twenty-five cblC patients underwent clinical and ophthalmic examination at the National Institutes of Health between August 2004 and September 2012. Patient ages ranged from 2 to 27 years at last ophthalmic visit, and follow-up ranged from 0 to 83 months (median, 37 months; range, 13-83 months) over a total of 69 visits. Nystagmus (64%), strabismus (52%), macular degeneration (72%), optic nerve pallor (68%), and vascular changes (64%) were noted. c.271dupA (p.R91KfsX14) homozygous patients (n = 14) showed early and extensive macular degeneration. Electroretinography showed that scotopic and photopic responses were reduced and delayed, but were preserved remarkably
in some patients despite severe degeneration. Optical coherence tomography images through the central macular lesion of a patient with severe retinal degeneration showed extreme thinning, some preservation of retinal lamination, and nearly complete loss of the outer nuclear layer. Despite hyperhomocysteinemia, no patients exhibited lens dislocation. This longitudinal study reports ocular outcomes in the largest group of patients with cblC deficiency systematically examined at a single center over an extended period. Differences in progression and severity of macular degeneration, optic nerve pallor, and vascular attenuation between homozygous c.271dupA (p.R91KfsX14) patients and compound heterozygotes were noted. The pace and chronicity of ophthalmic manifestations lacked strict correlation to metabolic status as measured during visits. The effects of prenatal or early treatment, or both, in siblings; the manifestation of severe disease in infancy; the presence of comorbid developmental abnormalities; and the possible laminar structural defect noted in many patients are findings showing that cblC deficiency displays a developmental as well as a degenerative ocular phenotype.

The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Studies: Design and Baseline Characteristics: ProgStar Report No. 1.


First ProgStar study report describing the design and baseline characteristics of patients enrolled into 2 natural history studies of Stargardt disease (STGD1): a multicenter retrospective cohort and a prospective study arm. Three hundred sixty-five unique patients aged 6 years and older at baseline harboring disease-causing variants in the ABCA4 gene and with specified ocular lesions were enrolled from 9 centers in the United States and Europe. In the retrospective study, patients contributed medical record data from at least 2 and up to 4 visits for at least 1 examination modality: fundus autofluorescence (FAF), spectral-domain (SD) optical coherence tomography (SDOCT), and/or microperimetry (MP). The total observational period was at least 2 years and up to 5 years between single visits. Demographic and visual acuity (VA) data also were obtained. In the prospective study, eligible patients were examined at baseline using a standard protocol, with 6-month follow-up visits planned for a 2-year period for serial Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected VA, SD OCT, FAF, and MP. In the retrospective study, 251 patients (458 eyes) were enrolled; mean follow-up ± standard deviation was 3.9±1.6 years. At baseline, 36% had no or mild VA loss, and 47% of the study eyes had areas of definitely decreased autofluorescence (DDAF) with an average lesion area of 2.5±2.9 mm² (range, 0.02-16.03 mm²). Two hundred fifty-nine patients (489 eyes) were enrolled in the prospective study. At baseline, 20% had no or mild VA loss, and 64% had areas of DDAF with an average lesion area of 4.0±4.4 mm² (range, 0.03-24.24 mm²). The
mean retinal sensitivity with MP was 10.8±5.0 dB.

**Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy.**


This nonrandomized, multicenter clinical trial provides an initial assessment of the safety of a recombinant adeno-associated virus vector expressing RPE65 (rAAV2-CB-hRPE65) in adults and children with retinal degeneration caused by RPE65 mutations. Eight adults and 4 children, 6 to 39 years of age, received a subretinal injection of rAAV2-CB-hRPE65 in the poorer-seeing eye, at either of 2 dose levels, and were followed up for 2 years after treatment. The primary safety measures were ocular and nonocular adverse events. Exploratory efficacy measures included changes in best-corrected visual acuity (BCVA), static and kinetic perimetry, and responses to a quality-of-life questionnaire. All patients tolerated subretinal injections and there were no treatment-related serious adverse events. Common adverse events were those associated with the surgical procedure and included subconjunctival hemorrhage in 8 patients and ocular hypere mia in 5 patients. In the treated eye, BCVA increased in 5 patients, static perimetry area increased in 6 patients, and kinetic perimetry area increased in 3 patients. One subject showed a decrease in BCVA and 2 patients showed a decrease in kinetic visual field area. The authors conclude that treatment with rAAV2-CB-hRPE65 was not associated with serious adverse events, and improvement in 1 or more measures of visual function was observed in 9 of 12 patients. The greatest improvements in visual acuity were observed in younger patients with better baseline visual acuity. They call for the evaluation of more patients and a longer duration of follow-up to determine the rate of uncommon or rare side effects or safety concerns.

**Visual Acuity Loss and Associated Risk Factors in the Retrospective Progression of Stargardt Disease Study (ProgStar Report No. 2).**


In this retrospective, multicenter cohort study, the authors examined the association between characteristics of Stargardt disease and visual acuity (VA), estimated the longitudinal rate of VA loss, and identified risk factors for VA loss. A total of 176 patients (332 eyes) with molecularly and clinically confirmed Stargardt disease enrolled from the United States and Europe. Standardized data report forms were used to collect retrospective data on participants’ characteristics and best-corrected or presenting VA from medical charts. Linear models with generalized estimating equations were used to estimate the cross-sectional associa-
tions, and linear mixed effects models were used to estimate the longitudinal VA loss. The median duration of observation was 3.6 years. At baseline, older age of symptom onset was associated with better VA, and a longer duration of symptoms was associated with worse VA. Longitudinal analysis estimated an average of 0.3 lines loss ($P < 0.0001$) per year overall, but the rate varied according to baseline VA. The authors conclude that VA is unlikely to be a sensitive outcome measure for treatment trials of Stargardt disease (given slow rate of VA loss) except in a subgroup of younger patients with an expected faster decline (~ 1.0 line per year).

**Visual Acuity after Retinal Gene Therapy for Choroideremia.**


The authors present 3.5 year results on six patients who underwent gene therapy for choroideremia. Similar to the technique used in the Lebers congenital amaurosis trials, an adenoviral vector was used to deliver the nonmutated choroideremia gene via subretinal injection. In the Lebers congenital amaurosis trials, initial gains in visual function were not sustained in the long term. In the choroideremia gene therapy trial, two of six eyes had improvement in visual acuity in the study eye, and this improvement was sustained over 3.5 years, suggesting a long-lasting effect. The authors discuss the fate of the other four treated eyes and the fellow control eyes. In summary, this pilot study shows some promising results of sustained visual improvement with choroideremia gene therapy.

**Exome Sequencing and the Management of Neurometabolic Disorders.**


Whole-exome sequencing has transformed gene discovery and diagnosis in rare diseases. The authors studied patients with intellectual disability and biochemical laboratory results suggesting a metabolic disorder. They studied 41 probands, predominantly children, with extensive phenotyping and with whole-exome sequencing analysis. These techniques led to a diagnosis in 68%, the identification of 11 candidate genes newly implicated in neurometabolic disease, and a change in treatment beyond genetic counseling in 44%. The study is relevant to pediatric ophthalmologists who may see undiagnosed children with ophthalmological abnormalities, intellectual disability, and biochemical results suggestive of an inborn error of metabolism. A thorough phenotypic and genotypic analysis could lead to a diagnosis that changes patient management.

**Recessive Retinopathy Consequent on Mutant G-Protein β Subunit (GNB3)**

Arno G, Holder GE, Chakarova C, Kohl S et.al. for the UK Inherited Retinal Dis-
The authors describe a novel retinopathy associated with homozygosity for a nonsense mutation in GNB3, a gene whose protein is expressed in cones and bipolar cells. This protein is critical for phototransduction and outer nuclear bipolar cell signaling. Whole exomic sequencing was conducted on the proband who presented with early onset nystagmus, high hyperopia, strabismus, a normal appearing fundus and subnormal vision. Spectral domain OCT revealed an abnormality in the ellipsoid zone and autofluorescence of the macula was abnormal as well. ERG testing revealed abnormalities in rod, but especially cone mediated responses. ERG findings may be compatible with an atypical enhanced S-cone syndrome. This novel mutation in a phototransduction gene is modeled in a naturally occurring homozygous chicken model and mouse knockout and correlates fairly well with the phenotype seen in this pedigree of affected patients.

Importance: This study adds to the differential of diseases associated with congenital nystagmus, normal funduscopic appearance and impaired vision. Whether this is a static or progressive retinopathy will require longer follow up of affected patients.

Ocular finding in children with 22q11.2 deletion syndrome.
Bahar Gokturk, Pinar Topcu-Yilmaz, Banu Bozkurt, Mahmut Selman Yildirim et al

This article describes the ocular features of patients diagnosed with 22q11.2 deletion syndrome in a Turkish population. Sixteen patients were included in this case series and they all had a complete eye exam including uncorrected visual acuity, best-corrected visual acuity, stereopsis, ocular motility testing, anterior and posterior segment examinations. The major ocular findings were eyelid abnormalities (such as eye hooding, narrow palpebral fissure, telecanthus, hypertelorism, sparse and thin eyebrows and eyelashes, blepharitis and distichiasis), posterior embryotoxon, and tortuous retinal vessels. The most common refractive error was hypermetropia and the prevalence of strabismus was 25%. Although serious ocular involvement is not very common, patients with 22q11.2 deletion syndrome should be referred to pediatric ophthalmology for detection of strabismus and correction of refractive errors.

Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy

In this multicenter clinical trial, the author assessed the safety of a recombinant adeno-associated virus vector expressing RPE65 (rAAV2-CB-hRPE65) in the poorer seeing eyes of 8 adults and 4 children with LCA or
SECORD (severe early-childhood onset retinal degeneration) caused by RPE65 mutations. At 2 years of follow-up all patients had tolerated sub-retinal injections and there were no treatment-related serious adverse events. Common adverse events were those associated with the surgical procedure and included subconjunctival hemorrhage in 8 patients and ocular hyperemia in 5 patients. In the treated eye, BCVA increased in 5 patients, static perimetry central 30 degrees increased in 6 patients, total visual field increased in 5 patients, and kinetic visual field area improved in 3 patients. One subject showed a decrease in BCVA and 2 patients showed a decrease in kinetic visual field area. The greatest improvements in visual acuity were observed in younger patients with better baseline visual acuity. Evaluation of more patients and a longer duration of follow-up will be needed to determine the rate of uncommon or rare side effects or safety concerns.

Comment: This preliminary study demonstrates initial safety of an exciting gene therapy strategy for LCA and SECORD.

Whole Genome Sequencing Increases Molecular Diagnostic Yield Compared with Current Diagnostic Testing for Inherited Retinal Disease

The author reviewed records of 562 patients diagnosed with inherited retinal disease (IRD) to compare the efficacy of whole genome sequencing (WGS) with targeted next-generation. Mutation detection rates and molecular diagnostic yields were analyzed. The authors compared the sensitivity and specificity of the 2 techniques to identify known single nucleotide variants (SNVs) using 6 control samples with publicly available genotype data. Across known disease-causing genes, targeted NGS and WGS achieved similar levels of sensitivity and specificity for SNV detection. WGS also identified 14 clinically relevant genetic variants that had not been identified by NGS diagnostic testing for 46 individuals with IRD. These variants included large deletions and variants in noncoding regions of the genome. Identification of these variants confirmed a molecular diagnosis of IRD for 11 of the 33 individuals referred for WGS who had not obtained a molecular diagnosis through targeted NGS testing. Weighted estimates, accounting for population structure, suggest that WGS methods could result in an overall 29% increase in diagnostic yield.

Comment: This study supports the use of whole genome sequencing with targeted next generation sequencing in the diagnosis of inherited retinal disease.

In this retrospective, multicenter observational case series the authors reported the clinical and genetic findings of nine Japanese patients from seven unrelated families with autosomal recessive bestrophinopathy (ARB). Genetic analysis was performed identifying seven pathogenic variants in BEST1 including two novel variants. Homozygous variants were found in four families and compound heterozygous variants were found in three families. Two patients were diagnosed as ARB only after the whole exome sequencing analyses. The Arden ratio of the EOG was less than 1.5 in all seven patients tested. Vitelliform lesions typical for Best vitelliform macular dystrophy were not seen in any of the patients. Seven patients shared some of the previously described features of ARB including: sub-retinal deposits, extensive subretinal fluid, and cystoid macular edema (CME). However, the other two patients with severe retinal degeneration lacked these features. Focal choroidal excavations were present bilaterally in two patients. One case had a marked reduction of the CME and expansion of subretinal deposits over an 8-year follow-up period. Of significance, all the Japanese patients in this case series lacked the vitelliform lesions typical of Best disease. Furthermore, the patients had some but not all of the previously described features of ARB. The lack of “classic” ARB features and phenotypic variability supports molecular testing as an essential component in Best disease diagnosis.

**Novel C8orf37 Mutations in Patients with Early-onset Retinal Dystrophy, Macular Atrophy, Cataracts, and High Myopia.**

This study investigated the clinical and genetic features of two Japanese siblings with early-onset retinal dystrophy. Whole-exome sequencing analysis identified novel compound heterozygous mutations, a splice site mutation (c.374 + 2T>C in intron 4) and a deletion mutation (c.575delC [p.T192MfsX28] in exon 6) of chromosome 8 open reading frame 37 (C8orf37) gene, which encodes a ciliary protein, in both siblings. The mother carried the truncating mutation, and an unaffected brother carried neither mutation. Both patients had diffuse retinal degeneration, macular atrophy, non-recordable electroretinography responses, cataracts, and high myopia. Recessive C8orf37 mutations have been identified in childhood retinitis pigmentosa (RP) and cone-rod dystrophy (CRD) with macular involvement. Due to the severity and early onset of the retinal degeneration in the siblings, it is uncertain as to whether to categorize their disease as RP or CRD. This highlights the fact that even though the first affected cell types are different between RP and CRD, it may be difficult to differentiate between RP and CRD later in the disease process when both cone and rod photoreceptor cells are severely impaired. However, if a good clinical history is available, this may be crucial in differentiating RP from CRD in such situations. This article is also pertinent
as this was the first reported C8orf37-associated retinal dystrophy in the Japanese population to date. There have only been two previous reports regarding C8orf37 mutations.

**Optic Neuropathy in Late-onset Neurodegenerative Chédiak-Higashi Syndrome.**

Chédiak-Higashi syndrome (CHS) is an autosomal recessive disorder caused by mutations in LYST. Typically, disease onset occurs in childhood with ocular albinism and vision loss related to foveal hypoplasia or nystagmus. Optic nerve involvement and ophthalmological manifestations of the late-onset neurodegenerative form of CHS are rarely reported and poorly detailed. This case series reviews the ophthalmological and neurological findings in three adult siblings with the late-onset form of CHS. All three affected siblings lacked features of ocular albinism and demonstrated significant optic nerve involvement. The severity of optic nerve damage corresponded linearly to patient age and neurological disease severity. The authors also described the presence of a ‘third line’ on macular OCT in all three siblings. This ‘third line’ is thought to be due to abnormal melanosomes. This report expands the ophthalmological phenotype of the late-onset neurodegenerative form of CHS to include optic neuropathy with progressive vision loss, even in the absence of ocular albinism. Additionally, an abnormally prominent interdigitation zone between cone outer segment tips and apical processes of retinal pigment epithelium cells on macular OCT was described for the first time.

**Novel Morphological Macular Findings in Juvenile CLN3 Disease.**

This study analyzed the retinal phenotype of patients with juvenile CLN3 disease, one of the most common neuronal ceroid lipofusinoses (NCLs), in order to distinguish it from other inherited retinal dystrophies. The following ophthalmic imaging was utilized: optical coherence tomography, fundus autofluorescence, and near infrared imaging and fundus photography. The Hamburg juvenile NCL (JNCL) score was also used during the assessment. A total of 22 eyes of 11 patients were included. The mean age at examination was 14.4 years (range 11.8–26.4 years), with an average age at initial diagnosis of 8 years (range 4.5–11 years). The mean Hamburg JNCL score was 7.3 (range 0–13). All patients showed a specific macular striation pattern on optical coherence tomography that was independent of age and progression of the disease. The authors presented the first
prospective observational case series documenting retinal abnormalities in CLN3 disease with the aid of the spectral domain optical coherence tomography. The major characteristic finding was a striated macular pattern in all patients studied. Macular striae can potentially help to discriminate CLN3 disease from other inherited retinal degenerations, particularly in early disease.


The authors performed whole-exome sequencing on a family that screened negative for mutations in genes associated with CSNB. Biallelic mutations in the guanine nucleotide-binding protein subunit beta-3 gene (*GNB3*) were identified. Two affected siblings were compound heterozygous for a deletion (c.170_172delAGA [p.Lys57del]) and a nonsense mutation (c.1017G>A [p.Trp339*]). An affected maternal aunt was homozygous for the nonsense mutation (c.1017G>A [p.Trp339*]). Mutational analysis of *GNB3* in a cohort of 58 subjects with CSNB identified a sporadic case individual with a homozygous *GNB3* mutation (c.200C>T [p.Ser67Phe]). *GNB3* encodes the b subunit of G protein heterotrimer (Gαβγ) and is known to modulate ON bipolar cell signaling and cone transducin function in mice. In this study affected human subjects showed an unusual CSNB phenotype with variable degrees of ON bipolar dysfunction and reduced cone sensitivity. The resultant phenotype ranged from severe to mild deficits. The *GNB3*-phenotype most commonly presented with childhood-onset night blindness and middle-age-onset photophobia with near normal vision, absent nystagmus, and lack of high myopia. This unique retinal disorder with dual anomaly in visual processing expands our knowledge about retinal signaling and CSNB.

**The Physiology of the Retinal Pigment Epithelium in Danon Disease.**

Danon disease is a rare X-linked, dominant lysosomal storage disease. It is caused by mutations in the lysosome-associated membrane protein-2 gene (*LAMP2*), which is localized to the retinal pigment epithelium (RPE) in the retina. Retinal abnormalities have been reported to occur in 64% to 69% of patients with Danon disease. The retinal findings include chorioretinal atrophy, a peripheral pigmentary retinopathy in women, and a near complete loss of peripheral retinal pigment in men. The authors sought to expand the ocular phenotype of Danon disease by recording electrooculograms (EOGs), an electrophysiological measure of the standing potential across the eye that depends on the integrity of the RPE, from four related patients with a known *LAMP2* mutation. EOG amplitude ratios of light rise:dark trough, the Arden index, fell at low-normal limits (range:
1.68–3.94) but misrepresent retinal pigment epithelium health, because the absolute dark trough voltages were abnormally low (median: 140 mV, range: 72–192 mV) as were the light rise amplitudes (median: 297 mV, range: 198–366 mV), and fullfield electroretinograms were normal. Low EOG voltages indicate that the RPE is unable to maintain its tight junctions in Danon disease. In summary, this is the first study to show that Danon disease causes a primary retinal pigment epitheliopathy, lowering the trans epithelium potential (TEP) amplitude, with early, widespread funduscopic appearances of RPE atrophy.


Gillespie syndrome (GS) is a rare variant form of aniridia characterized by non-progressive cerebellar ataxia, intellectual disability, and iris hypoplasia. De novo PAX6 mutations have been identified in two simplex families but otherwise molecular studies have failed to identify the disease causing mutation. Using a combination of trio-based whole-exome sequencing and Sanger sequencing in five simplex GS-affected families, the authors found homozygous or compound heterozygous truncating mutations (c.4672C>T [p.Gln1558*], c.2182C>T [p.Arg728*], c.6366.3A>T [p.Gly2102Valfs5*], and c.6664.5G>T [p.Ala2221Valfs23*]) and de novo heterozygous mutations c.7687_7689del [p.Lys2563del] and c.7659T>G [p.Phe2553Leu]) in the inositol 1,4,5-trisphosphate receptor type 1 gene (*ITPR1*). *ITPR1* encodes one of the three members of the IP3-receptors family that form Ca\(^{2+}\) release channels localized predominantly in membranes of endoplasmic reticulum Ca\(^{2+}\) stores. The truncation mutants, which encompass the IP3-binding domain and varying lengths of the modulatory domain, did not form functional channels when produced in a heterologous cell system. Furthermore, *ITPR1* p.Lys2563del mutant did not form IP3-induced Ca\(^{2+}\) channels but exerted a negative effect when co-produced with wild-type *ITPR1* channel activity. In summary, this paper demonstrates the coexistence of autosomal-recessive and autosomal-dominant patterns of inheritance of GS and further extends the spectrum of *ITPR1*-related eye diseases.


Gillespie syndrome (GS) is characterized by bilateral iris hypoplasia, congenital hypotonia, non-progressive ataxia, and progressive cerebellar atrophy. Deciphering Developmental Disorders (DDD) is a UK and Ireland-wide project that aims to use whole-exome sequencing to identify the cause of previously unexplained severe and extreme phenotypes that plausibly have their genesis in embryogenesis
or early fetal brain development. Thirteen patients with a clinical diagnosis were recruited to the DDD study. Trio-based exome sequencing identified de novo mutations in *ITPR1* in three unrelated individuals with GS. Whole-exome or targeted sequence analysis identified plausible disease-causing *ITPR1* mutations in 10/10 additional GS-affected individuals. These ultra-rare protein-altering variants affected only three residues in *ITPR1*: Glu2094 missense (one de novo, one cosegregating), Gly2539 missense (five de novo, one inheritance uncertain), and Lys2596 in-frame deletion (four de novo). No clinical or radiological differences were evident between individuals with different mutations. *ITPR1* encodes an inositol 1,4,5-triphosphate-responsive calcium channel. The homo-tetrameric structure has been solved by cryoelectron microscopy. Using estimations of the degree of structural change induced by known recessive- and dominant-negative mutations in other disease associated multimeric channels, the authors developed a generalizable computational approach to indicate the likely mutational mechanism. This analysis supported a dominant-negative mechanism for GS variants in *ITPR1*. In GS-derived lymphoblastoid cell lines (LCLs), the proportion of *ITPR1*-positive cells using immunofluorescence was significantly higher in mutant than control LCLs, consistent with an abnormality of nuclear calcium signaling feedback control. Super-resolution imaging supported the existence of an *ITPR1*-lined nucleoplasmic reticulum. Mice with *Itpr1* heterozygous null mutations showed no major iris defects. Purkinje cells of the cerebellum appear to be the most sensitive to impaired *ITPR1* function in humans. Iris hypoplasia is likely to result from either complete loss of *ITPR1* activity or structure-specific disruption of multimeric interactions. The authors presented evidence based on the predicted effect of mutations on the formation of multimeric channels suggesting that these mutations are likely acting in a dominant-negative fashion. This protein-structure-based analysis will likely have wide applicability in the interpretation of mutations, particularly in the important “channelopathy” class of human disease genes.

**Ocular Findings in Patients with the Hermansky-Pudlak Syndrome (Types 1 and 3).**


Patients with Hermansky-Pudlak syndrome (HPS) have bleeding diathesis, progressive pulmonary fibrosis, and granulomatous colitis in addition to albinotic findings. HPS is thought to be the most common single-gene disorder in Puerto Rico where it has been reported to occur in 1:1800. The authors retrospectively described ocular findings in 64 patients with HPS type 1 and 3. The patients underwent genetic analysis of selected albinism (*TYR* and *P* gene) and HPS genes (HPS-1 and HPS-3) by screening for common mutations and exon sequencing with DNA screening. About 70% of the patients were homozygous for common Puerto Rican mutations leading to the *HPS1* gene (16-BP DUP, 53.6%), while 30% had the 3904-BP DEL *HPS3* gene mutation. Best corrected visual acuity (BCVA) was poorer in patients with type 1 HPS than in patients with type 3 HPS.
Esotropia was more common among type 1 HPS patients, while exotropia was more common among patients with type 3 HPS. Most patients (97.6%) with type 1 HPS had periodic alternating nystagmus (PAN). Total iris transillumination was more common in patients with type 1 HPS and minimal iris transillumination in patients with type 3 HPS. The maculae were translucent in patients with type 1 HPS, while patients with type 3 HPS had opaque maculae. In summary, patients with type 1 HPS had poorer BCVA, increased incidence of esotropia, PAN, lighter iris and macular appearance. In contrast, patients with type 3 HPS had more exotropia. Of note, this is the largest series of type 3 HPS patients ever reported.

The Ophthalmic Phenotype of \textit{IFT140}-Related Ciliopathy Ranges from Isolated to Syndromic Congenital Retinal Dystrophy.


Conorenal syndrome is a systemic skeletal ciliopathy characterized by skeletal and renal findings and caused by biallelic mutations in the gene intraflagellar transport 140 Chlamydomonas homologue (\textit{IFT140}). To date, 15 families with biallelic \textit{IFT140} mutations have been reported in the literature, the majority of which had syndromic phenotypes. However, with the exception of two children from two Saudi families who the authors previously reported, the presenting ophthalmic phenotype children with \textit{IFT140}-related retinopathy has not been well characterized. In this study the authors highlight the ophthalmic findings in twelve subjects with confirmed homozygous \textit{IFT140} mutations (11 consanguineous families; 7 boys; assessed at age 10 months to 20 years, average and median age 6.5 and 4 years). All were homozygous for the same \textit{IFT140} mutation (c.1990G>A; p. Glu664Lys) except one who was homozygous for c.1541_1542delinsAA. All subjects had poor vision and nystagmus since birth. In early childhood, nine were noted to stare at lights. High hyperopia was a typical finding and electroretinography was found to be non-recordable in all individuals who underwent electrophysiology. Fundus appearance was grossly normal before the age of 1 year but thereafter appeared dystrophic. In older children, peripheral mottling and sometimes peripheral punched-out chorioretinal lesions were seen. In those who underwent autofluorescence and optical coherence tomography (OCT), autofluorescence showed increased central macular signal and OCT showed loss of outer retinal structures. Eight children had developmental delay, two had short stubby fingers, and one had renal disease. Another recurrent observation noted was a happy early childhood demeanor. Four patients had no evident extraocular disease, including one aged 18 years who also had two older affected siblings in their twenties who remained non-syndromic and were excelling academically. In this series, recessive \textit{IFT140} mutations caused a severe congenital retinal dystrophy with high hyperopia and often early photophilia. Developmental delay is common but not universal and not all patients have obvious extraocular findings. The c.1990G>A mutation represents a founder effect or mutational hotspot on the Arabian Peninsula.
The incidence of primary congenital glaucoma (PCG) varies among geographic regions and ethnic groups. The frequency of PCG in Lebanon and identification of disease-causing mutations have not been studied previously. *CYP1B1*, a member of the cytochrome P450 family located on chromosome 2p21 in the GLC3A locus, is the main known gene responsible for PCG, and mutations in this gene are detected in around 50% of PCG cases worldwide. Myocilin gene mutations (*MYOC*), have also been identified in a few cases of PCG worldwide, either independently or in association with *CYP1B1* mutations and are thought to contribute to the disease through common biochemical pathways with *CYP1B1* acting as a modifier for *MYOC*. The authors investigated the role of *CYP1B1* gene and *MYOC* gene mutations in PCG in the Lebanese population and studied genotype/phenotype correlations. Patients with unilateral or bilateral PCG diagnosed at the American University of Beirut Medical Center and their first-degree relatives (parents and siblings) were screened for *CYP1B1* and *MYOC* mutations. Eighteen Lebanese families (66 subjects) with at least one member affected with PCG were included in this study. Mutations in the *CYP1B1* gene were detected in 6 families (33%). Five previously described mutations (p.R444Q; p.E229K; p.R469W; p.G61E; p.M1T) and one new single nucleotide deletion were identified (1793delC). Patients in whom *CYP1B1* mutations were detected tended to have a more severe phenotype as evidenced by earlier age at diagnosis, higher rate of bilateral disease, and higher number of glaucoma surgeries than those in whom no *CYP1B1* mutations were present. *MYOC* gene mutations were not detected in any patients. The rate of *CYP1B1* mutations in Lebanese patients with PCG is lower than that reported in other Arab and Middle Eastern populations, where mutation rates reportedly reach 100% in Omani and Saudi, 80% in Israeli Bedouin, 70.6% in Kuwaiti and 70% in Iranian patients, suggesting other genes are responsible for PCG in the remainder. This discrepancy could be due to the more homogeneous genetic background in these groups as compared to the Lebanese population, in which there is more of an admixture of ethnic backgrounds. The absence of deleterious mutations in *MYOC* gene in this study was somewhat expected considering the modest contribution of this gene to PCG worldwide, with a mutation rate of approximately 5.55%, and more specifically its negligible role in Arabs and Middle-Eastern patients.

**Marfan syndrome: ocular findings and novel mutations-in pursuit of genotype-phenotype associations.**


The authors in this observational single-centre case series had studied the ocular involvement in eleven patients diagnosed with Marfan syndrome.
(MFS), and analyzed the association of ocular signs with the type of FBN1 mutation that was expressed on the genetic testing. All subjects met the Ghent criteria of MFS and the diagnosis was confirmed by genetic testing. They all underwent a complete ophthalmologic examination. Four of the 11 patients (36.4%) had ectopia lentis (EL), of which three developed secondary aphakic glaucoma. The mean spherical equivalent of the phakic eyes was -2.69 DS (median -2.50 DS), and 5/8 (62.5%) of the phakic patients had myopia. Other ocular abnormalities included strabismus, retinal tears, retinal detachment, and amblyopia. The encountered types of mutations were premature termination codon (PTC) in 7 patients (63.6%), missense in two cases, one aberration of splicing, and one indel mutation. Two novel mutations were found. This is different from earlier reports, in which PTC mutations were much less frequent. Of the patients with EL, two had a missense, one an indel, and one a nonsense mutation. The authors conclude that patients with a PTC mutation revealed to have a smaller risk of ectopia lentis; however they indicated that more studies are required to establish the mechanism of the correlation. The main limitation of this study as they had noted is the small group of patients with a great age variety and a possible selection bias, due to the fact that not all patients with MFS who meet the clinical diagnostic criteria are bound to undergo genetic testing.

Wide-Field Imaging of Nonexudative and Exudative Congenital X-Linked Retinoschisis.

Congenital X-linked retinoschisis (CXLRS) is an early-onset inherited retinal disease characterized by intraretinal splitting in the fovea and/or periphery. The authors described wide-field imaging features of 36 eyes from 18 patients with CXLRS. Wide-field color fundus photographs, optical coherence tomography images, and wide-field fluorescein angiography images were reviewed. Patients were classified to have either exudative or nonexudative retinoschisis based on the presence or absence of lipid exudates. Eleven eyes exhibited exudative retinoschisis (30%), whereas the remaining were nonexudative. Exudative disease occurred more commonly in older patients (14.4 vs. 4.0 years; P < 0.001). The most frequent location of exudation was the macula. Subretinal hemorrhage was present in 4 eyes (11%). Macular findings included an atypical foveal avascular zone in 7 eyes (19%) and submacular fibrosis or retinal folds in 6 eyes (17%). Peripheral characteristics included fibrosis or folds (11%), bridging vessels (8%), and vascular sheathing (8%). Thirteen of the 22 eyes (59%) demonstrated leakage on fluorescein angiography. Genetic results were available for 12 patients, all of which tested positive for abnormalities in the RS1 gene. One of the 12 patients also carried a mutation in the FZD4 gene. In conclusion, exudation may be more common in CXLRS than previously recognized. The authors observed exudative cavities in 30% of eyes, which is the highest frequency in the literature. The presence of exudates with concurrent angiographic leakage suggests that
exudation may be due to chronic vascular permeability and not solely caused by intraschisis hemorrhage, which has been classically described.


Crisponi syndrome (CS)/cold-induced sweating syndrome type 1 (CISS1) is a very rare autosomal-recessive disorder characterized by a complex phenotype with high neonatal lethality, associated with the following main clinical features: hyperthermia and feeding difficulties in the neonatal period, scoliosis, and paradoxical sweating induced by cold since early childhood. CS/CISS1 can be caused by mutations in cytokine receptor-like factor 1 (\textit{CRLF1}). However, the physiopathological role of \textit{CRLF1} is still poorly understood. A subset of CS/CISS1 cases remain yet genetically unexplained after \textit{CRLF1} sequencing. The authors had 64 case subjects referred to their center with a suspected diagnosis of CS/CISS1 between 2007 and 2014. Molecular genetic tests failed to detect mutations in \textit{CRLF1} in 25 of these patients. In five patients, exome sequencing and targeted Sanger sequencing identified four homozygous disease-causing mutations in kelch-like family member 7 (\textit{KLHL7}), affecting the Kelch domains of the protein. \textit{KLHL7} encodes a BTB-Kelch-related protein involved in the ubiquitination of target proteins for proteasome-mediated degradation. Mono-allelic substitutions in other domains of \textit{KLHL7} have been previously reported in three families affected by a late-onset form of autosomal-dominant retinitis pigmentosa. In this report, retinitis pigmentosa was present in two surviving children carrying bi-allelic \textit{KLHL7} mutations. This early-onset form of retinitis pigmentosa reveals that \textit{KLHL7} mutations are associated with a more severe phenotype in recessive than in dominant cases. Although these data further support the pathogenic role of \textit{KLHL7} mutations in a CS/CISS1-like phenotype, they do not explain all their clinical manifestations and highlight the high phenotypic heterogeneity associated with mutations in \textit{KLHL7}.


The authors reported the characteristic changes of fundus autofluorescence (FAF) in the nasal retina of patients with retinitis pigmentosa (RP). This report included 113 eyes of 113 patients with retinitis pigmentosa. Using wide-field FAF images the status of the retina nasal to the optic disk was evaluated. The patients were divided into the following three groups: those without nasal sparing (advanced), those with nasal sparing, and those with larger intact areas in addition to the nasal retina (early). Visual acuity, visual field area, age, and the duration of the symptom were compared among the groups. Twenty eyes (17.7%), 51 (45.1%), and 42 (37.1%) were classified as early, nasal sparing, and advanced,
respectively. Overall, the nasal retina was essentially preserved in the early group. The clinical characteristics’ analysis suggested that the disease progression appears from that represented by early groups, then nasal sparing groups, and finally advanced groups. The authors found that the nasal sparing pattern bears a close resemblance to the previously reported cone photoreceptor distribution. According to a detailed report on photoreceptor distribution in the human retina by Curcio et al, the density of cone cells is larger in the nasal retina. In RP, the rod cells are primarily affected and cones die secondarily. Thus, the FAF is relatively preserved in the areas with abundant cones such as the macula and nasal retina. Furthermore, in this study population, 76 of 113 patients (67.3%) had a preserved visual field in the temporal retina, which corresponds to the nasal retina. In summary, wide-field FAF imaging detected nasal sparing in RP. This is the first study to report the findings and the interpretation. The characteristic FAF pattern should reflect cone photoreceptor distribution in the human retina. This finding may be an example of the clinical appearance of asymmetric photoreceptor distribution. In addition, the authors have noticed that cone-rod dystrophy patients tend to show an inverse pattern; the nasal region tends to show decreased FAF in advance of the surrounding region. This would be an interesting theme for further investigation.

Choroidal and Retinal Thickness in Children with Different Refractive Status Measured by Swept-Source Optical Coherence Tomography

Myopia and myopic progression are increasing and are causing significant public health concern. Structural difference of the retina and choroid of myopic eyes is understood in adults, but not in children. Animal models of induced myopia and hyperopia have demonstrated choroidal changes that precede retinal changes. In this cross sectional study, the authors performed a swept sources OCT (SSOCT) on 276 Chinese children between the ages of 7-13 to better understand the anatomy of the retina and choroid in children with different refractive states. The authors found that myopic children had thinner choroid and had thinner retinas in the superior and the inferior perifoveal subfields when compared to their hyperopic counterparts. Additionally, subfoveal choroidal thickness was correlated with axial length and refractive error, and central retinal thickness in the fovea decreased with age and increased with IOP. Interestingly, compared to a previous study of white children done in Australia, the choroidal thickness in these Asian children was lower. This result is consistent with previous reports of variations of choroidal thickness with race/ethnicity. The authors point out that one of the limitations of this study is that it was only performed in Chinese children and might not be generalizable to all pediatric patients. The authors conclude that choroidal thickness and not retinal thickness is correlated with axial length and refractive error in Chinese children. The authors propose that the choroidal changes precede the retinal changes in early myopic progression.
17. TRAUMA

Cataract secondary to self-inflicted blunt trauma in children with autism spectrum disorder


In this short report three cases of bilateral cataract secondary to self-inflicted blunt eye trauma in children with autism spectrum disorder (ASD). All 3 children hit their foreheads, orbits, or globes repeatedly for long periods of time and developed cataracts. As the authors state, clinicians must be aware of this phenomenon to diagnose ocular pathology early and to provide adequate education, counseling, and services to affected patients and their families and to put appropriate postoperative care mechanisms in place to prevent permanent ocular damage.

Epidemiology of Sports-Related Eye Injuries in the United States


Sports related eye injuries, especially in children, can have a lifelong impact on numerous visual functions such as visual acuity, depth perception, and the need for regular monitoring of eye health, as in angle recession. This study examined data from the National Emergency Department Sample to determine the characteristics of eye trauma related to sports injury. The database contains information from 30 million ER visits annually in 900 hospitals nationwide. A three year period, 2010 through 2013 was studied and data extracted regarding age, sex, mechanism of injury, related activity, and factors associated with short-term impaired vision. 120,847 individuals presented with sports-related eye trauma. This was the primary diagnosis in 71% and injuries in males comprised 81% of the cohort. More than half of the males (41 775 [59.8%]) and females (10 814 [67.1%]) who sustained sports-related primary ocular injuries were 18 years or younger. The sports most commonly associated with eye injury were playing basketball (22.6%; 95%CI, 21.7%-23.6%), playing baseball or softball (14.3%; 95%CI, 13.7%-14.9%), and shooting an air gun (11.8%; 95%CI, 10.8%-12.8%). The most common type of eye injuries were open wounds of the adnexa (ICD-9-CM code 870.x; 33.5%) contusions of the eye and adnexa (ICD-9-CM code 921.x; 30.1%) and superficial injuries of the eye and adnexa (ICD-9-CM code 918.x; 21.1%). Impaired vision on presentation to the ER was most likely with paintball and air gun injuries relative to football-related injuries (odds ratio, 4.75; 95%CI, 2.21-10.19 and 3.71; 95%CI, 2.34-5.88, respectively; P < .001).

Conclusion: There are approximately 30,000 sport-related eye injuries to the emergency room each year in the United States. Injury with a projectile was most
likely to cause short-term vision impairment, although long-term sequelae was unable to be determined from this study. This study is useful to help plan eye injury prevention strategies.

**Association of Football Subconcussive Head Impacts With Ocular Near Point of Convergence**

Recent attention to traumatic brain injury suffered during football play has increased awareness about safety. This article examines the effect of subconcussive head impacts on near point of convergence (NPC). The aim was to determine if there were changes in NPC, and perhaps to use change in NPC as a surrogate for severity of subconcussive head impact. This was a prospective observational study of 29 football players in the National Collegiate Athletic Association Division I. Information was gathered baseline and preseason practices (1 non-contact and 4 contact) as well as post-season. An accelerometer-embedded mouth guard measured head impact kinematics. Players participated in regular practices, and all head impacts greater than 10g from the 5 practices were recorded using the i1Biometerics Vector mouthguard (i1 Biometrics Inc). Based on the sum of head impacts from all 5 practices, players were categorized into lower (n = 7) or higher (n = 22) impact groups. Linear and angular acceleration as well as number of impacts were, as expected, different between the 2 groups. Outcome measures were measure of near point of convergence and symptom scores. In the higher-impact group, there was a linear increase in NPC over time that plateaued and resolved post-season. In the lower-impact group, there was no change in NPC over time.

Importance: Playing football results in head impacts with significant force. In this study, 29 players received a total of 1193 head impacts, for an average of 41.1 impacts per player. Interestingly, players were asymptomatic, but this study suggests that repetitive subconcussive head impacts were associated with changes in NPC. Changes in NPC may become a useful clinical tool in assessing the severity of brain injury.

**Subconcussive Head Trauma and Near Point of Convergence**

In this invited commentary, the authors distinguish concussive vs subconcussive head impacts. They highlight that changes in NPC from such head impacts occur not only in football, and the reviewed study has pertinent implications for other types of head trauma, such as from military and nonmilitary related head impact injuries. Criticisms include that further studies need to show the reproducibility and generalizability of their findings.
Sequential traumatic and spontaneous corneal rupture in patient with osteogenesis imperfecta.

Osteogenesis imperfecta (OI) is a rare collagen synthesis disorder that is caused by mutations in genes that encode type I collagen. Given that type I collagen is an important structural component of the cornea and sclera, OI patients can have structural problems in the anterior segment and be vulnerable to trauma. The authors describe a unique case of an 18-month old boy, who sequentially experienced a corneal rupture by minor trauma in one eye and a presumed spontaneous corneal rupture in the other eye. Special strategies to minimize tissue loss and to achieve watertight sealing are reviewed. These include longer-bite sutures with 11-0 nylon, C3F8 gas tamponade in the anterior chamber, primary penetrating keratoplasty, and onlay epikeratoplasty followed by penetrating keratoplasty.

NON-ACCIDENTAL HEAD TRAUMA

The natural history of retinal hemorrhage in pediatric head trauma
This study determined the natural history of RH in infants and young children with suspected abuse or accidental head trauma and to identify helpful patterns which might suggest chronicity or help determined timing. This was an eight year retrospective review of children <2 years of age diagnosed with abusive or accidental head trauma. Ninety-one eyes of 52 children were included (abusive head trauma (AbHT) n=45 and accidental head trauma (AcHT) n=7). Mean subject age was 6.7 months. All 91 eyes had intra-retinal hemorrhages (IRH) at presentation and of these 62 eyes had IRH too numerous to count (TNTC). Sixty-eight eyes (75%) also had pre-retinal hemorrhages (PRH). Therefore at presentation, 25% only had IRH and none had only PRH. PRH only was not seen prior to a 1-week examination, and this pattern increased with further follow-up examinations (IRH clears faster than PRH). By the 1-week examination, no eyes had TNTC IRH. The longest an isolated single IRH persisted was 32 days. The longest isolated PRH persisted 111 days. This paper can help determine the timing of the injury and see if the clinical findings corroborate with the clinical history. This is an excellent paper which provides key data regarding retinal hemorrhages. The only assumptions that need to be made is that the abusive head trauma event occurred shortly before presentation (reasonable) and that the classification of AbHT versus AcHT was accurate (also reasonable).
**MISCELLANEOUS**

**Traumatic open globe injury in young pediatric patients: characterization of a novel prognostic score**
Read SP and Cavuoto KN. *J AAPOS* April 2016;20:141-144.

The authors propose the Toddler/Infant Ocular Trauma Score (TOTS) to assess prognostic factors in children ages 0 to 6 years who sustain an open globe injury. This was a 15-year retrospective review. High-risk characteristics including wound >6mm, hyphema, cataract/lens damage, retinal detachment and choroidal detachment were used to derive a score to predict a final visual acuity of 20/40 or better. Twenty-eight eyes of 28 patients with a mean age of 4.2 years were followed for a minimum of 4 weeks. A glass injury was the most common mechanism and 17/28 patients were male. TOTS analysis could be performed on 22/28 (the other 6 were too young to have an initial visual acuity recorded. There were evaluated using the ‘modified POTS’ score). POTS and TOTS scores were significantly correlated with final acuity. TOTS score had a high sensitivity (81%) and specificity (92%) for predicting good visual outcome. There was a high positive correlation between initial and final logMAR acuity. Poor prognostic factors were a complicating cataract and a wound >6mm. This study had a 25% lost to follow-up rate and overall injuries were less severe than those reported in adult trauma cases.

**18. RETINA**

**Carbonic Anhydrase Inhibitors for the Treatment of Cystic Macular Lesions in Children With X-Linked Juvenile Retinoschisis.**

Authors used carbonic anhydrase inhibitors (CAIs) to treat cystic macular lesions in 18 eyes of nine children with X-linked juvenile retinoschisis (XLRS). They evaluated the therapeutic effect of CAI treatment with the best-corrected visual acuity and foveal zone thickness (FZT) with spectral-domain optical coherence tomography. A reduction of at least 22.4% in FZT was defined as objective evidence of response. Five of nine (55.6%) XLRS patients showed a significant reduction of FZT in both eyes over a median treatment interval of 6.8 months (range, 1-23). In four of five (80.0%) patients, this reduction was already apparent after 1 month of treatment. An improvement of visual acuity was observed in five eyes (27.8%) of three patients (33.3%). Six patients (66.6%) reported minor side effects. Authors conclude that treatment with CAIs decreased FZT in more than half of the children with XLRS. This effect was observed within 1 month in
the majority of patients. Carbonic anhydrase inhibitor treatment restores retinal anatomy and may contribute to creating optimal circumstances for gene therapy.

**Juvenile X-linked retinoschisis presenting as juxtapapillary retinal fold mimicking combined hamartoma of the retina and retinal pigment epithelium.**


A 21-month-old boy presumptively diagnosed with combined hamartoma of the retina and retinal pigment epithelium was found to have juvenile X-linked retinoschisis with vitreomacular traction and prominent retinal folding.

**Choroidal Thickness in Healthy Chinese Children Aged 6 to 12: The Shanghai Children Eye Study**


Recent advances in enhanced depth imaging (EDI) technology in OCT have enabled accurate visualization of the choroid. The authors of this study report that the limited studies that have researched choroidal thickness characteristics and development in children to date have conflicting conclusions. Therefore they sought to study the characteristics of choroidal thickness and its relationship to systemic and ocular factors in normal Chinese children. 144 healthy children aged 6 – 12 years were enrolled. The choroidal thickness of subfoveal and peripheral locations 0.5, 1.5, and 2.5 mm away from the fovea were evaluated by EDI OCT and associations with ocular and systemic factors were studied. The mean subfoveal choroidal thickness was 302 +/- 63 um. In the nasal, superior, and inferior areas, the choroidal thickness of locations closer to the fovea was thicker than those further from the fovea. However, choroidal thickness was not significantly different among various locations in the temporal area. The choroidal thickness of the nasal quadrant was significantly thinner than that of other areas. Subfoveal choroidal thickness decreased with age, axial length, preterm history, and increased with height. Sex was not correlated with subfoveal choroidal thickness. Study limitations include a relatively small sample size and cross-sectional rather than longitudinal design. Noncycloplegic refraction was used in the study which is not accurate, especially in children with hyperopia, and this may be why no correlation between refractive error and subfoveal choroidal thickness was found. Given the high prevalence of myopia in Chinese children, further studies among this population may increase understanding of the relationship between the choroid and refractive error.

**Macular Microstructural Features in Children with Tilted Disk Syndrome Evaluated by Spectral Domain Optical Coherence Tomography**
This study assessed macular microstructure in eyes with tilted disk syndrome (TDS) to determine the relationship between TDS foveal morphology and visual function. 26 TDS eyes from 19 children (age 5 – 15 years) with spherical equivalent refraction -3.1 +/- 1.3 D and 28 control eyes from 14 children of similar age and spherical equivalent refraction were studied. Horizontal and vertical OCT scans through the fovea produced images that were segmented into 8 intraretinal layers. Thicknesses of the total retina and each layer were measured at the foveal center and at 12 other macular locations: 500um, 1,000um, and 1,500um along the horizontal and vertical meridians. The relationships between TDS BCVA and the presence of photoreceptor inner/outer segment (IS/OS) junction line, IS/OS foveal bulge, and cone outer segment tip (COST) line were evaluated. The thickness of TDS central fovea was not significantly different than controls. The total retinal thickness in TDS eyes was thinner than controls at all peripheral locations except at 500um and 1,000um superiorly, and 1,500um temporally. TDS intraretinal layer thicknesses in the nasal and inferior regions varied significantly from controls. 80.7% and 23.1% of TDS eyes had a normal foveal bulge and continuous COST line, respectively, compared to 100% and 96.4% of controls. The authors conclude that the loss of visual function in TDS may be attributed to morphological changes in the outer retinal microstructures. This study did not include measurements of visual fields, mf-ERGs, or color vision, and many of the subjects were too young to cooperate with these tests. However, combining knowledge of the macular microstructure with results of macular function tests would increase understanding of how structural changes in TDS affect vision.

Peripapillary Choroidal Thickness in Former Preterm and Full-term Infants Aged from 4 to 10 Years
The aim of the study was to investigate peripapillary choroidal thickness in former preterm and full-term infants with spectral-domain optical coherence tomography (SD-OCT). This was a subanalysis of infants with successful peripapillary choroidal thickness measurements of a prospective, controlled, cross-sectional, hospital-based study in a tertiary center of maximum care. The study examined 503 infants aged 4 to 10 years at the time of examination. Infants were divided into different groups: group 1 born with gestational age (GA) ≥37 weeks, group 2 born with GA between 29 and 32 weeks without ROP (retinopathy of prematurity), group 3 born with GA ≤28 weeks without ROP, and group 4 born with GA ≤32 weeks and presence of ROP. Peripapillary choroidal measurements were available for 388 of 503 participants. No significant differences were found among the four groups for global peripapillary choroidal thickness. Multivariable analysis revealed no association with low GA, birth weight, ROP occurrence, perinatal adverse events, and logMAR visual acuity. Only infants born small for GA (SGA) revealed peripapillary choroidal thinning in the superior (P = 0.033) and nasal (P= 0.024) sectors compared with infants born
appropriate for GA (AGA). Infants SGA had lower visual acuity than AGA infants (0.03 ± 0.07 logMAR SGA versus 0.01 ± 0.05 logMAR AGA; P = 0.029). The results indicate that prematurity itself does not affect choroidal thickness in the peripapillary region. Only infants born SGA revealed peripapillary choroidal thinning and more limited visual acuity compared with AGA infants. The data indicate that fetal growth restriction leads to choroidal long-term alterations in the peripapillary region. Although this study is cross-sectional in design, the results are compelling given the large number of patients included.

Evaluation of Choroidal Thickness in Children with Iron Deficiency Anemia

The purpose of this study was to determine whether there are differences in choroidal thickness in children with iron deficiency anemia (IDA). Fifty-two patients with IDA and 54 healthy children between 3 and 16 years of age were enrolled. After complete eye examinations were conducted for each participant, the choroidal thickness was measured using optical coherence tomography. There were no statistically significant differences between the two groups in terms of visual acuity, intraocular pressure, central corneal thickness, or axial length (P > 0.05). The choroidal thicknesses at the foveal center were 303.13 ± 27.14 µm in the IDA patients and 333.67 ± 39.77 µm in the healthy control children (P < 0.001); additionally, the choroidal thicknesses at each point within the horizontal nasal and temporal quadrants were thinner in the IDA group. There were positive correlations between the choroidal thickness and hemoglobin (r = 0.337; P < 0.001), mean corpuscular volume (r = 0.305; P = 0.001), iron (r = 0.264; P = 0.006), and ferritin (r = 0.287; P = 0.003) levels; however, there were no correlations between the clinical or ocular characteristics and the choroidal thickness. The patients with IDA had significantly thinner choroidal thicknesses than those of the healthy children. Choroidal thinning in childhood may be an early sign of deterioration in the ocular blood circulation (which could ultimately result in retinal vein or artery occlusion), without any risk of atherosclerosis in advanced age in the patients with IDA. This is the first study to date to evaluate choroidal thickness in children with IDA. The weaknesses of the study include relatively small sample size and lack of knowledge on duration of IDA prior to study.

Association of Pediatric Choroidal Neovascular Membranes at the Temporal Edge of Optic Nerve and Retinochoroidal Coloboma.

Chorioretinal colobomas are a rare congenital abnormality of the eye and can be complicated by retinal detachment or choroidal neovascular membranes (CNVs).
The CNVs associated with chorioretinal colobomas have not previously been described. This is a retrospective case series of 8 eyes of 8 patients over a 20 year period who had OCTs of the CNV associated with retinochoroidal and optic nerve coloboma. The mean age of the patients was 4 years and mean follow up was 21 months. Seven of the patients had handheld OCT during exam under anesthesia and one patient was imaged with the tabletop OCT in the office. The OCTs of the CNVs in these patients demonstrated subretinal fluid, intraretinal fluid, intraretinal cysts, and subretinal hyperreflective material. Vision ranged from 20/200 to 20/40 on presentation and from 20/400 to 20/30 on follow up in those for whom an acuity could be obtained. Most of the colobomas in this case series were associated with genetic abnormalities or a syndrome. Two of the eyes with active leakage from the CNV received intravitreal injection of bevacizumab and one also had focal laser. The OCT response in these patients treated demonstrated resolution of the subretinal fluid in both patients and improvement in the intraretinal fluid in one of the two patients. Two patients progressed to retinal detachment; neither of these patients was treated with injections. The CNV membrane developed at the junction of the normal and abnormal retina at the temporal margin of the coloboma in all of the eyes who developed CNV and the authors proposed pathophysiologic mechanisms for this. The most clinically relevant point of this paper is the location of the CNV being at the temporal margin of the coloboma in all of the patients in this series. The pediatric ophthalmologist is often looking for retinal detachments in these patients and without a cooperative patient, it is often difficult to get a detailed retinal exam. Finding CNV in patients with coloboma can be challenging, especially with an office exam, however by knowing where these are more likely to occur, the physician is more likely to identify this pathology.

The New Pretender: A Large UK Case Series of Retinal Injuries in Children Secondary to Handheld Lasers.

Reports of retinal injury from handheld lasers have increased recently. Many of these lasers look like laser pointers and some are marketed as toys, and while there are attempts to regulate the sales of such devices, many can be purchased online. The purpose of this study is to describe a large cohort of 16 children, 24 eyes, with retinal injuries due to handheld lasers and to describe the eye exam and OCT findings. This was a retrospective study over 4 years at one institution. The authors found that many of these injuries were in males and the age ranged from 9-16 years old. 1/3 of the patients were initially diagnosed with a retinal dystrophy by outside eye doctors. 11/16 patients had mild injuries with focal retinal disruption at the photoreceptor layer on OCT and a better prognosis with a mean acuity at presentation of 20/25. Three eyes of 2 children had moderate injuries with diffuse outer retinal layer disruption on OCT and 3 patients (4 eyes) had severe injuries with loss of retinal architecture and overlying hyper reflective material extending to the inner retina. Many children did not admit to being exposed
to the laser when asked with only half of the children admitting to this mechanism initially. The authors concluded that these injuries are likely underreported and difficult to diagnose. The vision in the patients did not improve over the somewhat short follow up time of 5 months. This is an important study for the pediatric ophthalmologist because it highlights a growing new public health concern and also helps the ophthalmologist better understand the OCT and exam findings so that laser retinal injury can be added to the differential diagnosis in cases where this mechanism might not be suspected.

**Fundus Photography as a Screening Method for Diabetic Retinopathy in Children With Type 1 Diabetes: Outcome of the Initial Photography.**


The incidence of type 1 diabetes (T1D) is increasing worldwide and is highest in Finland. The screening recommendation for diabetic retinopathy in Finland is to photo-screen patients beginning at the age of 10, regardless of duration of the disease. This is a retrospective observational cohort study of 213 patients age 9-17 diagnosed with type 1 diabetes at the Children’s Hospital of Helsinki. The goal of the study was to evaluate the success rate in initial photos at achieving gradable images and to look at factors that would determine success in obtaining these gradable images. After dilation, two 60 degree red free photos—one centered on the macula and the other centered on the optic nerve—were taken and photographic success was determined. The group defined complete photographic success if both images of both eyes were gradable. A partial success when 2 images of 1 eye were gradable. When only the macula or nerve images were gradable this was also recorded. Almost half of the children had complete success and partial success or better was achieved in more than 70% of patients. Most of the patients who did not achieve complete or partial success had at least one gradable image. 6% of patients had no reliable information. Ability to obtain images did not correlate with older age or gender as hypothesized. Gradable macula-centered images were more likely than gradable optic nerve-centered photos, and there was no difference in the success rates of right or left eyes. The main point of this study was to demonstrate that photo screening could work for screening children for diabetic retinopathy like it does in their adult counterparts.

**Clinical and Genetic Features of Choroideremia in Childhood**


In this retrospective case series, the authors describe the earliest features of choroideremia and to identify biomarkers useful for monitoring disease progression. 29 patients were identified with a mean age at referral of 9
years (range, 3-16 years). CHM mutations were identified in 15 of 19 pa-
tients tested. Nyctalopia was the predominant symptom (66%). Five of 29
patients were asymptomatic at presentation. At the final follow-up visit
(mean age, 16 years; range, 7-26 years), most maintained excellent visual
acuity (mean, 0.98-0.13 decimalized Snellen acuity). The first sign of reti-
nopathy was widespread pigment clumping at the level of the retinal pig-
ment epithelium (RPE). This later evolved to chorioretinal atrophy, most
marked in the mid-peripheral retina. Peripapillary atrophy also was an early
feature and was progressive in nature. Three different zones of FAF change
were visible. Persistence of the inner retinal layers, detected by SD OCT,
was visible at presentation in 15 of 27 patients. Subfoveal choroidal thick-
ness decreased with age, whereas central retinal thickness increased over
a similar interval. Four patients in whom visual acuity decreased over the
follow-up period recorded a reduction in central retinal thickness. The au-
thors concluded that progressive structural changes occur initially while
central visual function is maintained. Pigmentary changes at the level of
the RPE occur early in the disease. Peripapillary chorioretinal atrophy, cen-
tral retinal thickness, and subfoveal choroidal thickness are likely to be
valuable in monitoring disease progression and should be considered as
potential biomarkers in future therapeutic trials.

Comment: Wide-field fundus images and fundus autofluorescence in this
paper nicely complement the authors’ descriptions of clinical findings.

Clinical and Genetic Findings of Autosomal Recessive Bestro-
phinopathy in Japanese Cohort.
Aug;168:86-94.

Mutation in the BEST1 gene most commonly causes Best Vitelliform Macular
Dystrophy. However variants of the BEST1 gene cause a wide range of disease.
The purpose of this study was to describe the clinical and genetic findings in 9
patients of 7 unrelated families with a rare disease: Autosomal Recessive Be-
trophinopathy (ARB). Previous reports were small and describe a wide spectr-
um of exam finding so the goal of this study was to report the range of clinical
and genetic findings in this rare disease. In this study, patients presented with a
wide range of symptoms from floaters and night vision , to blurred vision and
metamorphopsia. The visual acuity varied from 20/20 to 20/200. The Arden ratio
was less than 1.2 in all patients. There were two novel mutations described. 3
patients with decreased vision had severely reduced ERG. The fundus findings
also varied with 6 patients having central yellowish subretinal deposits. No pa-
tients had any vitelliform lesions. 2 patients had massive subretinal deposits and
3 patients had prominent RPE atrophy. FAF demonstrated a mix of hyper and
hypoautoflourescence. 4 patients had serous retinal detachments with elongated
photoreceptor outer segments. The authors conclude that the ARB patients de-
scribed in this study had some but not all of previous reports and that due to the
wide range of phenotypic presentations, genetic analysis is essential for the di-
agnosis of ARB. This study is large considering the rarity of this disease but still only included 9 patients. Additionally, the patients were all Japanese, potentially limiting the generalizability of their results.

**Induction of posterior vitreous detachment in pediatric vitrectomy by preoperative intravitreal injection of tissue plasminogen activator.**
Chih-Chun Chuang; San-Ni Chen *Journal of pediatric ophthalmology & Strabismus.* March/April 2016; 53(2): 113-118

The induction of posterior vitreous detachment is difficult in children given the fact that the vitreous is strongly adherent to the retina. The induction of a PVD is very important in vitreomacular surgery and represents a challenge in pediatric population. This retrospective, interventional case series studies the efficacy of intravitreal injection of tissue plasminogen activator (tPA) with or without autoserum to induce posterior vitreous detachment (PVD) in pediatric vitrectomy. Six patients were included in the study (4 boys and 2 girls), age ranged from 39 weeks to 8 years. Indications for surgery included: traumatic macular hole (cases 1 and 2); premacular hemorrhage secondary to retinopathy of prematurity (case 3); abusive head trauma with premacular hemorrhage, subinternal limiting membrane hemorrhage, and macular hole (case 4); trauma with dense vitreous hemorrhage (case 5); and vitreous hemorrhage with unknown cause (case 6). All patients received intravitreal tPA injections 3 days prior to surgery and in cases with pre-existing vitreal hemorrhage 0.1 ml of intravitreal autologous serum was also co-administered. Main outcome measures included successful rate of posterior vitreous detachment in vitrectomy, visual outcome, and related ocular complications. Successful PVD was induced intraoperatively in all cases and that there were no intraoperative complications. The authors conclude that intravitreal injection of tPA 3 days before vitrectomy may be a helpful adjunct to induce pediatric PVD. The study is limited in each retrospective nature, small sample size and mainly by the absence of control group. Also, although the injection of tPA might facilitate the induction of a PVD, retinal toxicity has been reported in the past as well as endophthalmitis.

**Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery An International Multicenter Study**

In this multicenter, interventional, retrospective case series the authors determine evaluated the feasibility and safety of bilateral immediately sequential vitreoretinal surgery (ISBVS) in 344 surgeries including 172 ISBVS procedures in 167 pediatric patients (mean age 1.3y). Indications for ISBVS were rapidly progressive disease (74.6%), systemic morbidity placing the child at high anesthesia risk (76.0%), and residence remote from surgery
location (30.2%). ROP was the most common diagnosis (72.7%) with stage 3, 4A, 4B and 5 each making up 4.8%, 44.4%, 22.4% and 26.4%, respectively. Other indications were FEVR, abusive head trauma, PFV, congenital cataract, posterior capsular opacification, rhegmatogenous RD, congenital X-linked retinoschisis, Norrie disease, and viral retinitis. Mean surgical time was 143 minutes for both eyes. There were no reported intraoperative ocular complications. During the immediate postoperative period, 2 eyes from different patients demonstrated unilateral vitreous hemorrhage (0.6%). No cases of endophthalmitis, choroidal hemorrhage, or hypotony occurred. Mean total anesthesia time was 203 minutes. There were no cases of anesthesia-related death, malignant hyperthermia, anaphylaxis, or cardiac event. There was 1 case of reintubation (0.6%) and 1 case of prolonged oxygen desaturation (0.6%). This study found ISBVS to be a feasible and safe treatment paradigm for pediatric patients with bilateral vitreoretinal pathologic features when repeated general anesthesia is undesirable or impractical.

Comment: This paper describes almost no adverse events with bilateral immediately sequential vitreoretinal surgery. Multiple other publications pertaining to other intraocular procedure have demonstrated low complication rates when performed in a similar bilateral immediately sequential fashion as described in this study.

Retinal and Optic Nerve Hemorrhages in the Newborn Infant One-Year Results of the Newborn Eye Screen Test Study
Callaway NF, Ludwig CA, Blumenkranz MS, Jones JM et al. *Ophthalmology* May 2016;123:1043-1052

In this study, the authors prospectively evaluated 202 full term infants to report prevalence, risk factors, characteristics, and location of fundus hemorrhages (FHs) of the retina and optic nerve present in newborns at birth. The birth prevalence of FH in this study was 20.3% (41 infants). Of the group with FH, 95% involved the periphery, 83% involved the macula, and 71% involved multiple layers of the retina. The fovea was involved in 15% of FH cases (birth prevalence, 3.0%). No cases of bilateral foveal hemorrhage were found. Fundus hemorrhages were more common in the left eye than the right. Fundus hemorrhages were most commonly optic nerve flame hemorrhages (48%) and white-centered retinal hemorrhages (30%). Retinal hemorrhages were found most frequently in all 4 quadrants (35%) and more often were multiple than solitary. Macular hemorrhages most often were intraretinal (40%). Among the risk factors examined in this study, vaginal delivery compared with cesarean section (odds ratio [OR], 9.34) greatest level of association with FH. Self-identified ethnicity as Hispanic or Latino showed a protective effect (OR, 0.43). Other study factors were not significant.

Comment: Retcam image of FH included in this publication nicely illustrate the morphology of this common phenomenon.
The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Studies Design and Baseline Characteristics: ProgStar Report No. 1

This study describes the baseline patient characteristics and design of the ProgStar natural history studies in progress. The authors have developed both retrospective and prospective arms however only some baseline clinical patient data is reported in this paper. Over time the authors will collect functional (visual acuity) and structural (retinal imaging) data to assess for correlations. Patients aged 6 years and older with variants in the ABCA4 gene are eligible for this natural history study. The authors make reference to preclinical or early clinical phase treatment studies, including gene therapy (e.g., clinicaltrials.gov identifiers NCT01736592 and NCT01367444), stem cell therapy (e.g., NCT02445612 and NCT01920867), and pharmacologic interventions (e.g., NCT01278277 and NCT02402660).

Comment: For patients with Stargardt disease, there may be opportunities to participate in natural history and/or treatment studies in the US and Europe.

Diagnosis of retinopathy in children younger than 12 years of age: implications for the diabetic eye screening guidelines in the UK
A Hamid, H M Wharton, A Mills, J M Gibson, M Clarke and P M Dodson Eye July 2016; 30: 949-951; advance online publication, April 15, 2016; doi:10.1038/eye.2016.59

As the incidence of diabetes in children increases, there will be increasing need to screen children and young adults for the presence of diabetic retinopathy. In this study conducted in the UK, 143 children with Type 1 diabetes were examined and BDR was found in 9.6%. No retinopathy was seen in any child who had diabetes less than 6 years duration. The authors conclude that screening for retinopathy should begin 6 years after the diagnosis of diabetes is first established.

A 12-year review on the aetiology and surgical outcomes of paediatric rhegmatogenous retinal detachments in Hong Kong

The authors report the etiology and outcomes of 47 children younger than 18 years of age who where treated at a single center in Hong Kong over a 2 year period for rhegmatogenous retinal detachment. The most frequent causes for the detachments were idiopathic (28%), high myopia (24%) atopic dermatitis (18%)
congenital anomalies (16%) and trauma (8%). In the high myopia group, the average refraction was -11.00D. Overall structural outcomes with good final anatomic success rate of 87%, but final visual acuity was LogMAR 0.9±1.2 (Snellen equivalent 6/48). Lowest success and acuity outcomes were seen in the atopic dermatitis and congenital groups. The authors emphasize that there will be geographic variation in etiology of RRD in children and that their study reflects the unique characteristics of the study population.

**Increased Posterior Retinal Vessels in Mild Asymptomatic Familial Exudative Vitreoretinopathy Eyes**

Miner Yuan, Yu Yang, Hong Yan, Jiaqing Li, et al. *Retina* 2016 June; 36:1209-1215.

This study examined 20 individuals with mild Stage I or II FEVR with “normal-appearing” posterior poles and normal vision, and 20 healthy control eyes. The crossing number of retinal vessels within the peripapillary inner reference circle (PIRC), peripapillary outer reference circle (PORC), peripapillary temporal inner arc (PTIA), peripapillary temporal outer arc (PTOA), and branching points between the peripapillary outer reference circle and peripapillary inner reference circle were counted and compared between the FEVR and control groups. Vessel bifurcation was also evaluated. The mean crossing numbers in all categories were larger in the FEVR group. No significant difference was found in vessel bifurcation. A limitation of this study is that the individuals with FEVR were not confirmed by genetic diagnosis and other pediatric retinopathies with similar findings could not be definitively ruled out. However, this finding of increased vessels radiating from the optic disc is a newly documented clinical manifestation in patients with FEVR, especially those with mild asymptomatic FEVR with normal vision. The authors suggest that this anatomical abnormality may aid in screening for FEVR.

**Wide-Field Imaging of Nonexudative and Exudative Congenital X-Linked Retinoschisis**


This retrospective series of 36 eyes from 18 patients with congenital X-linked retinoschisis reviewed wide-field fundus photographs, OCT images, and wide-field FA images. Patients were classified to have exudative or nonexudative retinoschisis based on the presence or absence of lipid exudates. Eleven eyes (30%) exhibited exudative retinoschisis. Exudative disease occurred more commonly in older patients (14.4 vs. 4.0 years), and the most frequent location of exudation was the macula. Although FA in cases of X-linked retinoschisis typically shows normal findings with no vascular leakage, in this study 13/22 eyes in which FA was available demonstrated mid-phase to late-phase extramacular retinal vascular leakage. Among these eyes, 9 (69.2%) had nonexudative and 4
(30.8%) had exudative retinoschisis. The finding of leakage in both types of disease may implicate increased vascular permeability as a potential source of fluid and/or exudate accumulation, and the authors hypothesize that exudation may be a marker of chronicity. One important limitation of this study is that the imaging was obtained during standard clinical care and reviewed retrospectively and therefore the imaging and scans were biased towards areas of clinical interest. In addition, longitudinal data collection was not conducted, and functional correlation is unknown. Nevertheless, vascular leakage in both exudative and nonexudative congenital X-linked retinoschisis without the presence of hemorrhage may suggest vascular incompetence as one feature in schisis cavity formation.

**A Randomized, Placebo-Controlled Study of Intravitreal Ocriplasmin in Pediatric Patients Scheduled for Vitrectomy**


This Phase 2 single-center study evaluated the safety and efficacy of a single intravitreal injection of 175 ug of ocriplasmin as a preoperative adjunct to vitrectomy in infants and children, with the goal of facilitating the induction of posterior hyaloid separation during vitrectomy. 22 pediatric patients (24 eyes) scheduled for vitrectomy were randomized 2:1 to ocriplasmin injection or placebo. Patients in both treatment groups experienced at least 1 adverse event; those who received ocriplasmin did not demonstrate a higher risk compared to those receiving placebo. One case of lens subluxation due to zonular disruption was observed in the ocriplasmin group. Total macular PVD was observed in 1/8 (12.5%) placebo eyes and 2/16 (12.5%) ocriplasmin eyes before vitrectomy, and 5/8 (62.5%) and 8/16 (50%) respectively after suction. The authors discuss that despite favorable impressions by the investigators on the ease of vitrectomy in most of the ocriplasmin-treated patients, this was not apparent in objective tests such as vitrectomy duration or vitreous liquefaction grades. A clear efficacy difference was not observed between the two groups, though the study was limited by several factors including small sample size, the inability to perform OCTs and ERGs, and the complexities of the surgeries. In general, the authors conclude that the ability to dissociate the hyaloid from the retina with less mechanical force and improved visualization of surgical planes is advantageous, and future studies will be better able to make a direct comparison with more directed objectives.

**Long-term Outcome of Epiretinal Membrane Surgery in Young Children**


This paper describes the clinical characteristics and surgical outcomes in 13 patients less than 12 years of age with nonprogressive disease-associated epiretinal membranes (ERMs). In general, ERMs are rare in
young patients, and most prior studies have combined ERMs associated with progressive diseases such as ROP, uveitis, and FEVR with idiopathic ERMs or those related to nonprogressive diseases. This study included 7 cases of idiopathic ERM, 4 cases of combined hamartoma of the retina and RPE, and 2 cases of posttraumatic ERM. The membranes were dense, retractive, adherent, and sometimes responsible for traction on vessels, and were successfully removed in all cases. 12/13 children (92%) experienced functional improvement, and mean BCVA improved significantly from 20/160 to 20/40. The authors emphasize the importance of early identification of idiopathic ERMs associated with nonprogressive disease to allow early management and avoid amblyopia. Another important finding is that the diagnosis of ERM was fortuitous in 10/13 cases (77%), highlighting the importance of early vision screening to detect curable causes of long-term vision loss.

Smartphone-based fundus camera device (MII Ret Cam) and technique with ability to image peripheral retina.

This is a report on a new inexpensive smartphone-based fundus camera device (MII Ret Cam). It is designed in a form that has slots to fit a smartphone (built-in camera and flash) and 20-D lens. Using this device, fundus videos were taken with easy extraction of digitalized snapshot images. Using an indenter images of peripheral retina, including ora serrata and pars plana, were acquired. The authors claim that it is easier to train residents to use this device than indirect funduscopy, but only compare one resident, who was trained in smartphone-based indirect ophthalmoscopy to one resident trained in traditional indirect ophthalmoscopy. They conclude that their smartphone-based fundus camera can help clinicians to monitor diseases affecting both central and peripheral retina and that the device can also be an inexpensive tool for mass screening. This is an interesting concept that can be of value, especially in developing countries. The level of evidence was poor, and further studies are definitely required to thoroughly validate its use compared to other more acceptable forms of retinal imaging. There is also no mention of the type of smartphone that is suitable for this device.

Subtenon triamcinolone for cystoid macular edema due to retinitis pigmentosa unresponsive to oral acetazolamide
Retinitis pigmentosa (RP) is characterized by progressive loss of photoreceptor function because of mutations in over 100 gene loci. Cystoid macular edema (CME) is an important cause of central vision loss in up to 49% of patients. The exact origin of CME in RP has not been elucidated, various studies imply that inflammation plays an important role. CME in RP is treated with oral or topical carbonic anhydrase inhibitors (CAI). Unfortunately, only 40% of patients respond to topical treatment, whereas only 28% benefit from systemic treatment with CAIs. This is a case report of a successful alleviation of CME in a 43 year old RP patient with subtenon triamcinolone injections. A definite improvement in anatomy was demonstrated with reduction in central foveal thickness, the improvement in function is unclear.

Malignant transformation of retinocytoma treated with intra-arterial chemotherapy.

Retinocytoma is traditionally considered a benign tumor and therefore requiring no treatment. However, malignant transformations were documented in several individual case reports, and a recent study on 36 patients with retinocytoma showed that 12% of these tumors progressed into retinoblastoma. Little or no response to systemic chemotherapy is another characteristic of retinocytoma. This is a case report of two patients with unilateral and unifocal retinocytomas that were treated with intra-arterial chemotherapy after they had partially transformed into retinoblastoma. Although the retinoblastoma portions rapidly regressed with treatment, the retinocytomas remained unaltered, confirming that these tumors are also resistant to intra-arterial melphalan treatment.

Vitrectomy without laser treatment for macular serous detachment associated with optic disc pit: long-term outcomes.

At present, there is no single treatment that is universally accepted for serous macular detachment associated with optic nerve pit. In this retrospective case series the authors evaluate the clinical outcome of 8 eyes of 8 patients (mean age 27.25 years; range 12-57 years) following surgical treatment for macular serous detachment associated with optic disc pit with pars plana vitrectomy (PPV) without laser photocoagulation on the temporal edge. All patients underwent internal limiting membrane (ILM) peeling, and SF6 20% gas tamponade (case 1 was treated with silicone oil tamponade) during the PPV. Mean follow-up period of 59.25 ±46.61 months after surgery was reported. Complete retinal reattachment was achieved in 7 of 8 pa-
patients. The mean postoperative BCVA was 20/40 (range 20/200-20/20) and was significantly better than the mean preoperative best-corrected visual acuity (BCVA) was 20/83 (range 20/200-20/32) \( (p = 0.02) \). An improvement in mean foveal thickness was also noted from mean foveal thickness of 973 to mean postoperative foveal thickness of 363.5 micron \( (p<0.001) \). One case developed a macular hole following treatment. The authors conclude that pars plana vitrectomy, ILM peeling, and endotamponade (SF6 20% gas) without endolaser on the temporal edge of optic disc is an effective treatment. There are obvious limitations to this study. It is retrospective and it also lacks a control group (e.g. patients that had the same surgery with temporal laser photocoagulation). Therefore, we cannot clearly conclude from this study that this treatment modality is adventitious compared to other therapeutic options. We don’t know from the data presented what was the minimal follow-up, but we can see that for the duration of follow-up that was included, the majority of patients had a good anatomical result and that 50% of patients had improvement in BCVA of three lines or more.

**Retinal Injury Secondary to Laser Pointers in Pediatric Patients**

This case report study highlights four cases of children aged 9-16 who sustained visual injury secondary to laser pointers. Laser pointers are low energy light sources that emit focal nonionizing radiation and handheld lasers can be deceiving in their safety level because they emit more power than expected. In these children, laser pointers caused reduced visual acuity, disruption of the photoreceptor ellipsoid zone, retinal pigment epithelium atrophy, and choroidal neovascular membrane formation. Three factors that most strongly contribute to visual loss include the amount of energy delivered by the laser, duration of exposure, and location of retinal involvement. The vision loss and persistent central scotoma occur immediately after exposure. Possible treatments include observation, systemic corticosteroids, and possibly vascular endothelial growth factor inhibitor for those patients with neovascular membranes. With the increasing number of injuries and irreversible damage, laser pointers should raise public health concerns for children. Unsupervised usage of these devices should be discouraged and additional legislation is needed to limit the usage of laser pointers in children.

**OCT IMAGING IN DISEASE**
Optical coherence tomography angiography of a retinal astrocytic hamartoma.

Retinal astrocytic hamartomas are rare, benign glial tumors that most commonly accompany tuberous sclerosis complex but may occur with neurofibromatosis type 1 or as isolated cases. A case is presented of an isolated retinal astrocytic hamartoma, evaluated with multimodal imaging, including spectral domain optical coherence tomography (SD-OCT), en face OCT, and OCT angiography. OCT angiography is a novel, noninvasive method for analyzing the retinal capillary system. This modality revealed a central feeder vessel with an associated abnormal vascular plexus, which correlated with the topographic location of the tumor on en face OCT. The authors claim that this is the first report on the use of OCT angiography to characterize an astrocytic hamartoma and its associated vasculature.

Optical coherence tomography to monitor vigabatrin toxicity in children

This study evaluates whether OCT can detect RNFL changes in children taking vigabatrin. A total of 31 patients were enrolled over five years; 28 patients had OCT data and 19 had complete dosing data available. Mean age was 5 years. Children with tuberous sclerosis (TS) were treated 4x as long as patients with other seizure disorders and therefore were exposed to a higher mean dose of vigabatrin. Higher vigabatrin dose was associated with thinner mean RNFL. This trend only reached significance for TS patients (nasal, superior and inferior quadrants). Once the cumulative dose exceeded 1500g the trend for thinner RNFL was more pronounced. The authors provide evidence to support their recommendation that the risks of general anesthesia for the child are only outweighed when the cumulative dose of vigabatrin approaches 1500g. Therefore if a child cannot perform awake serial OCTs, general anesthesia should only be considered at the aforementioned threshold.

Surgical Management of Advanced Familial Exudative Vitreoretinopathy with Complications

This retrospective study reported the management of 34 eyes of 25 patients with advanced FEVR with complications including retinal detachment, corneal opacity, shallow or flat anterior chamber, cataract, posterior pupillary adhesion, second-
ary glaucoma, vitreous hemorrhage, and preretinal hemorrhage. The average age of the patients was 3.52 years. 22 eyes underwent lensectomy, 9 underwent lensectomy with vitrectomy, 2 underwent staged lensectomy and vitrectomy, and 1 underwent lens-sparing vitrectomy. After surgery, the shallow or flat anterior chamber became normal in 26/28 eyes; corneal opacity improved in 10/22 eyes; and secondary glaucoma was controlled in 22/24 eyes. Among the 12 eyes that underwent vitrectomy, the retina was attached in 5 eyes and partially attached in 7 eyes. Final visual acuity ranged from NLP to 30/200, and all 5 eyes with pre-operative and postoperative visual acuity records showed improvement. Although this study is limited by its retrospective nature and small sample size, the authors demonstrated that, although difficult to manage, surgical intervention for advanced FEVR with complications might benefit patients in helping to preserve vision. Changes in ocular appearance due to leukocoria or phthisis bulbi may also be prevented.

**OCT IMAGING – DATA ON NORMAL EYES**

Study of spectral-domain optical coherence tomography in children: normal values and influence of age, sex, and refractive status


The main limitation when interpreting OCT results in children is the absence of a normal database. Spectral-domain OCT values for children are limited. In order to establish normal values for retinal nerve fiber layer (RNFL), macular thickness, and macular volume in children on spectral-domain optical coherence tomography (OCT), this descriptive cross-sectional study enrolled 162 Caucasian healthy children, mean age 8.1 +/- 3.03 years (range 3-14 years). They all underwent a comprehensive ophthalmic examination that included OCT scans with Spectralis (Heidelberg Engineering, Heidelberg, Germany). The influence of age, sex, and refraction on OCT measurements was also analyzed. They were able to obtain adequate SD-OCT images in 95.39% of the cases. The average values were 263.69 +/- 4.54 micron for central macular thickness, 0.21 +/- 0.01 mm³ for central macular volume, and 100.45 +/- 1.98 micron for RNFL. The spherical equivalent was 0.03 ± 0.19 D (range ±4 D, astigmatism <1 D). A significant correlation between RNFL and spherical equivalent was found for the nasal (p = 0.001), inferior (p = 0.009), and inferior nasal (p = 0.005) sectors. No differences were found with regard to gender (p>0.05). However, central macular thickness and central macular volume were correlated with age (p = 0.027, p = 0.02), which suggest that the development of the foveal structure continues beyond 5 years of age.
This study provides reference values for macular thickness, macular volume, and RNFL in healthy Caucasian children using Spectralis (Heidelberg Engineering, Heidelberg, Germany). Tables with percentiles $P_1, P_5, P_{95}, P_{99}$, are also provided for four age groups, which can be very useful. Its limitations are the exclusion of large refractive errors and small sample size.

**COAT’S DISEASE**

**Extramacular Fibrosis in Coats’ Disease**


A current Coats’ disease classification system stratifies the amount and location of retinal lipids and the extent of exudative retinal detachment at presentation, but subretinal and vitreoretinal fibrogenesis, particularly outside of the macula, is less often considered. This study determined the rate, risk factors, and outcome of extramacular fibrosis in 69 patients with Coats’ disease from a single center. 28 patients (40.6%) showed evidence of extramacular fibrosis with mean follow-up of 58.2 months. The mean time of fibrosis onset was 17.4 months. The extent of retinal exudation and rate of exudative retinal detachment at baseline were significantly higher in eyes that developed extramacular fibrosis compared to those that did not. Extension of telangiectasia, number of cryotherapy or laser sessions, and treatment with anti-VEGF were not associated with extramacular fibrosis. Final visual acuity was worse, and the rates of tractional retinal detachment and macular fibrosis were higher, in patients with extramacular fibrosis. Although the actual disease duration cannot always be accurately determined in children since the date of symptom onset can be difficult to estimate, the authors conclude that treatment should target rapid resolution of exudation to limit the development of extramacular fibrosis and poor visual outcomes.

**577-nm Yellow Laser Photocoagulation for Coats Disease**


This was a retrospective consecutive case series of 17 eyes (16 patients) with Coats disease treated with 577-nm yellow laser indirect ophthalmoscopy under anesthesia at a single institution between 2011 – 2014. Full treatment was defined as complete ablation of all visible telangiectasias and resolution of subretinal fluid. No patients were treated with cryotherapy or bevacizumab. At the time of treatment, disease was classified as Stage 1 (1 case), 2A (2), 2B (6), 3A1 (2), 3A2 (1), and 3B (5 cases). Patients underwent an average of 2.5 laser treatments. 16/17 eyes (94.1%) achieved full treatment, with mean time-to-full-treatment of 11.2 months. One eye developed glaucoma and end-stage disease. 577-nm laser alone was effective in this small study even in the setting of total exudative retinal detachment. Laser can be used even in areas of high retinal de-
tachment which cannot be reached with the cryo probe, and the risks of intrav-itreal anti-VEGF in this setting are avoided. Prospective studies comparing laser photocoagulation at different wavelengths and comparing laser with different treatment modalities would be helpful, though larger randomized studies may be difficult to coordinate for such a rare disease.

**MISCELLANEOUS**

**Comparison of Short-Wavelength Reduced-Illuminance and Conventional Autofluorescence Imaging in Stargardt Macular Dystrophy.**


The most common juvenile macular degeneration, Stargardt Macular Dystrophy, is an autosomal recessive disorder caused by ABCA4 gene mutations. One of the early findings in this disease is the retinal flecks, which are areas of accumulation of lipofuscin. On fundus autofluorescence (FAF) accumulation of lipofuscin is increased or hyper-autofluorescent and the areas of atrophy associated with disease progression demonstrate hypo or decreased autofluorescence. There are emerging studies that aim to look at the natural history of Stargardts and many hope to use autofluorescence as a potential endpoint in these studies. However, optimal parameters for the laser to obtain these images is unknown and there is concern about potential risk of high-intensity and short-wavelength excitation light used in the FAF that could theoretically increase the rate of lipofuscin accumulation and retinal toxicity in these patients. The goal of this study was to compare the images in patients with known Stargardt disease obtained with short wavelength reduced illuminance FAF imaging and those obtained with conventional FAF. Subjects over the age of 6 with molecularly confirmed Stargardt disease, atrophic lesion of at least 300um and clear media were included. The patients had one eye scanned. The first scan was done with 25% laser power. The second image was taken with 25% laser power but the photographer was able to adjust the total sensitivity to optimize the illumination of the image. The third image was taken with the 100% laser power. The authors found no difference in the ability to determine the presence or absence of decreased autofluorescence in the 3 images. The authors conclude that reducing the intensity of the laser illumination will not compromise the detection and measurement of decreased autofluorescence in patients with Stargardt Macular Dystrophy.

**Distinguishing optic pathway glioma and retinitis pigmentosa with visual field testing.**

The authors describe an interesting diagnostic dilemma in this case report of an 11-year-old boy, who complained of progressive vision loss OS greater than OD in the year prior to his presentation. The patient denied any peripheral visual field loss, nyctalopia, or photophobia. Multiple family members had molecularly confirmed autosomal dominant retinitis pigmentosa (RP) caused by a heterozygous Val87Asp mutation in the rhodopsin gene. Initially no RAPD was noted OS. Goldmann kinetic perimetry revealed a relatively incongruous left homonymous quadrantanopsia. Although he had a strong family history of RP, his fundus examination findings and visual fields were different from those of other family members. This had led to further investigations, including MRI brain that demonstrated increased signal at the optic chiasm and bilateral proximal optic nerves, which extended posteriorly into the optic tracts, lateral geniculate bodies, and the right Meyer's loop. This was consistent with an optic pathway glioma.

19. RETINOBLASTOMA / INTRAOCULAR TUMORS

RETINOBLASTOMA

Secondary and tertiary intra-arterial chemotherapy for massive persistent or recurrent sub retinal retinoblastoma seeds following previous chemotherapy exposure: long-term tumor control and globe salvage in 30 eyes


The results of intra-arterial chemotherapy (IAC) for control of persistent or recurrent subretinal seeds (SRS) following previous chemotherapy for retinoblastoma are described in this retrospective case series. The investigators reviewed the medical records of patients with massive persistent or recurrent SRS after intravenous and/or intra-arterial chemotherapy and subsequently treated with superselective ophthalmic artery infusion of melphalan (3, 5, or 7.5 mg) and/or additional topotecan (1 mg) and/or carboplatin (20 or 30 mg) as necessary from January 2009 to March 2014. The main outcome measures were SRS control and globe salvage. A total of 30 eyes of 29 patients were included. Mean patient age was 19 months (median, 14 months; range, 2-58 months). Previous treatments included intravenous chemotherapy (n = 28) and intra-arterial chemotherapy (n = 5). The SRS occupied a median of 6 clock hours. Retinal detachment was present in 5 eyes (17%). IAC was offered due to massive SRS, which refers to SRS that are not amenable to focal therapies (la-
ser, cryotherapy, or plaque radiotherapy), often exhibiting 2 or more quadrants of SRS involvement. Each eye received a mean of 3 IAC sessions (median, 2; range, 1-7) on a monthly basis. After a mean follow-up of 24 months (median, 18; range, 1-71 months), 8 of 27 eyes (30%) that initially achieved control had recurrence of SRS. Overall, globe salvage was achieved in 15 eyes (50%). Fifteen eyes were enucleated because of recurrent SRS (4 eyes), recurrent SRS and vitreous seeds (3 eyes), recurrent solid tumor (1 eye), and neovascular glaucoma from total retinal detachment and/or vitreous hemorrhage (7 eyes), none of which had active tumor. The authors conclude that IAC can be an effective second- or third-line therapy in the management of massive persistent or recurrent SRS from retinoblastoma following previous chemotherapy. Many inconsistencies were found while reading the article, which may confuse the reader. Limitations of the study include retrospective nature and short follow-up period. Long-term survival data would be of interest in the future.

Clinical significance of high levels of surviving and transforming growth factor beta-1 proteins in aqueous humor and serum of retinoblastoma patients.


This prospective, comparative study evaluated the diagnostic and prognostic values of survivin and transforming growth factor beta-1 (TGF-B1) expression in aqueous humor and serum of retinoblastoma (RB) in comparison to the conventional RB marker lactate dehydrogenase (LDH). It also aimed at elucidating a possible correlation between them and the clinic-pathological features of the disease. Included in the study 88 newly diagnosed children with RB and 80 age-matched controls with ophthalmic conditions other than tumors prepared for intraocular surgeries. Enucleation was indicated at time of diagnosis in all RB patients. Concentrations of survivin, TGF-B1, and LDH were measured in serum and aqueous humor before and 6 months after completion of therapy. High serum and aqueous humor concentrations of the three proteins were detected in RB patients before treatment compared to the control group (P < 0.01), with a significant reduction of serum concentrations after treatment (P < 0.01). For the highest sensitivity and specificity, the optimal cut-off values of serum and aqueous survivin were 12.9 pg/ml and 25.2 pg/mg, with a significant positive correlation between aqueous survivin and RB staging and presence of optic nerve infiltration (r = 0.43, P = 0.04); the best cut-off values of serum and aqueous TGF-B1, 370.7 pg/ml and 39.8
pg/mg, with a significant positive correlation between aqueous TGF-B1 and poor differentiation of the tumor (r = 0.69, P = 0.001). The authors conclude that the high sensitivity, specificity, and accuracy of serum and aqueous humor survivin and TGF-B1 proteins make them promising markers for early detection and follow-up of RB patients. A thorough review of the literature is presented and the general characteristics of these proteins are discussed. However, the role of these two proteins in RB pathogenesis still remains to be determined.

Prenatal versus Postnatal Screening for Familial Retinoblastoma.


In this retrospective, observational study, the authors compare overall outcomes of conventional postnatal screening of familial retinoblastoma and prenatal RB1 mutation identification followed by planned early-term delivery. The study participants are Twenty children with familial retinoblastoma born between 1996 and 2014 and examined within 1 week of birth. Cohort 1 included spontaneously delivered neonates examined within 1 week of birth and confirmed postnatal to carry their family's RB1 mutant allele. Cohort 2 included infants identified by amniocentesis to carry their family's RB1 mutant allele, and therefore scheduled for early-term delivery (36-38 weeks' gestation). Main outcome measures are Age at first tumor in each eye, eye stage, treatments given, ocular salvage, treatment success (defined as avoidance of enucleation, external-beam irradiation, or both), visual outcome, number of anesthetics, pregnancy or delivery complications, and estimated treatment burden. Vision-threatening tumors were present at birth in 4 of 8 infants in cohort 1 and in 3 of 12 infants in cohort 2. Eventually, all infants demonstrated tumors in both eyes. At the first treatment, 1 of 8 infants in cohort 1 had eyes in stage cT1a/cT1a or cT1a/cT0 (smallest and least vision-threatening tumors), compared with 8 of 12 infants in cohort 2 (P = 0.02). Null RB1 germline alleles induced earlier tumors than low-penetrance alleles (P = 0.03). Treatment success was achieved in 3 of 8 children in cohort 1 compared with 11 of 12 children in cohort 2 (P = 0.002). Acceptable vision (better than 0.2 decimal) was achieved for 8 of 16 eyes in cohort 1 compared with 21 of 24 eyes in cohort 2 (P = 0.014). Useful vision (better than 0.1, legal blindness) was achieved for 8 of 9 children in cohort 1 compared with 12 of 12 children in cohort 2. There were no complications related to early-term delivery. Median follow-up was 5.6 years, cohort 1 and 5.8 years, cohort 2. The authors conclude that when a parent had retinoblastoma, prenatal molecular diagnosis with early-term delivery increased the likelihood of infants born with no detectable tumors, better vision outcomes, and less invasive therapy. Prenatal molecular diagnosis facilitates anticipatory planning for both the child and family.

Detection of Retinoblastoma at Risk for Metastasis Using Clinical and Histopathologic Features and Now mRNA
In this invited commentary, the author highlights current methodologies for determining which children with retinoblastoma are at high risk for metastasis. Pathologic analysis of enucleation specimens (optic nerve invasion, massive choroidal invasion), clinical exam (iris or any anterior chamber involvement or exophytic growth pattern, tumor thickness 15 mm or greater, and vitreous hemorrhage), and International Classification of Retinoblastoma (17% of Group D & 24% of Group E eyes had HRPF’s in one study.) Ideally, a less invasive biomarker, especially of those patients who do not undergo enucleation, would be useful to predict risk for metastasis. Assessment of minimal dissemination via quantitative PCR has the potential to be a such a marker, but a larger group of patients is needed to validate such an approach.

Minimal Disseminated Disease in Nonmetastatic Retinoblastoma With High-Risk Pathologic Features and Association With Disease-Free Survival

Retinoblastoma continues to afflict thousands of children world-wide, but when detected and treated early, children have a high survival rate. The authors want to address the question of how to anticipate metastatic disease in children with retinoblastoma with high risk prognostic features (HRPFs). The use of cone-rod homeobox (CRX) transcription factor messenger RNA for minimal dissemination (MD) evaluation in metastatic retinoblastoma was previously reported, but no data in nonmetastatic cases with HRPFs are available. The goal of this study was to evaluate whether MD is detectable in patients with nonmetastatic retinoblastoma and to assess its prognostic effect on disease-free survival. The study evaluated CRX messenger RNA by quantitative polymerase chain reaction (qPCR) in bone marrow and cerebrospinal fluid at diagnosis and follow-up. In 14 patients, GD2 synthase was used instead of CRX for cerebrospinal fluid evaluation. Patients were treated according to uniform guidelines. The study included 96 children with non-metastatic retinoblastoma and high risk prognostic features which included isolated massive choroidal invasion in 14, postlaminar optic nerve invasion in 51 (26 had concomitant massive choroidal and 13 with scleral invasion), 12 with scleral invasion without postlaminar optic nerve invasion, and 7 with tumor at the resected margin of the optic nerve. Minimal dissemination was detected in 9 patients and was associated with extension beyond the resection margin of the optic nerve and scleral involvement. MD occurred in 8 of the 43 International Intraocular Retinoblastoma Classification group E eyes with glaucoma (18.6%) and in 8 of 80 (10%) and 1 of 16 children (6.3%) who underwent primary or secondary enucleation, respectively. Children with MD had a 3-year disease-free survival of 0.78 compared with 0.98 in those without MD (95% CI for the difference in DFS, 0.17-0.23; P = .004).
Conclusion: These findings identified a population of children with retinoblastoma and HRPFs and some, but not all, had minimal dissemination identified by qPCR in bone marrow and cerebrospinal fluid, which correlated with less disease free survival. However, because the number of events was small, these results should not yet be considered a reliable biomarker for predicting metastatic disease in children with non-metastatic retinoblastoma.

**Ocular Pharmacology of Chemotherapy for Retinoblastoma**

This paper reviewed 21 studies to assess the preclinical and clinical pharmacokinetics of carboplatin, topotecan, and melphalan delivered by intravenous, periocular, ophthalmic artery, and intravitreal routes. Some preclinical studies were done before translation to the clinics. Others, despite favorable preclinical data such as that reported for periocular tepotecan, did not correlate with clinical use. In addition, some routes of drug delivery are clinically effective despite nonfavorable preclinical information, such as melphalan delivered as ophthalmic artery chemosurgery. The authors report that complete knowledge of the pharmacokinetics of these medications is lacking and additional study may guide retinoblastoma therapy in favor of safety and efficacy. However, they emphasize that results obtained in preclinical models must be translated to the clinics with caution.

**DNA Duplex-Based Photodynamic Molecular Beacon for Targeted Killing of Retinoblastoma Cell**

This study proposes and evaluates a novel RB treatment protocol based on a photodynamic therapy (PDT) with a designed molecular beacon that specifically targets the murine double minute x (MDMX) high-expressed RB cells. Retinoblastoma selectively amplifies murine double minute x (MDMX), an antagonist of p53. The aberrant expression leads to an inactivation of the p53 pathway via the formation of inactive p53-MDMX complexes, contributing to the development and progression of retinoblastoma formation. In this study, an MDMX mRNA triggered photodynamic molecular beacon was designed by binding a photosensitizer molecule (pyropheophorbide-a, or PPa) and a black hole quencher-3 (BHQ3) through a complementary oligonucleotide sequence. Cells with and without MDMX high expression were incubated with the beacon and then irradiated with a laser. The fluorescence and reactive oxygen species were detected in solution to verify the specific activation of PPa by the perfectly matched DNA targets. The cell viabilities were evaluated with CCK-8 and flow cytometry assay. The fluorescence and photo-cytotoxicity of PPa was recovered and significantly higher in the MDMX high-expressed Y79 and WERI-Rb1 cells, compared to that with the
MDMX low-expressed cells. The synthesized beacon exhibits high PDT efficiency toward MDMX high-expressed RB cells. Although this beacon is still in the in vitro stage of study, this data suggest that the designed beacon may provide a potential alternative for RB therapy and secures the ground for future investigation.

**Primary intravenous chemotherapy for group D retinoblastoma: a 13-year retrospective analysis**
Ido D Fabian, Andrew W Stacey, Kenneth P Johnson, Zerrin Onadim, et al.
*Br J Ophthalmol* January 2017;101:82-88

Eye salvage rate for group D retinoblastoma using intravenous chemotherapy (IVC) as a primary modality is <50%. This study is a report by the London Retinoblastoma Service looking at 13 years' experience with the use of primary IVC for group D retinoblastoma. The authors acknowledge that although intravascular artery chemotherapy (IAC) has gained popularity, it has possible drawbacks including the potential for systemic spread and the advanced infrastructure and expertise necessary for the success of this type of delivery. The authors conducted a retrospective analysis of 64 group D eyes (52 patients) treated with primary IVC, from 2002 to 2014. The median age at presentation was 11.0 months (mean: 18.6, range: 0.6–144.0), 35 (67%) patients had bilateral disease, 38 (73%) germline disease and 8 (15%) cases were familial. In addition to IVC, patients received a median number of three treatments (mean: 6, range: 0–24), including thermotherapy/cryotherapy, plaque radiotherapy, intravascular artery chemotherapy (IAC) and/or intravitreous chemotherapy. External beam radiotherapy (EBRT) was used in five eyes, all of which were eventually enucleated. During a median follow-up time of 55 months (mean: 64, range: 14–156), 63% of eyes were salvaged. By the Kaplan-Meier survival analysis, globe salvage rate was 83%, 70%, 59% and 45% at 1, 3, 5 and 10 years, respectively. There were no cases of metastatic spread from intraocular retinoblastoma and no deaths. IVC-related adverse events included febrile neutropenia in 21 (40%) patients and anaphylactic reaction to carboplatin in 2 (4%), all conservatively resolved. Of the patients receiving IAC, third and sixth nerve palsies were documented in two (10%) and one (5%) eyes, respectively. The authors concluded that primary IVC for group D eyes, with adjuvant treatments as required, was found to be a safe and efficient approach, achieving 63% eye salvage rate, no metastatic spread from intraocular retinoblastoma and no deaths. IAC has now replaced EBRT as a successful salvage treatment.

**Retinoblastoma Control With Primary Intra-arterial Chemotherapy: Outcomes before and during the intravitreal chemotherapy Era.**
Carol L. Shields, Adel E. Alset, Emil Anthony T. Say, Emi Caywood et al.
In this retrospective interventional case series, 66 eyes of 66 patients with untreated retinoblastoma were reviewed. All patients received intra-arterial chemotherapy into the ophthalmic artery under fluoroscopic guidance using melphalan, with additional topotecan as needed (Era I). Intravitreal chemotherapy using melphalan and/or topotecan (Era II) was employed also as needed in cases of active vitreous seeding. The two groups of patients had similar features in terms of mean age, International Classification of Retinoblastoma (ICRB) groups, mean largest tumor diameter (19 vs 17 mm), mean largest tumor thickness (10 mm vs 10 mm), vitreous seed presence (56% vs 59%), subretinal seed presence (67% vs 62%), retinal detachment (70% vs 66%), or vitreous hemorrhage (0% vs 5%). Following therapy, there was a significant difference between the two groups in the need for enucleation overall (44% vs 15%, p = .012), especially for group E eyes. For group B and C, the enucleation rate was 0% for the two eras, and non-significant for Group D. The authors conclude that in the current management of retinoblastoma the use of intra-arterial chemotherapy combined with intravitreal chemotherapy in cases of severe vitreous seeding, has improved the globe salvage rates in eyes with advanced retinoblastoma.

Choroidal infiltration by Retinoblastoma: Predictive clinical features and outcomes.
Swathi Kaliki, Prerano Tahiliani, Sadiya Iran, Mohammed Hasnat Ali et al

In this retrospective chart review, 403 patients with retinoblastoma who underwent enucleation were studied histopathologically. Out of 403 patients, 113 were found to have choroidal tumor infiltration and 290 patients had no choroidal tumor infiltration. The clinical features predictive of high risk retinoblastoma included older age at presentation (age > 2 years), duration of symptoms for more than 6 months, buphthalmos, staphyloma, hyphema, pseudohypopyon, secondary glaucoma and orbital cellulitis. The clinical features predictive of choroidal tumor infiltration by retinoblastoma were delayed presentation with symptoms present for more than six months (three fold greater risk) and secondary glaucoma (two fold greater risk including 40% of cases with neovascular glaucoma). The authors believe that high intraocular pressure and delayed presentation can actually cause direct invasiveness of the tumor with breakdown of retinal pigment epithelium/Bruch’s membrane complex and then choroidal infiltration. In this study all patients with choroidal infiltration received prophylactic adjuvant chemotherapy with no systemic metastasis related deaths, whereas patients with massive choroidal infiltration and features such as ciliary body infiltration/post-laminar optic nerve infiltration/scirr infiltrative and microscopic external scleral infiltration developed metastasis despite adjuvant chemotherapy.

Prenatal versus Postnatal Screening for Familial Retinoblastoma
In this retrospective observational study, the authors compare overall outcomes of conventional postnatal screening of familial retinoblastoma and prenatal RB1 mutation identification followed by planned early-term delivery. Cohort 1 (n=8 patients) included spontaneously delivered neonates examined within 1 week of birth and confirmed postnatal to carry their family’s RB1 mutant allele. Cohort 2 (n=12 patients) included infants identified by amniocentesis to carry their family’s RB1 mutant allele, and therefore scheduled for early-term delivery (36-38 weeks’ gestation). Vision-threatening tumors were present at birth in 4 of 8 infants in cohort 1 and in 3 of 12 infants in cohort 2. Eventually, all infants demonstrated tumors in both eyes. At the first treatment, 1 of 8 infants in cohort 1 had eyes in stage cT1a/cT1a or cT1a/cT0 (smallest and least vision-threatening tumors), compared with 8 of 12 infants in cohort 2 (P=0.02). Null RB1 germline alleles induced earlier tumors than low-penetration alleles (P=0.03). Treatment success was achieved in 3 of 8 children in cohort 1 compared with 11 of 12 children in cohort 2 (P=0.002). Acceptable vision (better than 0.2 decimal) was achieved for 8 of 16 eyes in cohort 1 compared with 21 of 24 eyes in cohort 2 (P=0.014). Useful vision (better than 0.1, legal blindness) was achieved for 8 of 9 children in cohort 1 compared with 12 of 12 children in cohort 2. There were no complications related to early-term delivery. Median follow-up was 5.6 years, cohort 1 and 5.8 years, cohort 2. When a parent had retinoblastoma, prenatal molecular diagnosis with early-term delivery increased the likelihood of infants born with no detectable tumors, better vision outcomes, and less invasive therapy. Prenatal molecular diagnosis facilitates anticipatory planning for both the child and family. Comment: Although a small sample, the results are impressive and would seem to warrant a prospective interventional study.

Multimodal Therapy for Stage III Retinoblastoma (International Retinoblastoma Staging System)


The authors of this prospective comparative study aimed to compare the efficacy of 2 chemotherapeutic drug combinations as part of multimodal therapy for stage III orbital retinoblastoma. Treatment protocol included neoadjuvant chemotherapy, enucleation, orbital external-beam radiotherapy, and adjuvant chemotherapy. For chemotherapy, patients were randomized into 2 groups: group A was treated with vincristine, etoposide, and carboplatin (VEC) and group B was treated with carboplatin and etoposide, alternating with cyclophosphamide, idarubicin, and vincristine. 54 children were recruited (27 in each group) with mean follow-up of 21.3 months. There were 9 deaths in group A and 15 deaths in group B. The Kaplan-Meier survival probability at 1 year was similar between the groups: 81% and 79% for groups A and B, respectively. At 4 years, the survival probabil-
ity for group A was higher: 63% vs. 25% for groups A and B, respectively. The major cause of death was central nervous system relapse. Grade 3 and grade 4 hematologic toxicities were more common in group B, with a significant difference in grade 4 neutropenia (P=0.002). The authors concluded that the VEC combination of chemotherapy was more effective than the 5-drug combination of vincristine and carboplatin, alternating with cyclophosphamide, idarubicin, and vincristine, for stage III retinoblastoma. Comment: Although not directly addressed in this paper, I find this article interesting in the context of how treatment for these lethal and disfiguring malignancies has moved away from the more destructive orbital exenteration procedure to chemo, radiation and enucleation with better survival results and less disfigurement from the surgery.

Incidence and survival of retinoblastoma in Taiwan: a nationwide population-based study 1998–2011


This is a descriptive epidemiology study of the incidence of retinoblastoma in Taiwan from 1998 to 2011. The study was conducted using claims data from Taiwan National Health Insurance Research Database (NHIRD), which insures more than 99% of the population. All enrollees were first diagnosed with retinoblastoma (ICD-9-CM code: 190.5). The authors included patients who had applied for a catastrophic illness certificate of retinoblastoma (Registry of Catastrophic Illness Database, a subpart of the NHIRD) or received clinical treatment during the observation period to confirm the diagnostic accuracy of retinoblastoma. The study identified 154 patients (92 males) with retinoblastoma and the documented overall retinoblastoma incidence was 1 in 17,373 live births without a notable trend over the study period. The incidence per million live births examined by gender was 65.8 for males and 48.5 for females. The age-specific sex ratio increased from 1.4 at age younger than 1 year to 3.0 above age 4 years. Enucleation was performed in 109 (70.8%) children with retinoblastoma, and it was more prevalent in males than in females (77.2% vs 61.3%, p=0.03). Multivariate Cox regression analyses with adjustment for diagnostic age, sex, and birth year elucidated that enucleation was a significant factor associated with survival (OR 0.27, 95% CI 0.10 to 0.61). The authors found that the incidence of retinoblastoma in Taiwan exhibited no marked trend over time. There were more cases among males than females and the male-to-female rate ratio increased with age. Survival outcome was significantly associated with the intervention of enucleation. During the study period, new interventions such as intraarterial chemotherapy and new therapeutic agents were introduced.

Intra-arterial Chemotherapy for Retinoblastoma A Systematic Review

The purpose of this study was to conduct a meta analysis of studies to determine outcomes, both beneficial and deleterious, of intra-arterial chemotherapy (IAC) for retinoblastoma. The authors conducted online searches of various databases to identify articles with at least 4 patients which included outcomes related to efficacy or toxicity. 28 publications were identified with an aggregate 655 patients, 757 eyes, and 2350 catheterizations. None had comparison groups and most were retrospective. Globe salvage was achieved for 502 (66%) of all eyes. Most common reported toxicities were chorioretinal atrophy and vascular occlusions. There were at least 13 reports of children with metastases. After publication, 7 additional children had metastases. The 4 different classification systems used challenged the comparison of disease severity at presentation. Visual outcome was not addressed in most studies. Meta-analyses were not possible because no study had a comparison group.

Importance: The authors could not conduct a meta analysis, just a review of the literature which is limited by the predominance of retrospective case series, absence of comparison groups, short follow-up, heterogeneous definitions and tumor classifications, and frequent duplicate reporting. Intraarterial chemotherapy is highly touted for treatment in some tertiary medical centers and the authors emphasize caution. The most dreaded complication of cancer treatment, metastases, has been observed with IAC. The authors emphasize the need for randomized prospective studies, and until results are available from such studies, intra-arterial chemotherapy should be offered selectively among other options, with extensive discussion about all possible risks as well as benefits.

**Cytopathological Evaluation of Ocular Surface and needle washings following intravitreal melphalan injections for Retinoblastoma.**

Jasmine H. Fancis, Ijah Mondesire-Crump, Brian P. Marr, Scott E. Brodie et al


There is concern that the intravitreal injections in eyes with retinoblastoma have a significant risk for the dissemination of the tumor. This study investigates the presence of malignant cells in the ocular surface and in the needle washings of eye with retinoblastoma receiving intravitreal melphalan injections. Two hundred (n=200) ocular surface and two hundred two (n=202) needle washing samples were obtained from two hundred eighty injections (n=280) of melphalan and were sent for cytopathological examination in order to detect the presence of malignant cells. The patients had 10 months of follow-up and none of these eyes had developed tumor growth at the needle site or in the subconjunctival space. The authors document that no malignant cells were detected in any of the samples. The presence of squamous cells, red blood cells and inflammatory cell was documented in a few samples of ocular surface washings. Only squamous cells were present in four needle washings. The authors conclude that the intravitreal injection of melphalan is a low risk procedure as far as the extraocular dissemination
of malignant cells in concerned. Safety measures should be undertaken though such as careful inspection of the injection site, cryotherapy to the site, reduction of intraocular pressure, needle gauze size, and drug volume.

Classification of Vitreous Seeds in Retinoblastoma Correlations with Patient, Tumor, and Treatment Characteristics
Francis JH, Marr BP, Abramson DH. *Ophthalmology* July 2016;123:1601-1605

In this retrospective cohort study of 135 eyes with active RB vitreous seeds, the authors evaluated the patient, disease, and tumor characteristics of the 3 morphologically distinct groups of vitreous seeds presenting for treatment with ophthalmic artery chemosurgery (OAC): dust (class 1), spheres (class 2), and clouds (class 3) in primary and recurrent vitreous seeds. In patients with primary disease, patients with eyes containing class 3 (cloud) vitreous seeds were significantly older than patients with class 1 or 2 seeds (P < 0.05). The median age of patients with class 1, 2, and 3 seeds was 11, 15.5, and 32 months, respectively. Eyes containing class 3 seeds were significantly more likely to occur in the equator-ora region of the fundus (P < 0.0001), in a diffuse pattern (P < 0.0001), and in patients with unilateral disease (P < 0.05), compared with class 1 and 2 seeds. In patients with recurrent disease, recurrent vitreous seeds were significantly more common to class 2 (P < 0.05), occurring in a diffuse pattern (P=0.01) and in patients with bilateral disease (P < 0.001). The 3 classes of vitreous seeds have distinct clinical characteristics associated with the age of patient, laterality of disease, and extent and location of tumor-producing seeds. Recurrent vitreous seeds appear to have a unique clinical profile compared with seeds receiving primary treatment.

Comment: High quality fundus photos in this paper demonstrate class 1, 2 and 3 vitreous seeds.

High-Resolution Magnetic Resonance Imaging Can Reliably Detect Orbital Tumor Recurrence after Enucleation in Children with Retinoblastoma

In this retrospective case series high resolution orbital MRI findings after enucleation were evaluated for evidence of retinoblastoma recurrence and compared with clinical/histopathologic evidence of tumor recurrence. A total of 103 MRI examinations of 55 orbits (50 children, 27 male/23 female, mean age 16.4 months with a median time of 8 months after enucleation for retinoblastoma. Abnormal orbital enhancement was a common finding after enucleation (100% in the first 3 months after enucleation, 64.3% >3 years after enucleation). All histopathologically confirmed tumor recurrences (3 of 55 orbits, 5.5%) were correctly judged as “definitive tumor” in MRI. Two
orbits from 2 children rated as “suspicious of tumor” received intravenous chemotherapy without histopathologic confirmation; further follow-up (67 and 47 months) revealed no sign of tumor recurrence. In 90.2%, no tumor was suspected on MRI, which was clinically confirmed during follow-up (median follow-up after enucleation, 45 months.

Comment: High-resolution MRI with orbital surface coils may reliably distinguish between common postsurgical contrast enhancement and orbital tumor recurrence, and therefore may be a useful tool to evaluate orbital tumor recurrence after enucleation in children with retinoblastoma. This appears to be a useful adjunct to current clinical diagnosis. However given that this is a retrospective study and the post-enucleation indications for imaging were not given, one might suspect that higher recurrence risk patients were imaged and therefore biased the frequency or severity of MRI abnormalities observed in this series. The images included in the paper demonstrate the quality of MRI to detect recurrence in some patients.

Intravitreous Chemotherapy for Active Vitreous Seeding from Retinoblastoma: Outcomes After 192 Consecutive Injections. The 2015 Howard Naquin Lecture


This retrospective case series reported on the safety and efficacy of intravitreous chemotherapy in 40 eyes with viable vitreous seeding after standard treatment of retinoblastoma. All eyes received intravitreal melphalan injection (20-30 ug) and additional topotecan (20 ug) as needed via the trans pars plana route with triple freeze-thaw cryotherapy at needle withdrawal. The mean number of melphalan injections was 4 and topotecan was 3, fewer than the planned 6 injections because of rapid and complete vitreous seed control in most cases. At median 3-year follow-up, therapeutic success with continued seed regression was observed in all 40 eyes, and globe salvage was attained in 35 cases (88%). Treatment complications included RPE mottling, paraxial mild cataract not requiring extraction, mild transient vitreous hemorrhage, and mild transient hypotony. There were no complications of iritis, glaucoma, endophthalmitis, extraocular extension, metastasis, or death. Vitreous seeding from retinoblastoma has often previously required enucleation. This study confirms the safety of intravitreal chemotherapy and its efficacy in controlling vitreous seeding with a fewer than previously reported median number of injections. When cautious technique is followed, intravitreal chemotherapy is safe and has saved numerous children from enucleation.

Optic Nerve Infiltration by Retinoblastoma: Predictive Clinical Features and Outcome

This study reviewed 403 patients who underwent primary enucleation for retinoblastoma to identify the clinical features predictive of any optic nerve infiltration and postlaminar optic nerve infiltration on histopathology, and to report the outcome in these patients. 196 patients had optic nerve tumor infiltration (Group 1), and 207 had no evidence of optic nerve infiltration (Group 2). Group 1 included patients with prelaminar (24%), laminar (38%), and postlaminar tumor infiltration with or without involving optic nerve transection (38%). On multivariate analysis, clinical feature predictive of any optic nerve tumor infiltration was secondary glaucoma (HR=5.38), and those predictive of postlaminar tumor infiltration included iris neovascularization (HR=2.66) and secondary glaucoma (HR=3.13). This large study confirms that the degree of optic nerve infiltration by retinoblastoma influences metastatic potential and survival. No cases with isolated prelaminar/laminar optic nerve involvement developed metastases, and 7 patients with postlaminar optic nerve involvement including 2 cases with optic nerve cut section involvement developed metastases despite 6 undergoing post-enucleation adjuvant chemotherapy.

**Advanced unilateral retinoblastoma: a case of sparing enucleation treatment failure.**

Over the last few years, intra-arterial chemotherapy (IAC) has become an effective alternative for treatment of intraocular retinoblastomas (RB), allowing improved globe salvage and reducing systemic chemotherapy toxicities. This is a case report of a child with unilateral heavily pretreated RB (group D) who developed a relatively small intraocular recurrence with a massive postlaminar optic nerve invasion after IAC. No germline mutation was recognized. MRI prior to treatment did not demonstrate extraocular involvement.

**NON-RETINOBLASTOMA**

**The Pediatric Choroidal and Ciliary Body Melanoma Study A Survey by the European Ophthalmic Oncology Group**

In this retrospective multicenter observational study, the authors studied 299 patients of whom 114 were children and 185 were young adults in order to collect comprehensive data on choroidal and ciliary body melanoma (CCBM) in children and to test the hypotheses that children younger than 18 years, males, and those without ciliary body involvement (CBI) have more favorable survival prognosis than young adults, females, and those with CBI. Cumulative frequency of having CCBM diagnosed increased steadily by 0.8% per year of age between 5 and 10 years of age and, after a
6-year transition period, by 8.8% per year from age 17 years onward. Melanoma-related survival was 97% and 90% at 5 years and 92% and 80% at 10 years for children compared with young adults, respectively (P=0.013). Males tended to have a more favorable survival than females among children (100% vs. 85% at 10 years). Increasing TNM stage was associated with poorer survival (stages I, II, and III: 100% vs. 86% vs. 76%, respectively). By multivariate analysis, being a young adult (adjusted hazard rate [HR], 2.57), a higher TNM stage (HR, 2.88 and 8.38 for stages II and III, respectively), and female gender (HR, 2.38) independently predicted less favorable survival. Ciliary body involvement and cell type were not associated with survival.

Comment: Kaplan-Meier plots in the figures demonstrate difference in survival for factors such as age group, gender, presence of congenital ocular-dermal melanocytosis, ciliary body involvement, extraocular extension, and tumor-node-metastasis stage over a 25-year period.

Retinal Astrocytic Hamartoma: Optical Coherence Tomography Classification and Correlation with Tuberous Sclerosis Complex

This retrospective chart review examined clinical and SD-OCT features of retinal astrocytic hamartomas in 43 patients with an established diagnosis of tuberous sclerosis complex. The retinal astrocytic hamartomas were classified into 4 morphologic groups, and each group was correlated with systemic manifestations of TS complex. Patients with Type II had greater number of cutaneous fibrous plaques (OR=64.8), those with Type III had higher incidence of subependymal giant-cell astrocytoma (OR=43.2), and those with Type IV had higher incidence of pulmonary lymphangiomyomatosis (OR=126). If these correlations are confirmed in population-based studies and pathologic findings, SD-OCT could become a fundamental tool for noninvasively screening patients, providing ophthalmologic classification and prediction of related systemic findings.

20. ORBIT
Isolated schwannoma involving extraocular muscles

Progressive strabismus initially considered idiopathic may be caused by isolated schwannomas of motor nerves to extraocular muscles, detectable only on careful imaging. This retrospective case series study reviewed the clinical experience of a referral practice in identifying schwannomas on magnetic resonance imaging
(MRI). Of 647 cases imaged for strabismus, schwannomas were identified by gadodiamide-enhanced, high-resolution surface coil orbital MRI and thin-section cranial MRI, as fusiform intraneural enlargements in 8 cases: 1 affecting the trochlear nerve; 2, the abducens nerve; and 5 the oculomotor nerve. Involved muscles were atrophic. Both abducens schwannomas, 1 superior oblique, and 1 oculomotor schwannoma were subarachnoid; 3 were intraorbital, and with one bilateral case of oculomotor lesions, which extended from the cavernous sinus to orbit. Associated strabismus progressed for 3-17 years. Abducens schwannoma caused esotropia; trochlear schwannoma caused hypertropia and cyclotropia. Intracranial oculomotor schwannoma caused mydriasis and exotropia. Intraorbital schwannoma caused exotropia with or without hypertropia. Since lesion diameters were 3-9 mm, 6 had been previously missed on routine MRI. Progressive, acquired strabismus may be caused by isolated cranial nerve schwannomas, representing about 1% of strabismus cases in this cohort, involving the oculomotor more than abducens nerve. Because most schwannomas are small and deep in the orbit, findings could be readily missed by routine imaging, leading to a possible diagnosis of idiopathic strabismus. The authors conclude that schwannomas should be suspected when extraocular muscles are atrophic. Targeted, high resolution MRI is necessary to identify these small lesions, which are nodular or fusiform hyperintense neural lesions in on T2-weighted and contrast-enhanced T1-weighted MRI. This small case series raises schwannomas as a possible diagnosis in clinical situations with progressive clinical course, atrophy of involved muscles, and highly selective involvement of cranial nerves.

Management of frontal sinusitis-associated subperiosteal abscess in children less than 9 years of age


In the treatment algorithm for subperiosteal abscess (SPA) in children younger <9 years of age, surgery is only recommended if one of eight additional surgical criteria is met. One surgical inclusion criterion for children <9 years of age is frontal sinusitis. This retrospective case series investigated the practice patterns for cases of subperiosteal abscess (SPA) with concomitant frontal sinusitis and identified factors favorable to medical management in children <9 years of age. The medical records of all pediatric cases of orbital and periorbital cellulitis admitted at a tertiary care center from 1999-2014 were reviewed retrospectively. Cases were included if radiog-
raphy demonstrated sinusitis-associated SPA in children <9 years of age. Cases of SPA with ipsilateral frontal sinusitis were compared to cases of SPA without ipsilateral frontal sinus involvement. A total of 21 cases with ipsilateral frontal sinusitis and 76 without were included. Patients with frontal sinusitis had a higher incidence of non-medial wall SPA compared to those without frontal sinus involvement (6/21 vs 5/76, P = 0.01). Yet a majority of SPAs in the frontal sinusitis group were located medially (15/21 [71%]). All patients with superior or superomedial SPA underwent early surgical intervention. However, 14 of 15 patients (93%) in the frontal sinusitis cohort with medial SPAs were managed successfully with medical therapy alone, with no increase in hospital stay and visual acuities returning to 20/25 or better. The authors concluded that medical management of frontal sinusitis-associated SPA appears safe for select children <9 years of age with medial abscess. Authors state that although frontal sinusitis is cited as a criterion for surgical drainage of SPA, this criterion should be refined to frontal sinusitis with superiorly located abscesses only. Despite some limitations in study design, this study makes an interesting argument for the medical management of patients with frontal sinusitis and medial wall SPA.

Local Resection and Brachytherapy for Primary Orbital Rhabdomyosarcoma: Outcome and Failure Pattern Analysis
Schoot RA, Saeed P, Freling NJ, Blank LE, et al
Survival rates in patients with orbital rhabdomyosarcoma (RMS) is excellent. New local modalities such as brachytherapy have been developed to minimize adverse events. This retrospective study described the outcome of 20 patients with primary orbital RMS and to assess risk factors for treatment failure. After induction chemotherapy patients were treated with either surgery and brachytherapy, external beam radiotherapy or no local treatment if complete remission was achieved with chemotherapy alone. 7 patients relapsed but the authors could not find any patient, tumor or treatment characteristics that predisposed for treatment failure. Ten year overall survival was 89%. Ten year event-free survival was 65%. Surgery and brachytherapy resulted in fewer adverse events than external beam radiation. Limitations of this study include its small sample size.

Orbital and Periorbital Extension of Congenital Dacryocystoceles: Suggested Mechanism and Management
Orbital and periorbital extension of congenital dacryocystoceles is rarely observed in neonatal infants. Congenital dacryocystoceles is considered a transito-
ry, self-resolving condition and pressure massage is traditionally recommended as a conservative treatment. The authors four cases of congenital dacryocystoceles that presented with extension to the orbital and periorbital regions. The awareness of this potential complication implies a lower threshold for orbital imaging in cases of rapidly enlarging dacryocystoceles. It also has to be considered that forceful massage may spread contents of the mucocele unpredictably into the orbit. In the authors’ experience, transconjunctival orbitotomy with sac marsupialization followed by nasolacrimal intubation has proven effective for the management of this rare complication.

**Oral Propranolol as an Alternative Therapy for Orbital Angiolympoid Hyperplasia with Eosinophilia**

Case report on an 8 year old patient presenting with eyelid swelling. MRI revealed an orbital mass involving the lacrimal gland. Incisional biopsy led to the diagnosis of angiolympoid hyperplasia with eosinophilia (ALHE). Traditionally treatment includes excision or steroid therapy, both with high rates of recurrence or systemic side effects, respectively. The patient was initially started on oral steroids but due to systemic side effects an alternative treatment was needed. Oral propranolol is often used in the treatment of large capillary hemangiomas. Mechanism of action is thought to be localized vasoconstriction or stimulated apoptosis of capillary endothelial cells. The current patient was started on oral propranolol and had a positive response with no untoward effects. The dystrophic vascular endothelial cells in ALHE may explain the positive response of these lesions to beta-blocker therapy. This case is the second case report that the authors could find that used oral propranolol as a treatment for ALHE. The case lends more evidence that propranolol may be considered a noninvasive treatment option for ALHE.

**Graves’ Disease**

This review is of relevance to the strabismologist who encounters patients with Graves’ disease. Graves' disease is an autoimmune disorder in which the thyroid is activated by antibodies to the thyrotropin receptor. The hyperthyroidism that develops is one of many somatic and psychiatric manifestations of the disease that can affect the quality and length of life.

Epidemiology: Graves’ disease is the most common cause of hyperthyroidism, with an annual incidence of 20 to 50 cases per 100,000 persons. The incidence peaks between 30 and 50 years of age, but people can be affected at any age. The lifetime risk is 3% for women and 0.5% for men. Severe ophthalmopathy is
more likely to develop in older men than in younger persons. Orbital imaging reveals subtle abnormalities in 70% of patients with Graves’ disease. In specialized centers, clinically consequential ophthalmopathy is detected in up to 50% of patients with Graves’ disease, and it is vision threatening due to corneal breakdown or optic neuropathy in 3 to 5% of such patients. Hyperthyroidism and ophthalmopathy typically occur within 1 year of each other but can be separated by decades. In 10% of persons with ophthalmopathy, either thyroid levels remain normal or autoimmune hypothyroidism develops.

**Thyroid-associated ophthalmopathy:** Orbital involvement represents a parallel consequence of the underlying autoimmunity occurring within the thyroid. The active phase lasts up to 3 years and includes evolving symptoms and signs of inflammation and congestion. In a cohort of consecutively assessed patients with Graves’ disease, the prevalence of distinct abnormalities was as follows: eyelid retraction, 92%; exophthalmos, 62%; extraocular muscle dysfunction, 43%; ocular pain, 30%; increased lacrimation, 23%; and optic neuropathy, 6%.

The activity of ophthalmopathy can be graded by assigning 1 point for each of the following manifestations: eyelid erythema and edema, conjunctiva injection, caruncular swelling, chemosis, retrobulbar pain, and pain with eye movement. A score of 3 or higher indicates active disease. Pathogenesis of thyroid-associated ophthalmopathy: The immune pathogenesis of ophthalmopathy and that of hyperthyroidism are presumed to be similar. The orbital process primarily targets fibroblasts. During active disease, orbital tissues are variably infiltrated with lymphocytes. Interactions between T cell lymphocytes and fibroblasts result in tissue activation and induction of genes involved in inflammation and tissue remodeling. These events are mediated by several cytokines, including IL-1 beta, IL-6 and CD40 ligand. Orbital fat and extraocular muscles expand from accumulating hyaluronidase-digestible material and adipogenesis. Extraocular muscles remain intact, but fibers become widely separated. In later stages, extraocular muscles become fibrotic, resulting in restricted motility. It remains uncertain what provokes lymphocyte infiltration, but a shared antigen in the orbit and thyroid gland, such as the thyrotropin receptor, seems likely. This view is supported by the relatively low level of expression in orbital fat and orbital fibroblasts. Fibroblasts inhabiting the orbit in Graves’ disease are heterogeneous, and when activated by cytokines, can produce hyaluronan and several inflammatory mediators. The unique presence of fibrocytes in the orbit in ophthalmopathy suggests they play a part in disease development. When activated by thyrotropin or thyroid stimulating immunoglobulins, fibrocytes release cytokines that have been implicated in Graves’ disease. Fibrocytes can differentiate into adipocytes or myofibroblasts and thus might contribute to the tissue remodeling in ophthalmopathy. Medical treatment of thyroid-associated ophthalmopathy: Most assessments of therapy for Graves' hyperthyroidism suggest that radioactive iodine ablation increases the
risk of new or worsening ophthalmopathy. Glucocorticoids mitigate this risk. In contrast, most studies have failed to detect differences in the effect on ophthalmopathy between surgical thyroidectomy and medical therapy. Agents blocking the thyrotropin and insulin-like growth factor receptors are under consideration. For example, a randomized, placebo-controlled clinical trial of the efficacy and safety of teprotumumab, an insulin-like growth factor 1 receptor–blocking monoclonal antibody, in patients with active, severe ophthalmopathy has recently been completed. Laboratory evaluation: In patients with suspected Graves’ disease, the article recommends that the first two ordered studies are TSH (thyrotropin) and free T4 (free thyroxine). A table shows the follow up laboratory tests and diagnostic entities that are considered depending on the results of these two initial laboratory studies.

Orbital/Periorbital Plexiform Neurofibromas in Children with Neurofibromatosis Type 1 Multidisciplinary Recommendations for Care

This consensus statement provides recommendations for ophthalmologic monitoring, outlines treatment indications and forthcoming biologic therapy. Comprehensive ophthalmic evaluation is recommended every 6 months until visual maturity. After that, frequency of examination should be guided by the clinical course. Patients with OPPN confined to the upper eyelid may not need to undergo neuroimaging. For patients with orbital, periorbital, or facial involvement, high-resolution magnetic resonance imaging (MRI) with and without contrast of the orbit, face, and cavernous sinus should be performed. Treatment for related ophthalmic issues, such as ptosis, lacrimal involvement, or amblyopia, is supportive. Early intervention is recommended with the exception of strabismus surgery. Strabismus caused by orbital or periorbital tumor involvement while the tumor is in its rapid growth phase carries a high risk for recurrence after strabismus surgery. Associated problems such as amblyopia and refractive error should be managed aggressively and surgery deferred until the tumor growth has stabilized, if clinically appropriate. Debulting surgery may be indicated for the following: visual decline, progressive tumor growth involving a vital structure, progressive disfigurement or functional decline. Debulting is more successful in older patients and adults. Younger patients have a high risk of recurrent progression and need for more surgery. Clinical trials using biologic agents (i.e., MEK inhibitors) are underway, but no definitive recommendations can be made at this time. Comment: This paper provides a concise description of current evaluation and management priorities. Unless vision threatening, surgical interventions for neurofibroma are typically deferred until after tumor growth has ceased.

The ophthalmic sequelae of Pfeiffer syndrome and the long-term visual outcomes after craniofacial surgery.
Pfeiffer syndrome is a rare, genetic condition characterized by craniosynostosis and midface hypoplasia, with resultant ophthalmic sequelae. The gold standard of treatment is fronto-orbital advancement. The medical records of Pfeiffer syndrome patients examined between 1988 and 2010 were examined retrospectively. Diagnosis was based on clinical and genetic testing. Long-term data were presented as a rate of incidence per person-year to overcome variable follow-up times. A total of 22 patients were included. Proptosis (n = 21 [95%]), refractive error (n = 13 [59%]), and strabismus (n = 12 [55%]) were the most common primary features at presentation. Exposure keratitis (n = 9 [41%]) and amblyopia (n = 3 [14%]) were the most common secondary features. At presentation, 24 eyes [86%] with documented best-corrected visual acuity were normal; 4 [14%] were impaired; and none were blind. Fronto-orbital advancement reduced the rate of proptosis from 28%/person-year at presentation to 2%/person-year. There were no cases of active exposure disease postoperatively. At last follow-up, there was a 7%/person-year rate of impaired vision secondary to corneal scarring and amblyopia and a 3%/person-year rate of blindness-all from optic atrophy.

In this study, the rates of proptosis and exposure keratitis were high in Pfeiffer syndrome, especially compared to Apert and Crouzon syndromes. Fronto-orbital advancement was successful in correcting orbital abnormalities. The authors conclude that long-term ophthalmic follow-up is essential to ensure best visual outcome.

Risk of optic pathway glioma in children with neurofibromatosis type 1 and optic nerve tortuosity or nerve sheath thickening


Optic nerve tortuosity and nerve and sheath thickening are observed on MRI in some patients with neurofibromatosis type 1 (NF-1). This study aimed to determine if tortuosity and thickening are associated with the development of optic pathway glioma (OPG) and subsequent vision loss. Children with NF-1 who underwent brain MRI between 1992 and 2005, and had at least 1 year of subsequent visual acuity (VA) follow-up, were identified retrospectively. The baseline MRI was blinded and independently reviewed by three neuroradiologists for consensus assessment using validated criteria. Tortuosity was identified using validated operational criteria. Optic nerve and sheath thicknesses and VA at last follow-up were directly measured. Of 132 evaluable children, seven (5%) had tortuosity on baseline MRI. Twenty subjects (15%) ultimately developed OPG at a median of 1.9 years (range 7 months–8.0 years) following the baseline MRI. Subjects with tortuosity were significantly more likely to develop OPG than those without tortuosity (57% vs 13%, p=0.01). In subjects who developed OPG, the prevalence of tumor-related vision loss was not significantly different between
those with and without baseline tortuosity (14% vs 4%, p=0.28). No difference existed between mean baseline optic nerve (2.3 vs 2.2 mm) or sheath (5.2 vs 5.4 mm) thicknesses comparing subjects who did and did not develop OPG. Optic nerve tortuosity at baseline is associated with OPG development among patients with NF-1, but does not predispose to aggressive OPG with associated vision loss. Neither nerve nor sheath thickening at baseline was associated with OPG development. The study time period of 1992 to 2005 was chosen to allow for 10 years of follow-up data that is deemed to be the critical period vision deterioration due to OPG. The authors point out that at the time the study was designed, any nerve with enhancement or enlargement was considered to be an OPG. However, there is ongoing debate in the NF-1 field regarding the minimal thickness criteria for an OPG and the clinical significance of nerve enhancement.

Clinical management of orbital rhabdomyosarcoma in a referral center in Spain.
Luciano Bravo-Ljubetic, MD; Jesús Peralta-Calvo, MD, PhD; Paula Larrañaga-Fragoso, MD; Nuria Olivier Pascual et al *Journal of pediatric ophthalmology and strabismus*. March/April;53(2):119-126

This article reviews the systemic and ocular outcomes of ocular rhabdomyosarcoma between 1982 and 2011 in a tertiary center at La Paz University Hospital, Madrid, Spain. The clinical presentation, management, complications, ocular and systemic outcomes were reviewed. The mean age at presentation was 8 years (range: 3 months to 12.5 years). In all cases, the rhabdomyosarcoma was located primarily in the orbit. Treatment included surgical debulking and various regimens of chemotherapy and radiotherapy. All of the patients underwent surgical biopsy for diagnosis confirmation. Orbital exenteration was performed in 4 cases (28%). Twelve patients received radiotherapy. The long-term visual outcomes of the 10 patients who maintained their globe was as follows: best corrected visual acuity 20/20 to 20/40 in 6 patients (60%), 20/50 to 20/100 in 2 patients (20%), and 20/200 to no light perception in 2 patients (20%). Intraocular complications (primarily cataracts: 50%) were present in 7 patients (70%), ocular surface lesions occurred in 6 patients (60%), and orbital sequelae were found in 8 patients (80%). Local tumor recurrence was detected in 5 patients (35%) and distant metastasis occurred in 2 patients (14%). Tumor-related death occurred in 1 patient (7%). The authors conclude that although orbital rhabdomyosarcoma has an excellent prognosis local complications and more specifically surgery related are common and that initial surgical planning based on individual patient characteristics and an accurate diagnosis of relapses is mandatory.

Incision and Curettage Versus Steroid Injection for the Treatment of Chalazia: A Meta-Analysis
The purpose of this study was to compare the efficacy of chalazia treatments, incision and curettage (I&C) and intralesional steroid injection (SI). While not a study of the pediatric population, chalazia is the most common eyelid lesion seen in the pediatric population and thus this article is included. Data was extracted from 8 different publications. There were 288 patients treated with SI (intrale- sional) with a success rate of 60% with 1 injection and 72.5% with 2 injections. 264 patients were treated with I&C. The success rate was 78% with one procedure and 91% with 2 procedures. Overall the analysis showed that I&C is more effective than SI with one procedure although that benefit is reduced when comparing a second procedure. There was no significant difference in time to resolution between the two groups. In both modalities, no serious complications occurred. Mild complications of SI included yellow/white deposits or depigmentation at the injection site, atrophy of the orbital or subcutaneous fat and increased IOP. I&C was related with more pain and inconvenience than SI.

**Dermis-Fat Graft in Children as Primary and Secondary Orbital Implant**


The use of dermis fat graft has been shown to be useful in children both as a primary and secondary implant. The aim of this case series was to assess the indications and evaluate the outcome of this procedure in the pediatric population. An analysis of 22 clinical charts was performed. They found as a primary procedure the dermis fat graft was useful in children with severe scleromalacia or following ocular trauma. It is also an option for children with congenital anophthalmia after socket expansion to help with continued expansion. Dermis-fat graft can also be used as a secondary implant following explantation of exposed implants as well as in contracted sockets.

**Pediatric Idiopathic Orbital Inflammation: Clinical Features of 30 Cases**


While Idiopathic Orbital Inflammation (IOI) is well described in adults, it has a low incidence in children and therefore little is known about the spectrum of the disease in the pediatric population. The authors performed a retrospective chart review of 30 patients diagnosed with IOI. In this study 13% of cases were bilateral. Previous studies have reported 1/3 of pediatric IOI cases present bilaterally. Post-treatment recurrence was found in 37% of cases. Recurrence was more likely to be associated with bilateral disease and had a female preponderance. The most common ophthalmic findings were periorbital edema and blepharoptosis. All patients had orbital radiography with common findings of dacryoadenitis, orbital mass, or myositis. Having an orbital mass on radiography was significantly related to the clinical presence of blepharoptosis. The most common treat-
ment was steroid therapy, but a few patients were treated with steroid sparing therapy including IVIG and Rituximab with good results.

Predicting complications with pretreatment testing in infantile haemangioma treated with oral propranolol


Since 2008, orally administered propranolol has rapidly gained acceptance as the preferred therapy for hemangiomas, and is usually initiated by ophthalmologists, dermatologists, or plastic surgeons who do not routinely use propranolol for any other indication. During the initial years when experience was limited, most healthcare professionals justifiably adopted a cautious approach when initiating and monitoring treatment. A consensus recommendation from the American Society of Dermatologists suggests routine observation, monitoring and cardiology assessments prior to propranolol initiation. This study analyzed treatment initiation in a large tertiary children's hospital in the UK and investigated the value of pretreatment testing in predicting commonly seen adverse reactions of propranolol. This is a retrospective chart review of 104 eligible patients treated between January 2009 and July 2012. The study cohort was typical for IH, with the majority of patients under 1 year of age at commencement of treatment. All patients underwent pretesting either with protocol A (administration of test dose with admission for 1 day observation) or protocol B (cardiology clinic assessment, including two-dimensional echocardiography without test dose). The authors found that over one-third (38.5%) of patients developed adverse reactions during treatment; however, there were no severe or life-threatening reactions. The most commonly encountered adverse reactions were breathing-related problems, cold extremities, gastrointestinal upset and sleep disturbance, in approximately 10% of patients in each protocol. There were no serious adverse reactions, and alteration of dose was successful in resolving the adverse reactions in the majority of cases. Protocol A has a sensitivity of 0 (95% CI 0 to 0.17) and specificity of 0.95 (95% CI 0.83 to 0.99). Protocol B has a sensitivity of 0.07 (95% CI 0 to 0.34) and specificity of 0.86 (95% CI 0.63 to 0.96). The study concludes that neither protocol was effective in identifying children who may develop adverse reactions.

Rebound Growth of Infantile Hemangioma After Propranolol Therapy


Propranolol has become the first line therapy for treatment of infantile hemangiomas. Rebound growth occurs after discontinuation between in 19-25% of patients. This large, multi-center, retrospective cohort study aimed to identify the rate of rebound growth and predictive factors for rebound growth. The study enrolled 997 patients and found an incidence 25% rebound growth. Treatment was
determined to be effective in 81% of patients after 12 months. The mean age of rebound growth was 17.1 months of age which is different from the natural progression of typical infantile hemangiomas. Significant risk factors for rebound growth include female gender, a deep component of the infantile hemangioma, and discontinuation of propranolol prior to 9 months of age. Limitations of the study include a possible referral bias because the patient population derives from tertiary care centers and patients that require systemic therapy. The findings of this study may help guide treatment decisions and counseling for the specific needs of each individual patient.

Lacrimal abscess mimicking a choroidal mass: an ultrawide field evaluation.

In this case report the authors describe a 13 year old boy with presumed acute suppurative bacterial dacryoadenitis (ASBD) masquerading as a choroidal mass. He presented with S-shaped eyelid swelling, but with no fever. Ultrasonography showed an oval lesion in the choroid. Posterior to the lesion, there was an echolucent zone suggestive of fluid in the subtenon space. Fundus imaging using the ultrawide field imaging (UWFI) by Optos™ (Optos Inc, Marlborough, Mass.) had helped the authors rule out a true choroidal mass. Patient improved after intravenous antibiotics.

Visual acuity and astigmatism in periocular infantile hemangiomas treated with oral beta-blocker versus intralesional corticosteroid injection

This study compared the efficacy and time course for treatment of astigmatic anisometropia in 17 patients with periocular infantile hemangiomas treated with systemic propranolol versus intralesional corticosteroid injection. Treatment choice was consecutive. This was a 4+ year retrospective chart review of propranolol use with a comparison to corticosteroid use in the preceding years. Propranolol treatment showed monphasic regression of the tumor in a steady fashion. For comparison, the corticosteroid treated group showed a biphasic regression. There was an early rapid regression followed by a delayed slower regression. Initial and final astigmatism for the corticosteroid group was twice that of the propranolol group. A large number of patients were excluded from this study due to incomplete data.

Inheritance Patterns of Infantile Hemangioma
Infantile hemangiomas (IH) are the most common tumor of infancy occurring in 4-10% of children. The known risk factors include female subjects, white subjects, twins, pre-term infants, children of parents with advanced maternal age, placental anomalies, and low birth weight. This study aims to determine an inheritance pattern of infantile hemangiomas. A retrospective study identified patients through ICD-10 coding at a pediatric vascular clinic in Finland. 185 patients were identified who had true IH’s and sent surveys to determine whether other family members had IH’s. Of the 136 respondents, 34% were found to have a positive IH family history and 66% with negative family history. The family pedigrees of those with a positive family history were found to have an autosomal dominant with incomplete penetrance or maternal transmission. 11 of the 40 families with IH reported greater than 4 affected family members. Additional information is needed to understand the inheritance of this common tumor.

Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review

With the recent and widespread usage of propranolol for infantile hemangiomas, it is important to understand the safety profile of this medication. This study performed an in depth literature search revealing 83 studies that matched inclusion criteria which included a total of 5862 propranolol treated patients. These studies included clinical trials for the medication, compassionate use programs, and medical literature. The most common propranolol-related events included sleep disorders, diarrhea, peripheral coldness, and agitation. Most are not serious, transient, and manageable with appropriate education provided to caregivers. The article identifies pre-treatment screening for cardiovascular and pulmonary problems, risks for heart block, arrhythmia, reactive airways, or pulmonary abnormalities. These adverse events occurred very rarely in these studies. Routine echocardiography and EKG’s are not considered necessary prior to starting therapy but it is recommended to monitor blood pressure and heart rate after the first dose for at least 2 hours. The studies did not suggest monitoring glucose at the time of treatment but to give medication during or right after feeding and to stop the medication during times of fasting or vomiting. With these precautions, patients can prevent hypoglycemia and seizures related to low blood sugar. Oral propranolol appears to be well-tolerated and safe medication if medical providers appropriately screen patients for the potential serious adverse events and perform within-treatment monitoring.

Topical Timolol Maleate Treatment of Infantile Hemangiomas
There is limited information that exists about the usage of off-label use of ophthalmic timolol maleate for infantile hemangiomas. This study is a retrospective, multi-center trial observing the treatment effects and adverse events associated with topical usage of the medical. There were 731 subjects and the treatment effects were determined by comparison between digital photographs at time of initiation and at each follow up visit. Most patients used one drop of timolol maleate 0.5% twice daily. The most common indication for treatment was risk of disfigurement. A majority of patients had an improvement in the size and color with the most effect after 6-9 months of therapy. The infantile hemangiomas that showed the most improvement were < 1mm thick, superficial, and therapy for 9 months or longer. 7.3% required subsequent systemic beta-blocker. Adverse events occurred in 3.4% and mostly were local irritation (e.g. scaling). There were no cardiovascular adverse events but three patients experienced bronchospasm. No patients discontinued therapy due to an adverse event. With these study results, it is safe for physicians to initiate topical timolol therapy in patients with thin and superficial infantile hemangiomas that do not risk functional impairment.

21. **OCULOPLASTICS**

**Embryologic and Fetal Development of the Human Eyelid**
Tawfik HA, Abdulhafez MH, Fouad YA, Dutton JJ

This article is a review of all major studies detailing human embryologic and fetal eyelid morphogenesis. Ocular and eyelid development occurs in a step-wise fashion and any misstep will be followed by failure of subsequent steps. Morphogenesis of the eyelids involves formation, fusion, development, separation and maturation of the eyelid structures. Tissue folding, proliferation, contraction and even migration occur either simultaneously or in succession. It has been suggested that the process of adult wound healing involves a synchronized series of tissue remodeling and movements that are remarkably similar to the embryonic process of eyelid fusion. Understanding lid development may help to understand and assist in wound remodeling.

**Success Rates of Conventional Versus Endoscope-Assisted Probing for Congenital Duct Obstruction in Children 12 years and Youngers.**
Alicia Galindo-Ferreiro, Patricia Akaishi, Augisto Cruz, Rajiv Khandekar et al.
In this retrospective, nonrandomized case series, the success rates for congenital nasolacrimal duct obstruction (CNLDO) treated with conventional probing versus endoscope-assisted probing were compared. A total of 200 eyes were included in the study (n=198 conventional probing group, n=72 endoscope-assisted group). The success of the procedure was evaluated with a subjective method (observations of the parents on tearing) and objective method (fluorescein dye disappearance test after 5 min). The subjective and objective success rates were 76.1% and 75.9% respectively in the conventional probing group and 95.7% and 95.7% in the endoscope-assisted probing group (p<.005). The success rate decreased in older children in the conventional probing group but remained the same in the endoscope-assisted probing group. The authors suggest that endoscope assisted probing provides significantly higher success rates mainly in older children and in bilateral cases. The use of stents does not improve the success rates of either procedure. The study is limited by the fact that is retrospective, non-randomized. Although the use of an endoscope significantly increase the cost of the procedure and requires a learning curve from the physician's perspective, the high success rates might justify the use of endoscope-assisted probing.

**Congenital Nasolacrimal Duct Obstruction: comparison of two different treatment algorithms.**


In this retrospective chart review, a total of 177 patients (n=246 eyes), aged 0 to 9.8 year of age were included in the study. After an initial probing, 79% of children aged 1 to 2 years had a successful outcome with an overall success rate of 76% for primary probing across all ages. In the rest of the cases, the patients had persistent symptoms despite the primary probing, and the patients received either a simple probing or silicone intubation as a secondary procedure. In this study, patients treated with intubation were significantly more likely to have a successful outcome (66.7% vs 91.7%, P=.037). In addition, the authors didn’t find a decline in probing success rates with age although it is well documented in the literature. They believe that their study included a larger number of older patients compared to the other ones and therefore their results might be more reliable. The study is limited by the small numbers in the comparative analysis of secondary interventions since primary probing is a highly successful procedure, its retrospective nature and the large number of surgeons participating.

**Outcomes of two surgical techniques using silicone rod for frontalis suspension to treat severe ptosis.**

In this retrospective, nonrandomized chart review, two different surgical techniques using silicone rod to treat severe ptosis were compared. In the open method, silicone rods were sutured to the tarsal plate through an eyelid crease incision, whereas in the closed method through stab incisions. Success was defined as a postoperative margin reflex distance (MRD) score of 2 to 4 or an improvement in the MRD. One hundred and fifty five eyelids were included in the study and success outcomes were nearly 50% with both surgical procedures even at 1.5 years postoperatively, indicating the stability of the outcomes with both procedures. Undercorrections were more frequent with the open method, granulomas were more frequent in the closed method, and eyelash ptosis and eyelid crease abnormalities occurred only in the closed method technique. Although this study is limited by its retrospective design and the number of surgeons, it is the largest data sample comparing the two methods, the demographic data are similar and the follow-up is lengthy allowing observation of outcomes, complications and stability of two procedures.

**Conservative management of Lower eyelid Epiblepharon in children.**
John W. Simon, Kathryn H. Williams, Jitka L. Zobal-Ratner, Gerard P. Barry
*Journal of Pediatric ophthalmology & strabismus.* January/February 2017; 54(1): 15-16

This study evaluates the need for surgical intervention in children with epiblepharon. It is a retrospective chart review of a total of 89 patients 69% of which had symptoms of tearing, discharge and eye rubbing. Many presented without symptoms and were first noted to have the eyelid deformity on ophthalmologic exam. Examination disclosed trichiasis in 17% of the cases, especially on down gaze and only 7% of the patients actually had corneal staining at presentation. Patients who presented with trichiasis, had corneal staining or symptoms of irritation were treated initially with antibiotic ointment or artificial tears. The rest of the patients were simply observed. Three children (3%) were referred for eyelid surgery because of persistent symptoms. No patient had corneal scarring or long-term complications. The authors conclude that although vision-threatening complications can result, a trial of topical antibiotic ointment and/or ocular lubricants was effective in nearly all patients. The study is limited from the fact that it is retrospective, not all children underwent slit lamp examination after fluorescein instillation and that the follow-up was limited.

**Association Between Head Tilt and Asymmetric Epiblepharon**

Study design is a retrospective review of patients with epiblepharon and anomalous head posture, specifically head tilt. Methods included review of photographs and eye examination to exclude superior oblique palsy (SOP) and dissociated vertical deviation (DVD). Congenital muscular torticollis was excluded by a pedi-
atric orthopedic surgeon. The authors defined asymmetric epiblepharon as a difference of the extent of epiblepharon between the 2 eyelids of more than one-fourth of the eyelid length. 1074 Korean children with epiblepharon were studied. The group was comprised of fairly equal numbers of boys and girls. 38 (3.5%) had a head tilt. The most common cause of head tilt was SOP in 18 patients (47.4%), followed by congenital muscular torticollis in 10 (26.3%) and DVD in 3 (7.9%). The remainder, 8 children, had head tilt of unknown cause. Of the 38 patients with head tilt, 23 individuals (60.5%) underwent subsequent surgical correction of epiblepharon. Predictably, head tilt persisted after epiblepharon was operated. Results revealed that the proportion of asymmetric epiblepharon in the patients with head tilt was significantly higher than that in those without head tilt (P < .001, Fisher exact test) Of the 34 patients with head tilt and asymmetric epiblepharon, 29 children (85.3%) showed more severe epiblepharon in the head-tilted side (13 [44.8%] on the right side, 16 [55.2%] on the left side). The direction of the tilt was consistent with the side having more severe epiblepharon (P = .009, Fisher exact test).

Importance: This is a unique study in that never before has a causal relationship been postulated between epiblepharon and head tilt. A major criticism of this study is their methodology. The authors examined photographs but they did not quantify head tilt with a readily available instrument, such as a goniometer. The authors did not exclude other non-ocular causes of head tilt such as unilateral hearing loss. They created their own definition of asymmetrical epiblepharon, which was not validated. They had a poorly supported conclusion that known causes of head tilt such as SOP, DVD and muscular were causative of asymmetrical epiblepharon, but did not address the mechanism of head tilt of unknown cause and asymmetrical epiblepharon. All children who present with a head tilt are thoroughly examined for ocular causes regardless of whether there is epiblepharon, whether symmetrical or asymmetrical. The finding of asymmetrical epiblepharon appears to be an epiphenomenon of head tilt.

Ocular Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children.

Stevens Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) are potentially fatal, but rare mucocutaneous diseases that are potentially fatal and have the potential to cause significant ocular morbidity. This study is a retrospective case series of 36 children diagnosed with either SJS, TEN or an overlap syndrome with the goal of describing the ocular manifestation of this spectrum of disease in the pediatric patient. The ultimate visual acuity was 20/40 or better in all but 3 patients. 81% of patients had ocular involvement with the most common sign being conjunctivitis. Other eye disease was lid margin ulceration, conjunctival ulceration, epithelial defects, symblepharon, corneal opacification, limbal stem cell failure, and corneal vascularization. The authors emphasize that many
of these eye problems can manifest many months after the acute phase of the disease and thus long term follow up is imperative.

Clinical outcomes of frontalis sling using silicone rod with two-point brow incisions in blepharoptosis.
Youngje Sung, Jong Seo Park, Helen Lew JPOS. July/August 2016; 53(4): 224-232
This article evaluates the surgical outcomes (functional and cosmetic) of the modified frontalis sling operation using the silicone rod with two-point brow incisions. In this retrospective chart review of seventeen patients (age ranged from 11 months to 66 years) who underwent frontalis suspension surgery, functional outcomes were measured using the marginal reflex distance and cosmetic outcomes were investigated with contour analysis and a Patient Scar Assessment Questionnaire. At the final visit, good and fair eyelid heights were achieved in 75% of patients in the unilateral group and 61.1% in the bilateral group. The average increase in margin reflex distance 1 was 1.9 mm in the unilateral group and 1.8 mm in the bilateral group. Satisfaction scores were 14.6, 8.2, and 11.8 for appearance, symptoms, and consciousness, respectively. In contour analysis, the normal arch generally increased. The authors concluded that the two-point brow incision has the same functional and cosmetic outcomes with the three-point brow incision technique. The main limitation of this study though is that (a) it included adult and pediatric patients with ptosis and (b) the procedure was performed by only one surgeon and (c) the patient were not randomized to receive the 3 point-brow incision and the modified 2 point-brow incision procedure.

Safety and long-term outcomes of congenital ptosis surgery: a population based study.
Ali Mokhtarzadeh, Elizabeth A. Bradley JPOS. July/August 2016; 53(4): 212-217
The purpose of this study was to report the long-term outcomes of childhood ptosis surgery in a population-based setting (Olmsted County, Minnesota). The medical records of all patients who were residents of Olmsted County, Minnesota, between January 1, 1965, and December 31, 2010, were retrospectively reviewed. Age at time of surgery, type of surgery, duration of follow-up, reoperation rates, amblyopia, postoperative lagophthalmos and dry eye were documented. Forty-seven children meeting inclusion criteria underwent ptosis surgery. The median age at time of first surgery was 5.6 years (range: 1.5 to 17.7 years). Fifteen of 47 (31.9%) patients required a second procedure. Three of 47 (6.4%) patients underwent three procedures. The median time was 1.1 years (range: 0.03 to 7.8 years) between the first and second surgery and 6.0 years (range: 0.3 to 6.1 years) between the second and third procedure. Seven of 47 (14.9%) patients had amblyopia. Nineteen of 47 (40.4%) patients were noted to have lagophthalmos and 3 of 47 (6.4%) presented for symptomatic dry eye postoperatively. In this study the authors conclude that most of the children required only one surgical procedure to correct the ptosis and one third of the patients required
reoperation. Postoperative lagophthalmos is common, but symptomatic dry eye is rare. The study is limited by the fact that it is a population based study and not a cohort study. Moreover, post-operative results were not defined by eyelid height parameters or marginal reflex distance.

Comparative Clinical Outcomes of pediatric patients presenting with eyelid nodules of idiopathic facial aseptic granuloma, hordeola, and chalazia.
Pinar Altiaylik Ozer, Asuman Gurkan, Bengi Ece Kurtul, Emrah Utku Kabatas et al JPOS July/August 2016; 53(4): 206-211

Idiopathic facial aseptic granuloma (IFAG) is a newly described pediatric dermatologic disorder. The etiology is yet to be determined with some hypotheses involving the role of mild trauma and insect bites and other proposing that IFAG might represent the granulomatous form of rosacea. This article describes the clinical features of the eyelid nodules described in idiopathic facial aseptic granuloma (IFAG), and compares them with the clinical features of eyelid lesions in children with acute hordeola and chalazia. Duration of the lesion, localization, presence of coexisting facial nodules, management strategies, and response time to topical/oral antibiotics were retrospectively reviewed in 50 children with IFAG(n=14), acute hordeolum (n=28), or chalazion (n=8). Children with IFAG on their eyelids and face presented earlier than children with acute hordeolum (P = .006). The duration of this lesion was similar among patients with IFAG on their eyelids and acute hordeolum (P = .53). Duration of the lesion and treatment response time were shorter in children with IFAG on their eyelids and face (P = .004) than in those with IFAG on their eyelids (P = .013). The lesions of patients with chalazion had a longer duration compared to those with IFAG on their eyelids (P = .005), IFAG on their eyelids and face (P < .001), and acute hordeolum (P = .04). Twenty patients with acute hordeolum recovered after topical antibiotics and had a similar treatment response time to those with IFAG on their eyelids and face (P = .06) and those with IFAG on their eyelids (P = .16). The authors concluded that IFAG should be considered in the differential diagnosis of painless eyelid nodules in children. IFAG is more easily diagnosed when there are accompanying granulomas of the face and it responds well to oral clarithromycin so unnecessary surgical procedures should be avoided. The main flaw of this study is that there is no histopathologic confirmation of the eyelid lesions( IFAG lesions versus hordeola or chalazia) and that the diagnosis was based on the presence of “typical” clinical features only.

Comparison of anisometropia and refractive status in children with unilateral and bilateral congenital nasolacrimal duct obstruction.
This descriptive cross-sectional study evaluates and compares the refractive state in children with nasolacrimal duct obstruction (unilateral or bilateral). It also compares how the laterality of congenital nasolacrimal duct obstruction affects the refractive state of the eye. One hundred sixty-one (n=161) patients with unilateral CNLDO and forty-six (n=46) with bilateral CNLDO were included and they were followed for up to one year. Cycloplegic refractions were performed in all patients. The rate of the anisometropia (≥ 1 dipters [D] difference between the two eyes) was 13.7% (n = 22) and 8.6% (n = 4) in patients with unilateral and bilateral CNLDO, respectively. The authors concluded that unilateral CNLDO is associated with statistically significant anisometropia compared to bilateral CNLDO which predisposes children to amblyopia. This is an important study that alerts the pediatric ophthalmologist for the importance of periodic eye exams and refractions in patients with congenital nasolacrimal duct obstruction in order to timely detect anisometropia and prevent the development of amblyopia.

**Bacteremia Following Nasolacrimal Duct Probing: Is There a Role of Preoperative Anibiotic Prophylaxis?**


Bacteremia following surgical procedures is a well-documented entity. Surgeries on the mucosal surfaces have received special interest due to the dense endogenous microbial flora and the potential to cause sepsis and infective endocarditis. Nasolacrimal duct probing involves mucosal surfaces. This study aimed to evaluate the incidence of nasolacrimal duct probing-induced bacteremia due to the implication of bacteremia in the pediatric population. Blood was drawn under strict aseptic conditions both pre and post endoscopic-guided probing by a single surgeon (MJA). Cultures were performed using the BacT/ALERT microbial detection system. Thirty one eyes of 25 patients were studied. One patient had a unilateral dacryocele with acute dacryocystitis. All pre and post-probe cultures were negative except the one with acute dacryocystitis. In this patient the bacteremia was caused by *Haemophilus influenzae*. The authors concluded that nasolacrimal duct probing does not induce bacteremia in routine cases and pre-operative antibiotic prophylaxis is perhaps not needed. However, in acute dacryocystitis, further evidence is needed to formulate guidelines on additional pre-operative antibiotic prophylaxis other than the routine treatment of infection.
Nonhealing traumatic wound over frontalis silicone sling.

Silicone is a commonly used material for the frontalis sling procedure in cases of ptosis with poor levator function. It is particularly advantageous in young children who have underdeveloped tensor fascia lata. Extrusion of the silicone through surgical wounds is an infrequent but recognized complication. This is a case report of an infant with silicone sling exposure through a post-traumatic wound that evolved into a non-healing ulcer.

Effects of epiblepharon surgery on higher-order aberrations

Higher order aberrations (HOAs) can effect visual quality by causing glare, halos and distortion. This study compares HOAs in children with epiblepharon after surgery. This was a 2-year retrospective chart review. Subjects were classified based on the degree of corneal erosion and cilia touching the cornea. Ocular aberrations were measured with the KR-1W Wavefront Analyzer. A total of 120 eyes of 60 patients were included with a median age at the time of surgery of 7.3 years. Pre- and postoperative best-corrected visual acuity and refractive errors were not statistically different. Corneal total HOAs decreased to a statistically significant degree at both 1- and 3-month postoperative periods. A statistically significant correlation between the degree of cilia touching the cornea or severity corneal erosions and HOAs did not exist. However, HOA decrease did correlate with a reduction in the severity of keratopathy (corneal staining grade) in the 6mm zone from preoperatively to 3-months postoperatively. The authors feel HOAs decreased because eyelid tension lessened postoperatively and the persistent mechanical trauma induced by cilia also declined.

Epiblepharon in Chinese children: relationships with body mass index and surgical treatment

This study evaluated the clinical characteristics of lower lid epiblepharon cases needing surgical repair in a cohort of Chinese children. This was a 3-year retrospective review. There were a total of 67 patients (130 eyes) and 178 age-matched controls. At presentation, 92.5% were symptomatic, ranging from foreign body sensation (n=29), tearing (n=25), photophobia (n=11), and conjunctival hyperemia (n=10). Superficial keratopathy was found in 63%. Ten patients had at least one prior surgical correction. No relationship was found between epiblepharon and age or sex. A significant correlation was found between the incidence of epiblepharon and BMI in 4- to 6-year old boys. No correlation was found in other groups. For the 10 patients with prior surgery, the rotating suture procedure was performed in 7 and the L-plasty procedure was performed in the remainder.
For the other 57 patients, 55 received the former surgery and 2 received the latter. Mean follow-up was 12.6 weeks and all patients experienced improved symptoms. Some parents and patients were unhappy with initial scarring, but this resolved during follow-up. The authors recommend waiting until age 2 years to consider surgery unless the patient has intolerable irritative symptoms since many infants with this condition resolve spontaneously. This study was retrospective, and there was a short duration of follow-up.

22. INFECTIONS

Use of Retinal Optical Coherence Tomography to Detect Congenital Zika Syndrome

In this invited commentary, the authors note that the effects of ZKV on the retina and choroid are not symmetric. They commend the authors for using OCT to define the microstructural areas of the retina involved in ZKV infection, in the hope of better understanding the pathophysiology of this neurotropic virus. However, they caution against using OCT as part of the standard of care in diagnosing CZS, since the OCT findings are not specific to ZKV infection.

Optical Coherence Tomography of Retinal Lesions in Infants With Congenital Zika Syndrome

Zika virus (ZIKV), a neurotropic flavivirus, transmitted to humans mainly via mosquito bites, has rapidly spread across the globe. In utero ZIKV exposure may result in an infant born with congenital ZIKV syndrome (CZS), characterized by microcephaly, ocular involvement, hearing loss and limb anomalies. The authors look at the effect of the virus on the retina and choroid and describe their experience in evaluating these lesions using optical coherence tomography (OCT). This is a cross sectional consecutive case series of 8 infants (3-5 months of age) born with CZS. ZIKV was confirmed by enzyme linked immunofluorescence analysis (ELISA) to detect IgM in the cerebrospinal fluid of 7/8 infants. Eleven of the 16 eyes had retinal lesions seen on indirect ophthalmoscopy and 9 of these eyes were imaged with OCT. The main OCT findings in the affected eyes included discontinuation of the ellipsoid zone and hyperreflectivity underlying the retinal pigment epithelium in 9 eyes (100%), retinal thinning in 8 eyes (89%), choroidal thinning in 7 eyes (78%), and colobomatous-like excavation involving the neurosensory retina, retinal pigment epithelium, and choroid in 4 eyes (44%).

Conclusion: The ocular findings in CZS include destructive effects on the retina and choroid. This is confirmed on OCT, which more so than a fundus photograph, elucidates the specific layers of the retina affected. This appearance is
seen in other conditions such as toxoplasmosis and cytomegalovirus, so the au-
thors caution using this OCT data to confirm ZKV infection. One limitation of the
study is the lack of point-to-point correspondence between the fundus photos
and OCT images.

Monitoring and Preventing Congenital Zika Syndrome


In this editorial, the authors advocate for a surveillance system to monitor for the
effects of congenital Zika infection. The devastating fetal and infant outcomes
associated with thalidomide use and rubella infection during pregnancy were key
factors in the establishment of population-based surveillance for birth defects in
the United States and globally to better monitor and address the effect of terato-
gens. This year, the recognition that Zika virus (ZIKV) infection during pregnancy
can cause microcephaly and serious brain abnormalities and growing evidence
of its association with other birth defects has similar potential to transform our
approach to global surveillance for, research on, and prevention of birth defects.
To ensure consistency in both pregnancy registries and ongoing birth defect sur-
veillance, the Centers for Disease Control and Prevention (CDC) has established
surveillance case definitions to monitor birth defects potentially related to ZIKV
infection during pregnancy: brain abnormalities with or without microcephaly,
nearly tube defects and other early brain malformations, eye abnormalities, and
other consequences of central nervous system dysfunction (www

Zika Virus.


Zika virus is a flavivirus, in the same family as Dengue. It was first isolated in
1947 from the blood of a sentinel rhesus macaque in the Zika Forest of Uganda.
In forests, it has a monkey–mosquito–monkey transmission cycle, but humans
can occasionally become infected via a mosquito bite. In 2007-09, the first Zika
epidemic took place in the Yap islands of Micronesia. The virus came to Brazil
around 2015, causing a massive outbreak, and has since spread in the Ameri-
cas. In suburban and urban settings, Zika virus is transmitted in a human–
mosquito–human transmission cycle, mostly involving *Aedes aegypti
mosquitoes. A. aegypti* has a wide geographic range. In the United States, its
range includes the entire South and extends in a northeast direction to Long Is-
land, New York. The primary routes of transmission to humans are via 1) mos-
quito bites, 2) sexual transmission (it is found in sperm), and 3) vertical, from
mother to fetus. Common symptoms of Zika virus infection in adults are pruritic
maculopapular rash (90%), fever (65%), arthritis or arthralgia (65%), nonpurulent
conjunctivitis (55%), myalgia (48%), headache (45%), retro-orbital pain (39%),
edema (19%), and vomiting (10%). A more concerning finding is the association
of Zika virus infection with Guillian Barre Syndrome. Fetal abnormalities detected
by ultrasonography occur in 29% of women with Zika virus infection during pregnancy. Zika-associated ultrasonographic findings include microcephaly, an absent corpus callosum, hydranencephaly, cerebral calcifications, ventricular dilatation, brain atrophy, abnormal gyration, hydrops fetalis, anhydramnios, and intrauterine growth retardation (IUGR). Infection during weeks 7-13 of gestation is highest risk for causing microcephaly. Ocular abnormalities occurred in 10 of 29 patients (35%) of suspected Zika-infected babies born with microcephaly. The most common ocular abnormalities were focal pigment mottling, chorioretinal atrophy, and optic-nerve abnormalities (hypoplasia and severe cupping of the optic disk). Other ocular manifestations were foveal reflex loss, macular neuroretinal atrophy, lens subluxation, and iris coloboma. Whether ocular manifestations occur after congenital Zika virus infection in infants without microcephaly remains unknown.

The diagnosis of Zika virus is primarily by reverse transcriptase PCR from serum during the first week of symptoms, or by a positive IgM titer, which likely remains positive for months. However, Zika IgM titers lack specificity due to cross-reactivity with other flavi-viruses, which are common in the same geographic areas as Zika. There is no way to determine whether a fetus is Zika-infected other than ultrasonography looking for brain malformations and IUGR, and these show up rather late in pregnancy. There is no treatment other than symptomatic treatment, and there is no vaccine. Prevention and control measures center on avoiding mosquito bites, reducing sexual transmission, controlling the mosquito vector, and limiting infection of pregnant women. This is a useful review article re: Zika virus infection. Ophthalmologists should know that Zika virus causes conjunctivitis and retro-orbital pain in adults, and babies exposed to Zika in utero may have chorioretinal and optic nerve abnormalities.

Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil

Zika virus (ZIKV) is quickly becoming a pandemic, with devastating impact on infants born to infected mothers. The epicenter of Zika infection is northeastern Brazil. Zika, an arbovirus, was first detected in a forest of the same name in Kampala, Uganda in 1947 in rhesus monkeys, and a few years later, in humans. Transmission to humans is usually via the Aedes aegypti mosquito. Other modes of transmission in utero include via sexual intercourse and postnatally via breastmilk. Infection of the neonate directly via mosquito bite has also been documented in the perinatal period. The virus has a predilection for the central nervous system, and was suspected when there was a spike in the number of infants born with microcephaly. The authors present a case series of 29 infants born in 2015 in Salvador, Brazil with microcephaly and presumed congenital ZIKV infection. There is no commercially available serological test for ZIKV. Symptoms and signs are similar to infections with dengue or chikungunya, also viruses transmitted via mosquito bite, and 80% of humans infected with ZIKV exhibit mild signs
and symptoms or are asymptomatic. In endemic areas where dengue, chikungunya and ZIKV are present, coinfection is not uncommon. Methods included systemic and ocular exam, including of the anterior segment and wide field imaging of fundus. The differential diagnosis included toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, syphilis, and human immunodeficiency virus, which were ruled out through serologic and clinical examinations.

The authors then describe their ocular findings. No statistical analysis is performed because this is a descriptive study. Twenty-three of 29 mothers (79.3%) reported suspected ZIKV infection signs and symptoms during pregnancy, 18 in the first trimester, 4 in the second trimester, and 1 in the third trimester. Of the 29 infants (58 eyes) examined (18 [62.1%] female), ocular abnormalities were present in 17 eyes (29.3%) of 10 children (34.5%). Bilateral findings were found in 7 of 10 patients presenting with ocular lesions, the most common of which were focal pigment mottling of the retina and chorioretinal atrophy in 11 of the 17 eyes with abnormalities (64.7%), followed by optic nerve abnormalities in 8 eyes (47.1%), bilateral iris coloboma in 1 patient (2 eyes [11.8%]), and lens subluxation in 1 eye (5.9%).

Importance: This is a large case series describing the ocular abnormalities of infants with presumed ZIKV infection. Almost 40% of the infants had eye abnormalities, many of which are potentially sight threatening. As of the publication of this article, there was no definitive serologic test, so one weakness of the study could be the presumptive assumption of systemic and ocular findings caused by ZIKV. However, the authors were meticulous to exclude infants who had family history of microcephaly, mothers who abused alcohol or illicit drugs, and ruled out serologically other common intrauterine infections.

**Zika Virus Infection and the Eye**

The invited commentators note that international travel has led to the rapid spread of previously remote infections across the globe. The authors note that the Centers for Disease Control and Prevention offer polymerase chain reaction testing for ZIKV as well as serologic testing, that is, IgM and plaque reduction testing. They advise that all infants with microcephaly have eye exams. However, it is unclear whether all babies, even without microcephaly, should have eye exams in areas affected by ZIKV outbreaks.

**Risk Factors Associated With the Ophthalmoscopic Findings Identified in Infants With Presumed Zika Virus Congenital Infection**

In this study, risk factors associated with eye abnormalities thought related to Zika virus congenital infection are identified. This is a cross-sectional study of 40 infants born in Recife, Brazil in the latter half of 2015 with microcephaly and pre-
sumed Zika infection. Methods included excluding other causes of congenital infection and testing of the cerebrospinal fluid (CSF) in 24/40 (60%) of the infants using IgM antibody-capture enzyme-linked immunosorbent assay. Infants and mothers were examined. Infants were divided into 2 groups for comparison, one with eye abnormalities and the other without. Ten mothers (71.4%) of infants with ocular findings reported symptoms during the first trimester (P = .04), but no mother reported conjunctivitis and exam revealed no uveitis in the mothers. A difference was also observed between the groups of infants with and without ocular findings regarding head circumference: mean (SD) of 28.8 cm (1.7) and 30.3 cm (1.5), respectively (frequency−1.50; 95% CI, −2.56 to −0.51; P = .004). Results revealed that all infants whose CSF was tested were positive for Zika virus, equally distributed between those who had and who did not have eye findings. Ocular involvement in infants with presumed ZIKV congenital infection were more often seen in infants with smaller cephalic diameter at birth and in infants whose mothers reported symptoms during the first trimester.

Importance: This study provides a guide to determining risk for ocular abnormalities in congenital Zika infection. Given the pandemic nature of this disease, such guidelines will be useful in allocating public health resources in an effective and specific way.

**Expanded Spectrum of Congenital Ocular Findings in Microcephaly with Presumed Zika Infection**


In this retrospective case series, the authors present 3 patients born with microcephaly to mothers with viral syndrome during the first trimester in an area of Brazil that subsequently demonstrated epidemic Zika infection. All 6 eyes demonstrated a pigmentary maculopathy, 4 eyes had well-delineated macular chorioretinal atrophy with a hyperpigmented ring. Three eyes demonstrated vascular tortuosity and 2 eyes demonstrated a pronounced early termination of the retinal vasculature on photographic evaluation. Two eyes demonstrated a washed out peripheral retina with a hypoluent spot. One eye had scattered subretinal hemorrhages external to the macula. One eye demonstrated peripheral pigmentary changes and clustered atrophic lesions resembling grouped congenital albinotic spots (polar bear tracks).

Comment: Color fundus photos of all 6 eyes are published this paper and demonstrate fundus abnormalities found in all 3 patients with congenital Zika infections.

**Zika Virus Disease: A CDC Update for Pediatric Health Care Providers**

In this review article about Zika virus, the current knowledge about the epidemiology, virus transmission, symptoms, treatment, and prevention are shared to update pediatric care providers. Zika virus is a mosquito borne flavivirus that has a resurgence in infection since September 2015 with local transmission identified in 31 countries as of February 2016. In children and adults, a Zika virus infection is largely asymptomatic. Some features include maculopapular rash, fever, arthralgia, and nonpurulent conjunctivitis with symptoms lasting several days to one week. Maternal-fetal transmission has been documented through reverse transcription polymerase chain reaction testing. Congenital anomalies thought to be caused by the virus include multiple neurological problems such as microcephaly, cerebral calcification, abnormally formed or absent structures such as the corpus callosum, thalami, and cerebellar vermis. Ophthalmic problems have included microphthalmia, cataracts, optic nerve hypoplasia and pallor, macular chorioretinitis, chorioretinal atrophy, and lens subluxation. Individuals with epidemiologic risk factors (traveled to infected regions) and signs/symptoms suggested of Zika infection should be tested for Zika virus. This testing can be arranged through the CDC and some state health departments. There are no current treatments for Zika virus and patients are provided symptomatic relief of acute symptoms. Additionally, therapeutic services are available for developmental problems associated with congenital Zika transmission. To prevent Zika virus through sexual transmission, it is recommended that couples practice abstinence or consistent/correct condom usage when either partner has been in mosquito infected regions. Pregnant women should postpone travel to areas with continued Zika virus transmission or actively prevent mosquito bites (staying in indoor air-conditioned areas, using DEET products, bed nets). Pediatric ophthalmologists need to be aware of the signs and symptoms of Zika virus to identify patients with potential risks and initiate appropriate testing and treatment.

The eye as a window to the brain: neuroretinal thickness is associated with microstructural white matter injury in HIV infected children.

This cross-sectional observational study included 29 cART-treated perinatally HIV infected children and 35 matched healthy controls. All participants underwent 3.0 Tesla magnetic resonance imaging (MRI), determining gray and white matter volumes from T1-weighted sequences, and white matter diffusivity using diffusion tensor imaging (DTI). Regional individual and total neuroretinal layer thickness was quantified using spectral domain optical coherence tomography. In HIV-infected children, lower foveal and pericentral neuroretinal thickness was associated with damaged white matter microstructure, in terms of lower fractional anisotropy and higher mean and radial diffusivity. In healthy controls only, neuroretinal thickness was associated with gray and white matter volume. Decreased neuroretinal thickness is associated with microstructural white matter injury, but not with lower cerebral volume in HIV-infected children, suggesting that HIV-
induced retinal thinning and microstructural white matter injury may share a common pathogenesis, and longitudinal assessment of neuroretinal alterations in parallel with MRI and neuroinflammatory markers may further our insight into the pathogenesis of HIV-induced cerebral injury in children. Despite being the largest and first combined OCT/MRI study in cART-treated HIV-infected children without retinitis to date, using a highly similar control group, this study is subject to some limitations, including modest sample size, not adjusting for multiple comparisons, no detailed assessment of specific brain areas, and inability to explain the mechanisms underlying the associations observed between retinal and cerebral changes.

23. PEDIATRICS/ INFANTILE DISEASE/ SYNDROMES

The ophthalmic sequelae of Pfeiffer syndrome and the long-term visual outcomes after craniofacial surgery


Pfeiffer syndrome is a rare, genetic condition characterized by craniosynostosis and midface hypoplasia, with resultant ophthalmic sequelae. The gold standard of treatment is fronto-orbital advancement. In this retrospective case series the rate of ophthalmic sequelae and the long-term visual outcomes after craniofacial surgery are reported. The long term ophthalmic sequelae of Pfeiffer syndrome are compared to other craniosynostosis syndromes. The medical records of Pfeiffer syndrome patients examined between 1988 and 2010 were studied retrospectively. Diagnosis was based on clinical and genetic testing. Long-term data were presented as a rate of incidence per person-year to overcome variable follow-up times. A total of 22 patients were included. Proptosis (n = 21 [95%]), refractive error (n = 13 [59%]), and strabismus (n = 12 [55%]) were the most common primary features at presentation. Exposure keratitis (n = 9 [41%]) and amblyopia (n = 3 [14%]) were the most common secondary features. At presentation, 24 eyes [86%] with documented best-corrected visual acuity were normal; 4 [14%] were impaired; and none were blind. Fronto-orbital advancement reduced the rate of proptosis from 28%/person-year at presentation to 2%/person-year. There were no cases of active exposure disease postoperatively. At last follow-up, there was a 7%/person-year rate of impaired vision secondary to corneal scarring and amblyopia and a 3%/person-year rate of
blindness-all from optic atrophy. The authors concluded that in their cohort of Pfeiffer patients the rates of proptosis and exposure keratitis were high, especially compared to Apert and Crouzon syndromes. Fronto-orbital advancement was successful in correcting orbital abnormalities. They emphasize that long-term ophthalmic follow-up is essential to ensure best visual outcome. This is a relatively large case series for a condition that is relatively rare with an incidence of 1 in 100,000 births. Various management issues are discussed in length.

**A cross-sectional examination of visual acuity by specific type of albinism**


Reports of best-corrected visual acuity (BCVA) in albinism are often based on overlapping clinical phenotypes. BCVA in albinism has been shown to improve with age. This retrospective study reports a large cross-sectional investigation to determine whether BCVA differs by specific type of albinism when age-corrected. Included in the study 170 individuals with a specific type of albinism identified by mutation(s) in a gene known to cause albinism (for OCA1, OCA2, and Hermansky-Pudlak syndrome ([HPS])) or a specific phenotype (white hair and no melanin pigment in OCA1A; pigmented mosaicism in the obligate carriers for males with OA1). Optotype binocular BCVA at final follow-up was recorded. Patients were age-grouped (2-5 years, 6-14 years, and >/=15 years) for comparison. Their results showed the greatest visual acuity deficit was found for OCA1A in all age groups. At age >/=15 years (n = 79), mean BCVA was 20/128 for OCA1A, 20/37 for OCA1B, 20/59 for OCA2, 20/63 for OA1, and 20/121 for HPS. Significant differences between BCVA at >/=15 years were found in the following: OCA1A vs OCA1B, OCA1A vs OCA2, OCA1A vs OA1, OCA1B vs HPS, OCA2 vs HPS, and OA1 vs HPS (P </= 0.02). Authors conclude that BCVA varies by albinism type, and there is overlap in BCVA, particularly in the younger age groups. For ages >/=15 years, there are significant differences in BCVA between several types of albinism. Even though this study provides a large sample size, it has several limitations in its design. We could not find data on length of follow-up. Would have been interesting to know the correlation of the BCVA with other clinical findings such as foveal hypoplasia and nystagmus.

**Characterization of the ocular findings in the nablus masklike facial syndrome.**

Nablus masklike facial syndrome (NMLFS), characterized by tight, expressionless facial features resembling a mask, was first described in 2000. Since then, 10 cases have been identified with the same phenotype and genotype. Although detailed descriptions of the facial and external ear characteristics unique to the syndrome exist, no clear description of the ocular anatomic findings and management of ocular complications has been detailed. The authors present a confirmed case of NMLFS with detailed descriptions of the ocular anatomy encountered in this patient and a discussion regarding the clinical significance of these findings.

**A cross-sectional examination of visual acuity by specific type of albinism.**

Reports of best-corrected visual acuity (BCVA) in albinism are often based on overlapping clinical phenotypes. BCVA in albinism has been shown to improve with age. This study reports a large cross-sectional investigation to determine whether BCVA differs by specific type of albinism when age-corrected. This retrospective review identified 170 individuals with a specific type of albinism identified by mutation(s) in a gene known to cause albinism (for OCA1, OCA2, and Hermansky-Pudlak syndrome ([HPS]) or a specific phenotype (white hair and no melanin pigment in OCA1A; pigmentary mosaicism in the obligate carriers for males with OA1). We recorded optotype binocular BCVA at final follow-up. Patients were age-grouped (2-5 years, 6-14 years, and ≥15 years) for comparison. The greatest visual acuity deficit was found for OCA1A in all age groups. At age ≥15 years (n = 79), mean BCVA was 20/128 for OCA1A, 20/37 for OCA1B, 20/59 for OCA2, 20/63 for OA1, and 20/121 for HPS. Significant differences between BCVA at ≥15 years were found in the following: OCA1A vs OCA1B, OCA1A vs OCA2, OCA1A vs OA1, OCA1B vs HPS, OCA2 vs HPS, and OA1 vs HPS (P ≤ 0.02). This study provides a large sample size and includes only those with a specific type of albinism. BCVA varies by albinism type, and there is overlap in BCVA, particularly in the younger age groups. For ages ≥15 years, there are significant differences in BCVA between several types of albinism.

**Ocular Manifestations of Noonan Syndrome: A Prospective Clinical and Genetic Study of 25 Patients**

In this prospective cross-sectional observational study, the authors elucidate the spectrum of ocular manifestations of Noonan syndrome (NS). Twenty-five patients with NS (mean age, 14 years; range, 8 monthse to 25 years) diagnosed clinically. Ocular abnormalities were amblyopia (32%), myopia (40%), astigmatism (52%), epicanthic folds (84%), hypertelorism (68%), ptosis (56%), high up-
per eyelid crease (64%), lower eyelid retraction (60%), abnormal upward slanting palpebral fissures (36%), downward slanting palpebral fissures (32%), and lagophthalmos (28%), strabismus (40%), abnormal stereopsis (44%), and limited ocular motility (40%), prominent corneal nerves (72%), posterior embryotoxon (32%), non-glaucomatous optic disc excavation (20%), low (<10 mmHg) intraocular pressure (22%), and optic nerve hypoplasia (4%). Mutations were established in 22 patients: 19PTPN11 mutations (76%), 1SOS1 mutation, 1BRAF mutation, and 1KRAS mutation. The patient with the highest number of prominent corneal nerves had an SOS1 mutation. The patient with the lowest visual acuity, associated with bilateral optic nerve hypoplasia, had aBRAF mutation. Patients with severe ptosis and nearly total absence of levator muscle function had PTPN11 mutations. All patients showed at least 3 ocular features (range, 3-13; mean, 7), including at least 1 external ocular feature in more than 95% of the patients.

Comment: This paper is different from past publications on this topic in that nearly all subjects had genetic testing to identify mutation responsible for NS and there is an attempt to correlate the mutation with ocular abnormalities. Unfortunately NS is uncommon and this sample is probably too small for subgroup statistical analysis. However, this paper provides a very practical view for the clinician seeing patients with NS.

Clinical and Genetic Features of Choroideremia in Childhood.


Retrospective case series reviewing the functional and anatomic characteristics of choroideremia in the pediatric population, aiming to describe the earliest features of the disease and to identify biomarkers useful for monitoring disease progression. Case notes and retinal imaging (color fundus photography [CFP], spectral-domain [SD] optical coherence tomography [OCT], and fundus autofluorescence [FAF]) were reviewed. Main outcome measures were presenting symptoms, visual acuity, fundus changes (CFP, SD OCT, FAF), and CHM sequencing results. Twenty-nine patients were identified with a mean age at referral of 9 years (range, 3-16 years). CHM mutations were identified in 15 of 19 patients tested. Nyctalopia was the predominant symptom (66%). Five of 29 patients were asymptomatic at presentation. At the final follow-up visit (mean age, 16 years; range, 7-26 years), most maintained excellent visual acuity (mean, 0.98±0.13 decimalized Snellen acuity). The first sign of retinopathy was widespread pigment clumping at the level of the retinal pigment epithelium (RPE). This later evolved to chorioretinal atrophy, most marked in the mid-peripheral retina. Papillary atrophy also was an early feature and was progressive in nature. Three different zones of FAF change were visible. Persistence of the inner retinal layers, detected by SD OCT, was visible at presentation in 15 of 27 patients. Subfoveal
choroidal thickness decreased with age, whereas central retinal thickness increased over a similar interval. Four patients in whom visual acuity decreased over the follow-up period recorded a reduction in central retinal thickness. Progressive structural changes occur at a time when central visual function is maintained. Pigmentary changes at the level of the RPE occur early in the disease course. Peripapillary chorioretinal atrophy, central retinal thickness, and subfoveal choroidal thickness are likely to be valuable in monitoring disease progression and should be considered as potential biomarkers in future therapeutic trials.

**Neonatal Abstinence Syndrome**


This review article is of relevance to pediatric ophthalmologists who encounter babies exposed to opiates in utero. Neonatal abstinence syndrome has been recognized for more than four decades, but there have been substantial changes in the past 10 years, including a dramatic increase in prevalence and changes in both the exposure substance and clinical management. In 2012, the syndrome was diagnosed in 21,732 infants in the United States, which represents an increase by a factor of 5 during the previous 12 years. The increase in cases corresponds with the reported rise in opioid use during pregnancy, which is attributed to the more liberal use of prescribed opioids for pain control in pregnant women, illicit use of opioids such as oxycodone and heroin, and a dramatic increase in opioid-substitution programs for the treatment of opioid addiction. The pattern of opioid use has also shifted from an inner-city, low-income population to a more socioeconomically and demographically diverse population. The neonatal abstinence syndrome is a complex disorder that primarily involves the central and autonomic nervous systems and the gastrointestinal system. The clinical manifestations of the syndrome vary, ranging from mild tremors and irritability to fever, excessive weight loss, and seizures. In utero opiate exposure leads to increased health care utilization. The American Academy of Pediatrics recommends that opioid-exposed newborns be observed for 3 to 7 days before discharge. The average length of stay for infants with neonatal abstinence syndrome is 17 days. Treatments include supportive care (limiting exposure to lights and noise, promoting clustering of care to minimize handling and promote rest, swaddling and holding the infant, and providing opportunities for non-nutritive sucking), oral morphine or methadone, and promoting breast feeding and rooming in with the mother. More research is needed on alternative drugs, including clonidine and buprenorphine, for the treatment of affected infants and on alternative methods of care, such as outpatient weaning from pharmacologic treatment.

**Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine.**

The study was a randomized, double-blind, placebo-controlled trial of amitriptyline, topiramate and placebo in patients 8 to 17 years of age with migraine. Inclusion criteria included a diagnosis of migraine with or without aura or chronic migraine without continuous headache. The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of a 24-week trial. A total of 361 patients underwent randomization, and 328 were included in the primary efficacy analysis (132 in the amitriptyline group, 130 in the topiramate group, and 66 in the placebo group). 68% of the patients were female. On average, enrolled patients had 11 days affected by headache during a 28 day baseline period prior to study initiation. The trial was concluded early for futility after a planned interim analysis. There were no significant between-group differences in the primary outcome, which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group (amitriptyline vs. placebo, P=0.26; topiramate vs. placebo, P=0.48; amitriptyline vs. topiramate, P=0.49). Note the strong placebo effect. Patients who received amitriptyline or topiramate had higher rates of several adverse events than those receiving placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. The results of this study argue against treating pediatric migraines with amitriptyline or topiramate.

Anesthesia and Developing Brains- Implications of the FDA Warning

This perspective reviews what is known and unknown about the effects of general anesthesia on developing brains and discusses the implications of an FDA warning. Data from studies in animals and in vitro research demonstrate that under experimental conditions, all general anesthetics tested, including both N-methyl-d-aspartate (NMDA) antagonists and gammaaminobutyric acid (GABA) agonists, have immediate neuroanatomical consequences and associated long-lasting, if not permanent, functional effects in species ranging from roundworms to nonhuman primates. Clinical data are more difficult to interpret. Studies of brief, single exposures for relatively minor procedures have been reassuring. The long-term adverse neurodevelopmental effects that have been observed after prolonged or repeated anesthesia administration are difficult to interpret because of confounding by indication. Otherwise healthy young children do not undergo lengthy (longer than 3 hours) or repeated procedures under general anesthesia. And the brains of children born prematurely or with cyanotic congenital heart disease may have been injured by inflammation or chronic hypoxia before the children underwent the surgery that required general anesthesia. The interim analysis of the General Anesthesia vs. Spinal Anesthesia (GAS) study and the Pediatric Anesthesia and Neurodevelopment Assessment (PANDA) study, both of which involved formal neurodevelopmental testing, revealed that a brief, single exposure to general anesthesia was not associated with poorer neurodevelopmental outcomes. On December 14, 2016, the FDA issued a "Drug Safety Com
munication” warning that general anesthesia and sedation drugs used in children less than 3 years of age or in pregnant women in their third trimester who were undergoing anesthesia for more than 3 hours or repeated use of anesthetics “may affect the development of children’s brains.” Texas Children’s Hospital has changed its practice in response to the FDA warning. The hospital has adopted the warning’s recommendation that a discussion occur among parents, surgeons and other physicians, and anesthesiologists about the duration of anesthesia, any plan for multiple general anesthetics for multiple procedures, and the possibility that the procedure could be delayed until after 3 years of age; parent-education materials will also cover these topics. Indicated procedures in pregnant women and young children that can safely be delayed are rare. Until reassuring new information from well-designed clinical trials is available, the authors express concern that the FDA warning will cause delays for necessary surgical and diagnostic procedures that require anesthesia, resulting in adverse outcomes for patients. They urge parents, patients, and physicians to carefully consider the risks of delaying indicated procedures.

In pediatric ophthalmology practice, this FDA warning may come up for discussion when anesthesia could potentially be delayed beyond age 3 years: should surgery for infantile esotropia patients who are brought to medical attention late (after age 2 years) be delayed an additional year; should surgery for the toddler with constant exotropia at distance fixation but intermittent exotropia or exophoria at near be delayed; should the toddler with acute/acquired esotropia who is otherwise developmentally and neurologically normal undergo a brain MRI? However, general anesthesia for pediatric ophthalmology indications is almost always shorter than 3 hours.

The ophthalmic presentation of Hermansky–Pudlak syndrome 6

Hermansky–Pudlak syndrome (HPS) may present to the ophthalmologist with signs suggestive of oculocutaneous albinism. Consideration of HPS as a differential diagnosis is important due to its potential systemic complications. Nine HPS genes have been identified. HPS6 is a rarely reported subtype. In this report, the authors describe three patients from two families who underwent clinical examination, imaging and targeted systemic investigations. Electrophysiology with visual-evoked potentials (VEPs) was performed in both children of Family 1. Whole exome sequencing (WES) was performed on the proband of Family 1. Bi-directional Sanger sequencing of the single exon and intron–exon boundaries of HPS6 was performed on all affected patients and segregation confirmed in available relatives. Two siblings presented in infancy with nystagmus and reduced vision. They were initially diagnosed with isolated foveal hypoplasia with no aberrant chiasmal misrouting on VEPs. WES performed in the proband at 10 years of age identified a novel homozygous missense variant in HPS6 and further questioning elicited a history of nose bleeds and mild bruising. Segregation supported causality of this variant in the affected younger sibling. In the third unrelated patient, an initial diagnosis of ocular albinism was made at 3 months with HPS only diagnosed at 26 years. Biallelic, truncating mutations in HPS6 were identified by
candidate Sanger sequencing and included a novel variant. Abnormal platelet function consistent with HPS was confirmed in all patients. The authors highlight that the diagnosis of HPS in all patients was delayed due to a mild systemic phenotype. Next-generation sequencing can aid diagnosis of syndromic conditions with important consequences for preventing morbidity.

**Characterization of Chorioretinopathy Associated with Mitochondrial Trifunctional Protein Disorders: Long-Term Follow-up of 21 Cases**


In this retrospective case series the authors aim to assess long-term effects of genotype on chorioretinopathy severity in patients with mitochondrial trifunctional protein (MTP) disorders. 18 patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and 3 patients with trifunctional protein deficiency (TFPD) were included. Participants were followed up for a median of 5.6 years (range 0.3-20.2 years). The median age of LCHADD participants at initial and final visits was 2.3 and 11.9 years, whereas that for TFPD participants at initial and final visits was 4.7 and 15.5 years, respectively. Four long-term survivors older than 16 years were included (3 with LCHADD and 1 with TFPD). The LCHADD participants demonstrated a steady decline in visual acuity from an average of 0.23 logMAR (Snellen equivalent, 20/34) at baseline to 0.42 logMAR (Snellen equivalent, 20/53) at the final visit, whereas TFPD patients maintained excellent acuity throughout follow-up. Participants with LCHADD, but not TFPD, showed an increasing myopia with a mean decrease in spherical equivalent refraction of 0.24 diopters per year. Visual fields showed sensitivity losses centrally associated with defects on OCT. Multimodal imaging demonstrated progressive atrophy of the outer retina in LCHADD, often preceded by the formation of outer retinal tubulations and choriocapillaris dropout. Electroretinography findings support the more severe clinical profile of LCHADD patients compared with TFPD patients; the function of both rods and cones are attenuated diffusely in LCHADD patients, but are within normal limits for TFPD patients. The authors conclude that despite improved survival with early diagnosis, medical management, and dietary treatment, participants with the LCHADD subtype of MTP disorder continue to demonstrate visually disabling chorioretinopathy. Multimodal imaging is most consistent with choriocapillaris loss exceeding photoreceptor loss. Comment: This paper includes many high quality fundus photos of LCHADD patients taken over several years demonstrating the initial accumulation of pigment in the macula followed by progressive patchy chorioretinal atrophy. This is a nicely detailed description of a rare disease
A clinical study of Aicardi syndrome in Northern Ireland: the spectrum of ophthalmic findings.

This population study (retrospective review of charts for seven patients) aims to determine the presence of ocular findings and identifies some novel associations patients with Aicardi syndrome. Aicardi syndrome is a rare disorder, affecting ~1 in 100,000 live births. Chorioretinal lacunae feature alongside agenesis of the corpus callosum and spasms in flexion to make up a diagnostic triad. Recently ophthalmic findings such as microphthalmia and optic disc anomalies have been recognized in association with Aicardi syndrome. The incidence of Aicardi syndrome in Northern Ireland was found to be 1 in 110,000 live births. Four patients who had microphthalmos also had iris abnormalities; two patients with bilateral microphthalmos had partial aniridia and two patients with unilateral microphthalmos had iris coloboma in the same eye. Optic disc abnormalities were found in 11 eyes of six patients. Two patients were found to have areas of fibrovascular proliferation with a thickened white ridge and avascular zone beyond the arcades. Both of these patients developed retinal detachments.

Ophthalmologic manifestations of Hallermann-Streiff-Francois syndrome: report of four cases.

Hallermann-Streiff-Francois syndrome (HSS) is a rare genetic disorder characterized by ocular and craniofacial anomalies. This report highlights the ophthalmological features in four such patients and outcomes of cataract surgery. A retrospective review of medical records of patients with cataract and/or microcornea due to HSS was done. Presenting features, ocular findings, ocular motility and visual outcomes were noted. The authors identified four children with microcornea/cataract who had associated clinical features suggestive of HSS. Mean age at presentation was 25.5±27.8 months. Three children presented with poor vision in both eyes and one with strabismus. All patients had a microcornea and microphthalmos. Three patients had a membranous cataract. Horizontal corneal diameter ranged from 5.5 to 10.5 mm and axial length ranged from 12 to 18 mm. Three patients had associated strabismus. Three patients underwent lens extraction and two underwent strabismus surgery. Best corrected visual acuity (BCVA) improved from fixing, following light to a median post-operative BCVA of 20/380. One eye developed retinal detachment.

Managing Procedural Anxiety in Children.

In this clinical video and accompanying written summary of the video, the authors discuss the anxiety children feel surrounding simple procedures such as veni-
puncture, and ways that doctors can minimize that anxiety to make the exam or procedure easier. The video includes common sense information on how to gauge the anxiety level of a child simply by observing the child with the caregiver, prior to doing or saying anything threatening. Suggestions on helping manage children’s anxiety include: arousing curiosity / engaging the child, using desensitization, and shifting awareness away from the procedure. There is also a table about the use of developmentally sensitive language; for example, instead of “the medicine will burn,” the preferred alternative would be “some children say this gives them a warm feeling.” Most pediatric ophthalmologists use anxiety-minimizing techniques and language as second nature, but the video and accompanying written summary may offer a few additional tools/tricks.

Molecular and Clinical Findings in Patients With Knobloch Syndrome

This study seeks to address the gap in knowledge regarding clinical and electrophysiologic findings in this rare recessive disorder, characterized by high myopia, retinal detachment, and occipital encephalocele. In this descriptive, retrospective study, 12 affected patients from 7 families are examined. In addition to full eye exam, including retinal imaging, also electrophysiological and neuroradiological testing was performed. Bidirectional Sanger sequencing of COL18A1 was performed on available relatives. Results revealed all patients presented in infancy with nystagmus and had high myopia in at least 1 eye. Three patients had inferotemporal lens subluxation, which has been previously described. Two patients had clinical features of pigment dispersion syndrome associated with glaucoma. Many of the retinal changes in this series are consistent with high myopia, such as peripapillary atrophy, tessellated fundus with prominent choroidal vessels. Macular atrophic lesions and vitreous condensation are important features of this syndrome. Detailed electrophysiologic testing of all affected patients demonstrated both cone and rod dysfunction, which is thought to be stationary or very slowly progressive.

Importance: The authors describe novel clinical and electroretinographic findings such as cone-rod dysfunction and pigment dispersion with glaucoma. Some patients may not have radiologic findings, just isolated ocular disease. They also discovered 2 new disease-causing mutations in Knobloch syndrome. The authors seek to highlight awareness of this rare syndrome and should be considered in all children who present with high myopia and findings described above.

Ophthalmic Manifestations and Long-Term Visual Outcomes in Patients with Cobalamin C Deficiency
In this retrospective observational case series, ocular findings in 25 patients, aged 2-27 years, with cblC deficiency seem at the NIH are reported. This inborn error of intracellular vitamin B12 metabolism affects 1/100,000 and leads to methylmalonic academia and hyperhomocysteinemia. The authors found visual acuity typically in the range of 20/200 or worse in most patients. Nystagmus (64%), strabismus (52%), macular degeneration (72%), optic nerve pallor (68%), and vascular changes (64%) were also present. c.271dupA (p.R91KfsX14) homozygous patients (n=14) showed early and extensive macular degeneration and vision loss. Electroretinography showed that scotopic and photopic responses were reduced and delayed, but were preserved remarkably in some patients despite severe regeneration. Despite hyperhomocysteinemia, no patients exhibited lens dislocation. The pace and chronicity of ophthalmic manifestations lacked strict correlation to metabolic status as measured during visits. Prenatal or early treatment, or both, may have mitigated ocular disease, leading to better functional acuity, but patients still progressed to severe macular degeneration.

Comment: Although this is a relatively rare condition, this paper presents the largest series of ophthalmic findings to date. In addition to providing detailed statistics on ocular finding, there are multiple fundus photos and OCT images to assist the reader in understanding the ocular pathology of the disease.
Brothers with ocular motor apraxia, juvenile nephronophthisis, and mild cerebellar defects.

Ocular motor apraxia (OMA) is a disorder of initiation of horizontal eye movements. Head thrusts compensate for poor saccades. These signs usually improve with time. Although most cases are sporadic, familial cases suggest either an autosomal dominant or recessive inheritance pattern. A small subset have extraocular findings. This is a case report of two brothers that initially presented as infants with general hypotonia and OMA. Only years later, in their childhood, they developed juvenile nephronophthisis and end-stage renal disease (ESRD). Nephronophthisis is a cystic renal disease and the most frequent cause of ESRD in the first three decades of life. Cysts are commonly seen by ultrasonography at the corticomedullary junction after the development of ESRD. Of the known genes that are associated with juvenile nephronophthisis only NPHP1, have been linked to OMA. In this report, both boys had a large homozygous deletion in NPHP1, but the diagnosis of Joubert syndrome was only made when they were adults with MRI that demonstrated the classic sign of the molar tooth deformity (cerebellar vermis hypoplasia) and ERG demonstrated panretinal cone dysfunction. The authors conclude that renal screening should be offered to patients with ocular motor apraxia and NPHP1 gene mutation.

24. UVEITIS/ SYSTEMIC

Ocular Hypotony in Patients With Juvenile Idiopathic Arthritis-Associated Uveitis.

Juvenile idiopathic arthritis (JIA) is the most common cause of pediatric uveitis. Ocular hypotony (OH) is occurs with JIA associated uveitis (JIAU) in about 3-9% of patients and it is unclear which patients with JIAU are at risk for this complication. Since it would be beneficial to determine the predictors of developing OH, the authors aimed to evaluate the risk factors, course, and occurrence rate of ocular hypotony in patients with JIAU. This was a retrospective cohort study of 365 patients with JIAU over a 12 year period at the Department of Ophthalmology at St. Franziskus Hospital in Germany. The authors defined OH as IOP less than 6 at two consecutive visits. Hypotony occurred in 57 of the 365 patients during a mean follow up of 4.5 years. In 40 of these patients the hypotony was not related to ocular surgery. Risk factors were duration of uveitis, bilateral uveitis, de-
creased visual acuity, high flare, presence of posterior synechiae. Overall the rate of hypotony in this cohort was 15.6% of patients, which is higher than in previous publications. The authors point out that the nature of being at a tertiary uveitis center might cause selection bias for more severe cases. This paper, not unlike an AJO paper published on the same topic 4 months earlier, points out the risk factors of prolonged inflammation in developing hypotony. This paper reports a much higher rate of hypotony in patients with JIAU than previous publications.

**Risk of Hypotony in Juvenile Idiopathic Arthritis-Associated Uveitis.**

Juvenile idiopathic arthritis (JIA) associated uveitis can be complicated by hypotony, which can carry a worse visual prognosis. This is a retrospective study of 196 eyes of 108 patients at the Wilmer Eye Institute over 30 years with JIA-associated uveitis. The goal of this study was to evaluate the prevalence, incidence, and visual outcomes of patients with hypotony in the setting of JIA-associated uveitis. The authors defined hypotony as ≤5mmHg and low IOP from 6-8mmHg. They found a rate of hypotony at presentation in 9.3% of patients. 78% of patients were seen in follow up with a mean follow up of 5.3 years. During follow up, 26 of the 137 at-risk eyes developed hypotony. 12 patients (20 eyes) had hypotony prior to presentation, 10 patients (14 eyes) presented with hypotony, 4 patients presented with bilateral hypotony and 1 patient had bilateral low IOP. Most hypotonous eyes (12 of 14) were legally blind on presentation. All patients with hypotony were over 14 years old and most were older (over 18). Male sex was a risk factor for hypotony but this was not statistically significant. Other risk factors for hypotony included ≥10 of duration of arthritis prior to presentation, patients referred to tertiary care clinic 4 or more years after being treated elsewhere, a younger diagnosis of arthritis, and other signs of increased severity of uveitis. More than half of the eyes with hypotony had vitreous or posterior pole involvement and those eyes were 17 times more likely to have hypotony than eyes with anterior uveitis. Oral steroid use, previous pericocular steroid injection and legal blindness at presentation were also statistically significantly correlated with hypotony and lower IOP. The authors note that the rate of patients referred to their center who were already receiving immunosuppressive drug therapy increased 4-fold over the timeline of this study and most importantly that the use of immunosuppressing drug therapy was associated with a substantial decrease in the rate of hypotony further supporting early and aggressive treatment of this blinding disease. The key findings of this large retrospective study were that prolonged inflammation, posterior involvement, and lack of systemic immunosuppressant were all risk factors for hypotony in patients with JIA associated uveitis.
Retinal Dystrophy in 6 Young Patients Who Presented with Intermediate Uveitis

In this short report, the authors describe a series of 6 patients aged 5-22 years who presented with intermediate uveitis with CME. CME was refractory to intraocular and periocular steroids, acetazolamide, immunomodulators and biologics in patients treated with these medications. ERGs demonstrated scotopic and photopic abnormalities in all patients. Genetic for retinal dystrophies revealed mutations in *CRB1* (3 patients), *RP1* (1 patient), *USH2A* (1 patient) and two dominant RD genes (2 patients). The authors describe how similarities of some retinal dystrophies to intermediate uveitis resulted in ineffective treatment with medications that are potentially harmful and that earlier genetic testing might have led to faster diagnosis and avoidance of unnecessary medical interventions.

Comment: The patients presented appear to be complex and at significant risk for permanent vision loss. Although genetic testing for retinal dystrophy probably would not have been my first thought in these patients, it seems very reasonable given the complexity of diagnosis and management and the potential for causing harm with interventions.

The ophthalmic phenotype of IFT140-related ciliopathy ranges from isolated to syndromic congenital retinal dystrophy


Conorenal syndrome is a systemic skeletal ciliopathy characterised by skeletal and renal findings and caused by biallelic mutations in the gene intraflagellar transport 140 Chlamydomonas homologue (IFT140). This study highlights the ophthalmic phenotype. In a retrospective consecutive case series (2010–2014), the authors identified twelve subjects with confirmed homozygous mutations (11 consanguineous families; 7 boys; assessed at age 10 months to 20 years, average and median age 6.5 and 4 years). All were homozygous for the same IFT140 mutation (c.1990G>A; p.Glu664Lys) except one who was homozygous for c.1541_1542delinsAA. All had poor vision and nystagmus since birth, with visual acuity after 5 years old of hand motions or light perception. In early childhood, nine were noted to stare at lights, four were noted to have a happy demeanor, high hyperopia was typical, and electroretinography was non-recordable. Fundus appearance was grossly normal before the age of 1 year but thereafter appeared dystrophic. Eight children had developmental delay, two had short stubby fingers, and one had renal disease. Four subjects had no evident extraocular disease, including one aged 18 years who also had two older affected siblings in their twenties who remained non-syndromic and were excelling academically. Recessive IFT140 mutations cause a severe congenital retinal dystrophy with high hyperopia and often early photophobia. Developmental delay is common but not universal and not all patients have obvious extraocular findings. The c.1990G>A mutation represents a founder effect or mutational hotspot on the Arabian Penin-
Novel morphological macular findings in juvenile CLN3 disease


Juvenile CLN3 disease, one of the most common forms of a group of lysosomal storage diseases called neuronal ceroid lipofuscinoses (NCLs), is a progressive neurodegenerative disorder with initial visual deterioration. In this study, the authors analyzed the retinal phenotype of patients with CLN3 disease with the help of recent ophthalmic imaging modalities to distinguish CLN3 disease from other inherited retinal dystrophies. Patients underwent ophthalmic evaluations, optical coherence tomography, fundus autofluorescence, near infrared imaging and fundus photography. Patients were also assessed according to the Hamburg juvenile NCL (JNCL) score. Each ophthalmic finding was assessed by three independent examiners and assigned to a clinical severity score. The study included 22 eyes of 11 patients. The mean age at examination was 14.4 years (range 11.8–26.4 years), with an average age at initial diagnosis of 8 years (range 4.5–11 years). The mean Hamburg JNCL score was 7.3 (range 0–13). All patients showed a specific macular striation pattern on optical coherence tomography that was independent of age and progression of the disease. Other previously described retinal features of CLN3 disease were classified into four severity grades. This study represents the first prospective observational case series documenting retinal abnormalities in CLN3 disease with the aid of the spectral domain optical coherence tomography. The major finding was a characteristic, striated macular pattern in all patients studied. Particularly in early disease cases, macular striae can potentially help to discriminate CLN3 disease from other inherited forms of retinitis pigmentosa. In these patients, the distinct macular striated pattern that occurs in the mid and late stages of this disease may help to discriminate CLN3 disease from other juvenile macular dystrophies, such as Stargardt disease or cone–rod dystrophies.

Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis


Since the introduction of biologic agents, tumor necrosis factor α (TNF-α) antagonists have notably improved the treatment options for severe juvenile idiopathic arthritis (JIA). However, a subset of patients fails to respond to TNF-α blockers or is intolerant to these therapies and may benefit from switching to a different biologic agent. Rituximab, the anti-CD20 B cell monoclonal antibody therapy, has
been used successfully in the treatment of rheumatoid arthritis (RA) and other autoimmune diseases that have responded inadequately to TNF-α blockers. In this paper, the authors conducted a retrospective review to evaluate the long-term efficacy of rituximab in patients with JIA-associated uveitis. The study found eight patients (15 eyes) with severe and longstanding JIA uveitis, who had an inadequate response in controlling uveitis to one or more biologic agents including TNF-α blockers and abatacept, received rituximab therapy. Inclusion criteria for treatment with rituximab were inadequate response in controlling uveitis with traditional immunosuppressives and at least one TNF-α inhibitor (etanercept, infliximab or adalimumab), and/or abatacept. Rituximab was given at a dose of 1000 mg per infusion on days 1 and 15 and then every 6 months. Clinical responses to treatment, including decrease in uveitis activity, visual acuity changes, reduction of concomitant local and systemic corticosteroid and/or immunosuppressants, and occurrence of adverse events, were assessed. Results showed that eight patients with a mean±SD age of 22.8±5.5 years were treated. The mean ocular disease duration was 17.7 years, the mean±SD follow-up time on rituximab was 44.75±4.9 months, and the mean number of rituximab infusions received was 8.75 (range 6–12). All patients achieved complete control of uveitis, but in two patients rituximab was discontinued due to inefficacy in treating arthritis. The decrease in uveitis activity was evident 4–5 months after the first infusion. Systemic corticosteroids and immunosuppressants used in association with rituximab were discontinued in five patients at the end of follow-up. None of the patients experienced visual worsening during the follow-up. No drug-related complications were encountered. The authors conclude that rituximab may be a promising effective treatment option for refractory uveitis associated with JIA leading to long-term quiescence of uveitis, particularly for patients who have not previously responded to other biologic therapies. This study presents 8 patients who had a mixed treatment modality of methotrexate and/or cyclosporine, systemic and topical steroids along with the rituximab during the observation period. The dosage of systemic and topical steroids needed was reduced. Rituximab should be considered in refractory cases to reduce steroid burden.

Specialty practice and cost considerations in the management of uveitis associated with juvenile idiopathic arthritis.
Alan G. Palestine, Jasleen K. Singh, Jason R. Kolfenbach, Daniel J. Ozzello
JPOS July/August 2016.53;(4): 246-251

This article investigates whether cost, prior insurance authorization concerns, and subspecialty practice influence therapeutic decisions in the treatment of uveitis associated with juvenile idiopathic arthritis (JIA). A total of 2,965 pediatric ophthalmologists, uveitis specialists, retina specialists, and rheumatologists across the United States were surveyed via e-mail regarding their choice in long-term therapy for a hypothetical patient with uveitis associated with juvenile idiopathic arthritis. The study showed that although the majority of the physicians in different specialties treat JIA in a similar manner, differences do exist among treatment choices between specialists. Also, cost and prior insurance authorization
concerns don’t seem to affect the decision making for the treatment of JIA associated uveitis. Although the results of the study are interesting, a larger sample is needed in order to reach reliable conclusions.

**Nuclear cataract as an early predictive factor for recalcitrant juvenile idiopathic arthritis-associated uveitis**

This study analyzed the long-term outcomes in patients with JIA-related uveitis to identify baseline features predictive of inadequate response to nonbiologic disease-modifying antirheumatic drugs (DMARDs). This was a medical record retrospective review from 10/05 to 3/13. Ninety-six cases (175 eyes) met inclusion criteria. There were 58 patients (108 eyes) in the recalcitrant group and 38 patients (67 eyes) in the non recalcitrant group. The most common findings in the nonrecalcitrant group were clear lens (70.1%), active uveitis (41.7%) and secondary glaucoma (20.9%). In the recalcitrant group the most common findings were permanent posterior synechiae (52.7%), cataract (49%) and active uveitis (57.4%). At least one ocular complication such as permanent posterior synechiae and cataract occurred more commonly in the recalcitrant group to a statistically significant degree. The cataracts in the recalcitrant group were more likely to have a nuclear component. During follow-up cataracts developed in the clear lens of 8.5% of the non recalcitrant group and 45% of the recalcitrant group. Multivariate analysis showed that among all relevant factors, having a nuclear cataract at presentation was significantly correlated with having recalcitrant JIA-associated uveitis. This data is retrospective, nonrandomized and comes from a highly specialized tertiary center so these findings may not be broadly applicable.

**Treatment of pediatric uveitis with adalimumab: the MERSI experience**

This study evaluated the off-label use of adalimumab (Humira) therapy in pediatric patients to achieve steroid-free remission of uveitis. This was a retrospective review in children treated with this medication and at least 1 year of follow-up. There were a total of 17 patients with a mean age of 12 years and a mean duration of therapy of 36 months. Sixteen had anterior uveitis and 1 patient had panuveitis. Bilateral uveitis was found in 14/17 (82%). The etiology of the uveitis was JIA (n=14), idiopathic (n=2) and sarcoidosis (n=1). Other agents were also being used in 14/17 of patients. Thirteen patients had active inflammation and four patients were placed on adalimumab to prevent future exacerbations. At the one-year follow-up (n=15), 12 patients were on combination therapy and 3 patients were on monotherapy. Eleven patients (65%) had no evidence of inflammation and 4/15 had active disease. Most patients were able to remain steroid-free. Six patients flared after discontinuing adalimumab, and 5 regained control of inflammation after restarting. Flare was noted 3-7 months after discontinuation.
Skin infections were the most common infections (n=4). One patient developed pneumonia and another developed sinusitis. Side effects included pain at the infection site (n=3), anemia (n=1) and depression (n=1). Adalimumab advantages include subcutaneous administration, biweekly or weekly dosage, and cost.

25. PRACTICE MANAGEMENT/ HEALTH CARE SYSTEM

Reasons for unplanned pediatric readmissions at a referral eye center in the Middle East


Unplanned hospital readmissions are of major interest for health care quality control across all medical subspecialties; however, published data for pediatric ophthalmology are lacking. In this retrospective case series the most common reasons for unplanned pediatric readmissions within 30 days of discharge at a referral eye center in the Middle East were reviewed. Readmission was for conditions that needed immediate surgical procedure or close follow-up over a period of several days. The authors acknowledge that this may not always justify readmission in other regions of the world. A total of 160 children (64 girls [40%]) were identified. In order of descending frequency, the 5 major diagnoses associated with unplanned readmission were loose corneal suture (17.6%), high intraocular pressure (IOP; 12.8%), retinal detachment or re-detachment (11.8%), wound dehiscence or leak (8%), and persistent epithelial defect (7.5%). Loose corneal sutures in the immediate postoperative period was the most common reason for unplanned readmission. The related conditions were: Previous primary repair following trauma (33%), previous penetrating keratoplasty (PKP; 30%), and cataract surgery (12%). This short report highlights the need for careful follow-up and vigilant postoperative care in children, who sustained penetrating ocular trauma, had PKP or cataract surgery.

Results of a primary care-based quality improvement project to optimize chart-based vision screening for preschool age children

Pediatric vision screening is an essential element of well-child care for young children given the importance of adequate vision to overall cognitive and social development. Appropriate vision screening in young children can detect amblyopia or amblyogenic risk factors at a time when treatment is effective, ideally before age 5. In this study, a quality improvement programme was designed to improve a chart-based vision screening for preschool-aged children administered by pediatric providers in a local network of practices. The program consisted of educational sessions for providers as well as hands-on training for practice staff. The vision-screening training sessions were attended by 163 professionals from 56 practices, representing 70% of the network’s 80 practices. The intervention was evaluated through pre- and post-intervention review of medical records. Completion of full vision screening (distance visual acuity in each eye plus stereovision beginning at 3 years of age, as recommended at the time of the project) at well-child visits improved for 5-year-olds (45.0% to 58.2%; risk difference +13.2% [95% CI, 1.7-24.7]) and 4-year-olds (39.3% to 51.4%; risk difference +12.0% [95% CI, 0.7-23.4]) but declined somewhat among 3-year-olds (23.1% to 14.3%; risk difference, -8.8% [95% CI, -17.7 to 0.0]). Risk factors for not being fully screened included being 3 years old (risk ratio of 4.1 compared to 5-year-olds) and being a patient of a small practice (risk ratio of 1.9 compared to large practices). The authors concluded that this quality improvement project showed that screening for visual acuity and stereovision among preschool-aged children using chart-based techniques is difficult to accomplish and unlikely to be consistently successful, especially among 3-year-olds. This study raises awareness to the obstacles that involved in vision screening preschool children. It highlights the need for technological solutions, such as portable photoscreeners and autorefractors to accomplish higher levels of screening among this age group. Authors acknowledge that further research is necessary to overcome barriers to the adoption of the new technologies that promise to substantially improve preschool vision screening in primary care settings.

Learning From Malpractice Litigation

The author notes that the database which was searched does not include claims settled out of court, which likely represents the outcome of most malpractice claims. The statute of limitations in which a claim may be filed is much greater for a pediatric patient compared with an adult, and the study’s findings were not adjusted to reflect this. The author notes that the most clinically significant finding of
the study was the paucity of pediatric malpractice cases which were adjudicated in the court system, a total of 68 in 84 years!

**Malpractice Litigation in Pediatric Ophthalmology**

A survey by the AMA found that in any given year, 5 % of ophthalmologists had an open malpractice lawsuit. The authors searched the Westlaw Database for search terms, ophthalmology, ophthalmologist and malpractice from January 1, 1930 through 2014. 68 cases involving plaintiffs who were 18 years of age or less at the time of the occurrence were identified. This is a database of verdicts and settlements, not claims. Cases involving retinopathy of prematurity were the most common and had the highest awards. In cases resolved in favor of the plaintiff, the reason for the malpractice was insufficient follow up of the disease. This included failure to properly transfer care between specialists, loss to follow-up, and failure to ensure that follow-up visits and treatment are conducted within current guidelines for follow-up and treatment. In a comparison with adult malpractice cases, the study confirms that the plaintiff was more likely to win if he or she was a child. Also, the plaintiff was more likely to win if the alleged injury resulted in legal blindness. Failure to diagnose or failure to treat comprised 61.5% of cases which were ruled in the plaintiff’s favor. All cases involving endophthalmitis were ruled in favor of the plaintiff.

Conclusion: According to the authors, this is the largest study of pediatric malpractice cases in the literature. Focusing on the types of cases and outcomes of cases brought to court can help ophthalmologists who care for children understand unique risk factors for a verdict or settlement in favor of the plaintiff.

**The effectiveness of a mobile clinic in improving follow-up eye care for at risk children.**

This article investigates the potential of a mobile ophthalmic unit in the school yard in order to improve compliance of children who have failed the optometric in-school screening program. In this study, out of a total of 132 students that were referred by the optometric program, sixty-two percent had a full ophthalmologic examination by the mobile unit. Compared to the historical rate of 53% for completion of ophthalmologic consultation, a statistically significant improvement in follow-up was noted. The authors stressed the potential benefit of a mobile eye unit in schools for children with poor access to ophthalmic care.

**Comparison of Pediatric and Adult Ophthalmology Consultations in an Urban Academic Medical Center.**
The purpose of this study is to compare the different features of pediatric and adult ophthalmology consultations in an urban academic center. A total of 751 inpatients and emergency department patients were evaluated by the Ophthalmology Consultation service of whom 20.4% were children and 79.6% were adults. The emergency department requested most of the consultations (42.8%), followed by internal medicine (39.1%) and pediatric inpatients (18.4%). More adults patients than children had abnormal findings (94.5% vs 76.5%, \( p < .001 \)). Altering management was recommended at a similar rate: 51.6% of pediatric patients and 54.3% of adult patients, \( p = .59 \). Children were more likely to be seen by attending physicians than adults (38.6% vs 9.0%, \( p < .001 \)) and children were more likely than adults to attend their recommended outpatient appointment (54.9% vs 42.7%, \( p = .027 \)).

In conclusion, there were many differences identified between the pediatric and adult consultation services. Altering management was recommended for more than half of each group.

**A Clinical Randomized Trial Comparing the Cycloplegic Effect of Cyclopentolate Drops Applied to Closed Eyelids Versus Open Eyelids**

Jocelyn Zuevinsky, Kallie Sawchuk, Hyun J. Lim, Chel Hee Lee, Shehla Rubab


The purpose of the study was to address the efficacy of placing a single drop of cyclopentolate 1% on the eyelids near the medial canthus in achieving complete cycloplegia for refraction in pediatric patients. Each eye in 90 patients was randomized to direct (inferior fornix) application or indirect (eyelid) application and the patients were retinoscoped at least 45 minutes later with fixation on a near target and a distant target. A difference between the near and distance refraction was considered a cycloplegic failure. Both methods were found to be equivalent in obtaining adequate cycloplegia, 82.8% in the indirect group and 83.9% in the direct group. This similarity was independent of age, eye color, spherical refractive error, presence of amblyopia, and astigmatic refractive error. The study also showed that a single drop of cyclopentolate 1% is adequate for light eyes but not for dark eyes (90.8% versus 61% success), this difference was independent of application method.

**Accuracy and Efficiency of Orthoptists in Comprehensive Pediatric Eye Examinations**

Jane Scheetz, Konstandina Koklanis, Maureen Long, Meg E. Morris


The purpose of the study is to investigate the accuracy of orthoptists when performing a comprehensive pediatric eye exam to assess their ability to examine and triage non-urgent ocular examinations. The orthoptists underwent training in
retinoscopy and binocular indirect ophthalmoscopy prior to intermediate and non-urgent (vision or motility issue) patients being being examined in the orthoptist-led triage clinic. Patients were initially evaluated by an orthoptist and on a subsequent visit an ophthalmologist, the exams findings were compared for consistency. The orthoptists and ophthalmologists agreed on the diagnosis of strabismus and/or amblyopia on 84.6% of the patients. There was no statistically significant difference found between refractive errors determined by retinoscopy between orthoptists of ophthalmologists. The third objective of the study, fundus examination, showed 95.7% agreement between the orthoptists and ophthalmologists. The authors conclude that orthoptists have the skills necessary to provide comprehensive ophthalmic care for children, which can help with the increasing demand on pediatric ophthalmologists and shorten the long waiting lists.

The impact of the transition to an Electronic Medical Record on patient perceptions in a pediatric ophthalmology practice.

This article assesses the impact of the transition from traditional paper-based medical records to electronic medical records in a pediatric ophthalmology practice at a tertiary care center. A survey was completed 2 weeks prior to (phase 1), 2 weeks after (phase 2), and 3 months after (phase 3) the electronic medical record transition. The survey consisted of 10 Likert-type scaled questions assessing patient satisfaction and two free response questions estimating the wait time, which was completed by patients or parents/guardians whose child/children (younger than 18 years) had an appointment in the pediatric ophthalmology and strabismus clinic. Satisfaction scores and waiting times were compared within each phase and across phases and between different appointment types. Overall, patient satisfaction was high at all three time points. Patients' estimates of waiting time compared to actual waiting time were not significantly different at any phase; however, patients' estimates of time spent with the physician were significantly underestimated in phase 1 (20 vs 25 minutes, \(P = .04\)) and were correct or overestimated in phase 3. The authors conclude that patients' satisfaction was the same regardless of the use of paper charts or electronic medical records but it had an impact on the perception of time spent with the physician.