

What's New and Important in Pediatric Ophthalmology for 2012

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I. AMBLYOPIA

Development of motor fusion in patients with a history of strabismic amblyopia who are treated part-time with Bangerter foils.

Abrams MS, Duncan CL, McMurtrey R. *J AAPOS* April 2011;15:127-130 (f11)

Strabismic amblyopes were treated with part-time Bangerter foils, and their motor fusion status was followed. Enrolled patients had amblyopic eye acuity $\geq 20/60$ and a manifest horizontal deviation of ≤ 20 PD. All subjects had no demonstrable motor fusion in the year preceding study entry. Motor fusion was evaluated with a 10 base-out prism, testing for prism vergence. 54 patients were enrolled and data was tabulated for those with 2 years of follow-up. Motor fusion developed in 61% (28/46). Those who developed motor fusion had a small but statistically significant improvement in their alignment and acuity. The authors comment that because Bangerter foils permit parafoveal binocular interaction, they may particularly be effective at restoring motor fusion. However, examinations were non-masked and there was no control group or other treatment modality groups. Sensory fusion testing was not reported.

Retinal nerve fibre layer and macular thickness in amblyopia as measured by spectral-domain optical coherence tomography

Christiane E Al-Haddad, Georges M E L Mollayess, Carol G Cherfan, et al
Br J Ophthalmol December 2011;95:1696-1699. (s12)

Background/aims To study peripapillary retinal nerve fibre layer (RNFL) and macular thickness in amblyopia using high-definition spectral-domain optical coherence tomography (SD-OCT) and to compare the results with available literature using the time-domain modality.

Methods This was a prospective institutional study of patients < 6 years of age with unilateral amblyopia (strabismic or anisometropic) and non-amblyopic anisometropia. RNFL and macular thicknesses were measured using SD-OCT and compared between fellow eyes.

Results The mean age was 20 (6-12) years; 45 patients had amblyopia: 14 strabismic and 31 anisometropic. 20 patients had non-amblyopic anisometropia. The mean macular thickness was significantly increased in the amblyopic (273.8 μm) vs fellow eyes (257.9 μm), $p < 0.001$. This difference remained significant in the anisometropic group ($p < 0.002$) but not the strabismic group. The mean RNFL thickness was similar in amblyopic (95.4 μm) and fellow eyes (94.0 μm). Similar results were obtained regardless of the level of visual acuity, age or refractive error. In the control group of non-amblyopic anisometropia, the interocular difference did not reach statistical significance.

Conclusions Central macular thickness was significantly increased in anisometropic amblyopia using SD-OCT. Anisometropia alone did not produce such a difference, which points to a possible correlation between amblyopia and the development of the retinal layers.

Comments: The strabismic amblyopes were fewer in number (n.14) than the anisometropic ones (n.31), which did not allow a fair comparison. The study did not have a control group of normal children; the retinal thickness of the sound eyes may not really reflect normal retinal thickness.

Analysis of spectral-domain optical coherence tomography measurements in amblyopia: a pilot study

Kyung-Ah Park, Do Young Park, Sei Yeul Oh. *Br J Ophthalmol*, December 2011;95:1700-1706 (s12)

Background/aims To compare the thickness of each retinal layer of amblyopic and fellow eyes in patients with unilateral amblyopia.

Methods Horizontal and vertical spectral-domain optical coherence tomography scans through the fovea were obtained for 20 patients with unilateral amblyopia. The thickness of each retinal layer in the amblyopic eyes was measured at the foveal centre, inner macular locations (a mean of 490 μm and 500 μm superior, inferior, nasal and temporal to the foveal centre) and outer macular locations (a mean of 1490 μm and 1500 μm superior, inferior, nasal and temporal to the foveal centre) and compared with corresponding locations in the fellow eyes.

Results In amblyopic eyes, there was significant thinning of the ganglion cell layer plus inner plexiform layer at all four nasal and temporal macular locations and at the outer superior and inferior locations. Other retinal layers, including the nerve fibre layer, inner nuclear layer, outer plexiform layer and outer nuclear layer, demonstrated significant differences in thickness at several macular locations.

Conclusions These data, obtained using spectral-domain optical coherence tomography, reveal differences between amblyopic and fellow eyes in the thickness of some retinal layers, including a notable difference in the ganglion cell layer plus inner plexiform layer.

Effect of Age on Response to Amblyopia Treatment in Children

Jonathan M. Holmes, BM, BCh; Elizabeth L. Lazar, MS, MPH; B. Michele Melia, ScM; for the Pediatric Eye Disease Investigator Group *Arch Ophthalmol*. November 2011;129(11):1451-1457. (s12)

The purpose of this paper was to determine whether age at initiation of treatment for amblyopia influences the response among children 3 to less than 13 years of age with unilateral amblyopia who have 20/40 to 20/400 amblyopic eye visual acuity. This paper was a meta-analysis of individual subject data from 4 recently completed randomized amblyopia treatment trials was performed to evaluate the relationship between age and improvement in logMAR amblyopic eye visual acuity. Analyses were adjusted for baseline amblyopic eye visual acuity, spherical equivalent refractive error in the amblyopic eye, type of amblyopia, prior amblyopia treatment, study treatment, and protocol. Age was categorized (3 to <5 years, 5 to <7 years, and 7 to <13 years) because there was a nonlinear relationship between age and improvement in amblyopic eye visual acuity. Children from 7 to less than 13 years of age were significantly less responsive to treatment than were younger age groups (children from 3 to <5 years of age or children from 5 to <7 years of age) for moderate and severe amblyopia ($P < .04$ for all 4 comparisons). There was no difference in treatment response between children 3 to less than 5 years of age and children 5 to less than 7 years of age for moderate amblyopia ($P = .67$), but there was a suggestion of greater responsiveness in children 3 to less than 5 years of age compared with children 5 to less than 7 years of age for severe amblyopia ($P = .09$). In summary, amblyopia is more responsive to treatment among

children younger than 7 years of age. Although the average treatment response is smaller in children 7 to less than 13 years of age, some children show a marked response to treatment.

A Prospective Pilot Study of Treatment Outcomes for Amblyopia Associated With Myopic Anisometropia

Yi Pang, MD, Christine Allison, Kelly A. Frantz, Sandra Block, Geoffrey W. Goodfellow, *Arch Ophthalmol.* Published online January 9, 2012. (s12)

The purpose of this paper was to determine the efficacy of refractive correction alone and patching treatment with near activities on amblyopia associated with myopic anisometropia in children aged 4 to less than 14 years. The associations of visual acuity (VA) improvement with age, degree of anisometropia, patching compliance, presence of strabismus, and presence of eccentric fixation were also investigated. Seventeen amblyopic children were recruited (range of VA in the amblyopic eye, 20/80 to 20/400). Visual acuity was assessed at 4, 8, 12, and 16 weeks while participants wore spectacles and/or contact lenses for full refractive correction. Patching treatment was initiated at the 16-week visit. The primary outcome was VA after 16 weeks of refractive correction alone and final VA after 16 weeks of patching. The mean (SD) baseline VA in the amblyopic eye was 0.96 (0.27) logMAR, which improved to a mean (SD) of 0.84 (0.24) logMAR with refractive correction and to a mean (SD) of 0.71 (0.30) logMAR after the addition of patching ($P < .001$). Comparing the final VA with the baseline VA, we found that VA improvement averaged 2.59 lines. The final VA in the amblyopic eye was associated with the baseline VA in the amblyopic eye ($P < .001$), the magnitude of anisometropia ($P < .001$), and the level of patching compliance ($P = .04$). The improvement in VA with patching was inversely associated with participants' age ($P = .03$) and presence of eccentric fixation ($P = .02$). Both refractive correction and patching significantly improved the VA of the amblyopic eye associated with myopic anisometropia, with 88% of participants' eyes improving 2 lines or more. Further improvement in VA was observed when patching plus near activities was added to refractive correction and patients were followed for 16 more weeks. We recommend that clinicians treat myopic anisometropic amblyopia with refractive correction and patching plus near activities.

Amblyopia and Strabismus in Iranian Schoolchildren

Mashhad Mohammad Faghihi, Hadi Ostagimoghaddam, Abbas Ali Yekta, *Strabismus*, 19 (4), 147-152 December 2011 (s12)

Refractive errors, amblyopia and strabismus are a major cause of visual impairment in children. The later two are less prevalent, but if not treatment in a timely fashion, the visual impact can be lifelong. In fact, amblyopia is one of the most important causes of unilateral blindness in adults. In some countries, there are protocols in place to ensure early diagnosis and treatment. This has led to recent studies demonstrating a decreasing trend for amblyopia and strabismus in some countries. In Iran, vision screening programs have been in place for over 10 years. The exams are performed annually in schools by teachers at the beginning of the year. Any abnormality leads to a referral to ophthalmology or optometry. The study presents prevalence of amblyopia and strabismus in the schoolchildren of Mashhad, Iran. Findings suggest an amblyopia prevalence of 1.9%, most commonly due to

anisometropia, which is the most common cause of amblyopia in general. The prevalence of strabismus was higher than amblyopia, with exotropia being most common. When comparing to other studies, the schoolchildren of Mashhad has a prevalence rate of amblyopia in the midrange and a prevalence rate of strabismus relatively higher.

An Exploratory Study: Prolonged Periods of Binocular Stimulation Can Provide an Effective Treatment for Childhood Amblyopia

Pamela J. Knox, Anita J. Simmers, Lyle S. Gray, and Marie Cleary. (Invest Ophthalmol Vis Sci. February 2012;53:817–824) DOI:10.1167/ iovs.11-8219 (s12)

PURPOSE. The purpose of the present study was to explore the potential for treating childhood amblyopia with a binocular stimulus designed to correlate the visual input from both eyes.

METHODS. Eight strabismic, two anisometropic, and four strabismic and anisometropic amblyopes (mean age, 8.5 ± 2.6 years) undertook a dichoptic perceptual learning task for five sessions (each lasting 1 hour) over the course of a week. The training paradigm involved a simple computer game, which required the subject to use both eyes to perform the task.

RESULTS. A statistically significant improvement ($t_{(13)} = 5.46$; $P = 0.0001$) in the mean visual acuity (VA) of the amblyopic eye (AE) was demonstrated, from 0.51 ± 0.27 logMAR before

training to 0.42 ± 0.28 logMAR after training with six subjects gaining 0.1 logMAR or more of improvement. Measurable stereofunction was established for the first time in three subjects

with an overall significant mean improvement in stereoacuity after training ($t_{(13)} = 2.64$; $P = 0.02$). **CONCLUSIONS.** The dichoptic-based perceptual learning therapy employed in the present study improved both the monocular VA of the AE and stereofunction, verifying the feasibility of a binocular approach in the treatment of childhood amblyopia.

The purpose of the present study was to explore the potential for treating childhood amblyopia with prolonged viewing of a binocular stimulus adapted to correlate the visual input from both eyes. The dichoptic-based learning therapy used in the present study appears to be effective in improving monocular VA(AE) and stereofunction in those children who did not have a large angle squint and who had a VA(AE) no worse than 0.5 logMAR. These results establish the feasibility of employing a binocular stimulus adapted to correlate the visual input to both eyes in the treatment of childhood amblyopia. The heterogeneous nature of amblyopia means that greater numbers of subjects would have to be studied to determine inclusion criteria for successful treatment with respect to type and degree of amblyopia. The results of the present study suggest that the angle of strabismus may be an important consideration.

Effects of Anisometropic Amblyopia on Visuomotor Behavior, III: Temporal Eye-Hand Coordination during Reaching

Ewa Niechwiej-Szwedo, Herbert C. Goltz, Manokaraanathan Chandrakumar, Zahra Hirji, and Agnes M. F. Wong. (Invest Ophthalmol Vis Sci. July 2011;52:5853–5861)
DOI:10.1167/iovs.11-7314 (f11)

PURPOSE. To examine the effects of anisometropic amblyopia on the temporal pattern of eye-hand coordination during visually-guided reaching. **METHODS.** Eighteen patients with anisometropic amblyopia and 18 control subjects were recruited. Participants executed reach-to-touch movements toward visual targets under three viewing conditions: binocular, monocular amblyopic eye, and monocular fellow eye viewing. Temporal coordination between eye and hand movements was examined during reach planning (interval between the initiation of saccade and reaching) and reach execution (interval between the initiation of saccade and reach peak velocity). The frequency and dynamics of secondary saccades were also examined.

RESULTS. Patients with severe amblyopia spent a longer time planning the reaching response after fixating the target in comparison with control subjects and patients with mild amblyopia

($P = 0.029$). In comparison with control subjects, all patients extended the acceleration phase of the reach after target fixation ($P = 0.018$). Secondary (reach-related) saccades were initiated during the acceleration phase of the reach and patients executed these saccades with greater frequency than control subjects ($P < 0.0001$). The amplitude and peak velocity of reach-related saccades were higher when patients viewed with the amblyopic eye in comparison with the other

viewing conditions ($P < 0.001$). **CONCLUSIONS.** This is the first study to show that patients with anisometropic amblyopia modified the temporal dynamics of eye-hand coordination during visually-guided reaching. They extended the planning and execution intervals after target fixation and increased the frequency of secondary, reach-related saccades. These may represent visuomotor strategies to compensate for the spatiotemporal visual deficits to achieve good reaching accuracy and precision. The authors postulated that patients with amblyopia optimized their reaching performance by adopting different kinematic strategies during planning (feed-forward stage) and execution (feed-back stage) of visually-guided reaching movements to compensate for their degraded spatiotemporal vision. They examined the effects of anisometropic amblyopia on the temporal pattern of eye-hand coordination during the planning stage (defined as the interval from target onset to the initiation of the reaching movement) and execution stage (defined as the interval from reach initiation to the end of movement) of visually-guided reach-to-touch movements (referred to as reaching movements from here onward). Specifically, they investigated whether patients spent longer time planning the reaching movement and whether they extended the acceleration phase of the reach after the eyes fixated the target. The authors demonstrated that patients with anisometropic amblyopia modified the temporal dynamics of eye-hand coordination during visually-guided reaching and that the severity of amblyopia affected the strategies that patients used. Patients with severe amblyopia extended the planning stage before reach initiation after the target was acquired by the primary saccade. All patients extended the

acceleration phase of the reaching movement after the eyes fixated on the target and executed more reach-related saccades during the acceleration phase of the reach, irrespective of their level of visual acuity. They propose that the extended planning and execution intervals after target fixation and the additional reach-related saccades are strategies that patients developed to compensate for their spatiotemporal visual deficits, allowing them to achieve good accuracy and precision during visually-guided reaching.

Efficacy of a Web-Based Intervention to Improve and Sustain Knowledge and Screening for Amblyopia in Primary Care Settings.

Wendy L. Marsh-Tootle, Gerald McGwin, Connie L. Kohler, Robert E. Kristofco, Raju V. Datla, and Terry C. Wall (ClinicalTrials.gov number, NCT01109459.) (Invest Ophthalmol Vis Sci. September 2011;52:7160 –7167) DOI:10.1167/iovs.10-6566 (s12)

PURPOSE. To evaluate the efficacy of a physician-targeted website to improve knowledge and self-reported behavior relevant to strabismus and amblyopia (“vision”) in primary care settings. **METHODS.** Eligible providers (filing Medicaid claims for at least eight well-child checks at ages 3 or 4 years, 1 year before study enrollment), randomly assigned to control (chlamydia and blood pressure) or vision groups, accessed four web-based educational modules, programmed to present interactive case vignettes with embedded questions and feedback. Each correct response, assigned a value of $_1$ to a maximum of $_7$, was used to calculate a summary score per provider. Responses from intervention providers (IPs) at baseline and two follow-up points were compared to responses to vision questions, taken at the end of the study, from control providers (CPs). **RESULTS.** Most IPs (57/65) responded at baseline and after the short delay (within 1 hour after baseline for 38 IPs). A subgroup (27 IPs and 42 CPs) completed all vision questions after a long delay averaging 1.8 years. Scores from IPs improved after the short delay (median score, 3 vs. 6; $P = 0.0065$). Compared to CPs, scores from IPs were similar at baseline ($P = 0.6473$) and higher after the short-term ($P < 0.0001$) and long-term ($P < 0.05$) delay. **CONCLUSIONS.** Significant improvements after the short delay demonstrate the efficacy of the website and the potential for accessible, standardized vision education. Although improvements subsided over time, the IPs’ scores did not return to baseline levels and were significantly better compared to CPs tested 1 to 3 years later.

In this article, the authors describe results of their web-based intervention, designed to increase knowledge about “vision” (strabismus, amblyopia, and self-reported preschool vision screening behavior). Their study is especially pertinent considering a recent report from the Office of the Inspector General which reviewed medical records of Medicaid-eligible children, noted low rates of vision screening, and recommended that states begin to “develop education and incentives for providers to encourage complete medical screenings.”

Optical Treatment of Strabismic and Combined Strabismic-Anisometric Amblyopia Writing Committee for the Pediatric Eye Disease Investigator Group: (PEDIG): Susan Cotter, MS, Nicole C. Foster, Jonathan M. Holmes, B. Michele Melia, David K. Wallace, Michael X. Repka, Susanna M. Tamkins, et al. *Ophthalmology* 2012 January; 119: 150-156 (s12)

Prospective, multicenter cohort study to determine visual acuity improvement in children with strabismic and combined strabismic-anisometric amblyopia treated with optical correction alone.

Study included 146 children from 3 to less than 7 years of age, who were treated with spectacles based on a cycloplegic refraction that were worn for the first time at the baseline visit and every nine weeks thereafter until no further improvement in visual acuity could be attained. Ocular alignment was also assessed at each visit. Optical treatment alone in both of these groups resulted in "clinically meaningful" improvement in amblyopic eye visual acuity for most children between 3 and 7 years of age. Study performed by PEDIG study group based at the JAEB Research Center. Tampa Florida, USA

COMMENT: When your patient no longer accepts patching or penalization for treatment you can still treat the amblyopia effectively by giving the full cycloplegic refraction and modifying it at regular intervals (one month per year of age or every six months for older children, and still get some improved vision)

II. VISION SCREENING

Validation of plusoptiX S04 photoscreener as a vision screening tool in children with intellectual disability

Ugurbas SC, Alpay A, Tutar H, et al. *J AAPOS*. 2011 Oct;15(5):476-9 (s12)

The study was conducted to determine the reliability of the plusoptiX S04 in detecting amblyopia risk factors in a cohort of children with intellectual disabilities. Testing was performed by ophthalmology residents instructed in using the plusoptiX S04. The examining ophthalmologist was masked to the screening results. 182 infants and children were included in the study. 58 (32%) were determined to have amblyopia risk factors. The negative predictive value of the plusoptiX S04 was 95.4%, sensitivity was 95%, and specificity was 50%. In 118 subjects (65%) the screening results agreed with the clinical examination with regards to amblyogenic risk factors. The false-negative rate was 5% and the false-positive rate was 50%. 21 of 24 children with manifest strabismus were referred by photoscreening. The three false-negatives were due to intermittent exotropia (n=2), or bilateral superior oblique palsy with straight eyes in primary position (n=1). The median testing time for plusoptiX S04 screening was 6 minutes. 97% of these children could be tested with the device. The authors calculate the monetary savings per child screened with the plusoptiX S04 would be 9\$ versus ophthalmic examinations. PlusoptiX S04 was also successful in

detecting accommodation insufficiency, which has a higher incidence in children with intellectual disability.

Preschool vision testing by health providers in the United States: Findings from the 2006-2007 Medical Expenditure Panel Survey

Kemper AR, Wallace DK, Patel N, and Crews JE J AAPOS. 2011 Oct;15(5):480-3 (s12)

This paper estimates the proportion of children ages 3 through 6 years who have had vision testing on the basis of parental reports collected at the Medical Expenditure Panel Survey (MEPS), a nationally representative dataset. Pooled data from 2006 and 2007 identified a total of 4,237 children. Overall, 64.9% of children ages 3 through 6 years were reported to have ever had vision testing. The proportion with reported previous vision testing increased with each year of age (increasing from 42.9% at age 3 to 79.4% at age 6). There was no statistically significant difference in the rates between non-Hispanic white children and non-Hispanic black children. However, Hispanic children were less likely to have been tested. High family income children were more likely to have reported vision testing than middle or low/poor family income (not confirmed on multivariate analysis). Children with private insurance were more likely to have reported testing than children with no insurance or public insurance. Children with special health care needs were also more likely to have reported vision testing. Children without a usual health care provider are approximately one-half as likely to report previous vision testing. The results of the study are nationally representative but no psychometric data are available to determine what respondents understood "vision testing" to mean.

Modification of Plusoptix referral criteria to enhance sensitivity and specificity during pediatric vision screening

Nathan NR and Donahue SP J AAPOS. 2011 Dec;15(6):551-5 (s12)

This study compared several proposed referral criteria for the plusoptix S08 in detecting amblyopia risk factors defined by AAPOS for preschool vision screening. 144 children were screened and had a comprehensive ophthalmological examination. 59% (85/144) had AAPOS Vision Screening Committee amblyopia risk factors. Use of manufacturer referral criteria yielded 100% sensitivity but 37% specificity. Using the Matta criteria improved this to 99% and 47% respectively. Using the Arthur criteria (based on AAPOS defined criteria), specificity increased to 76% but sensitivity decreased to 89%. By altering the Arthur astigmatism criteria slightly the specificity was increased to 90% while the sensitivity only decreased to 87%. The results of this study must be judged in light of the fact that the study group had a very high percentage of pathology (specifically strabismus) because they were culled from a Pediatric Ophthalmology clinic. Other patient populations may have yielded different results. Also the sensitivity and specificity percentages were massaged to best fit this study group- other patient groups with different profiles might require other best-fit models of referral criteria.

Improving the Rate of Preschool Vision Screening: An Interrupted Time-Series Analysis

Kember AR, Helfrich A, Talbot J, Patel N, Crews JE *Pediatrics* November 2011; 128(5):1279-84. (s12)

This paper details a 6-month quality improvement project in 13 clinics in North Carolina to improve vision screening rates for children 3 through 5 years of age. The researchers trained each clinic in approaches to vision screening and selected champions to provide feedback based on a 3-month baseline chart audit of up to 90 charts in each clinic and then 60 monthly chart audits in each clinic.

Overall, the baseline rate of distance vision testing (92%) and stereopsis testing (80%) was high. By the end of the project, there were increases in both the rate of distance vision testing (97%; $P < .001$) and stereopsis testing (89%; $P < .001$). Initially, there were many different tests used to assess distance visual acuity and some variation in the thresholds used for referral for eye care. Tests were standardized across clinics by the end of the project. The proportion of all children who were untestable was high throughout the project, including 45% among 3-year-olds by the end of the project. Follow-up rescreening was rarely documented. By the end of the project, only 48% of children with an abnormal screen result were documented to be referred. Within each clinic, concerns about the accuracy of testing persisted throughout the project. The authors concluded that they were successful in standardizing vision testing. Even with training, the proportion of untestable children was high. Rates of documented referral were low, which reflects provider concerns about testing accuracy. New strategies are needed to improve testability and ensure timely referral and follow-up after an abnormal vision screen result.

This study highlights many of the difficulties of primary care vision screenings in children. It raises some of the concerns that pediatricians and clinic staff have in evaluating and referring children with potential vision problems.

Congenital eye anomaly surveillance in England and Wales. How effective is the national system? Shah SP, Botting B, Taylor A, Abou-Rayyah Y, *Eye (Lond)*.

October 2011; 25(10):1247-9. (s12)

The authors estimate that only a small fraction of children in England and Wales with congenital anomalies of the eye are being reported to the National Congenital Anomaly System (NCAS) of the Office of National Statistics. This NCAS reporting system calls for ophthalmologists to voluntarily report patients with congenital eye anomalies by submitting a form, and for reporting by regional anomaly registrars. The authors compared children reported to NCAS with children in a data set that was created by active surveillance for congenital anomalies. Many children The NCAS is insensitive to detect changes in frequency of eye anomalies and therefore their risk factors.

The Effect of Developmentally-at-Risk Status on the Reliability of the iScreen® Photorefractive Device in Young Children.

Natalie C. Kerr, M.D., F.A.C.S., Grant Somes, Ph.D., Robert W. Enzenauer, M.D., M.P.H., M.S.S., M.B.A. *Am Orthopt J* Fall 2011; 61: 117 – 123. (s12)

The iScreen® is digital photoscreener that uses an off-axis retinoscopic image to detect the presence of amblyogenic factors. In this study, children deemed to be developmentally-at-risk included those with low birth weight or prematurity, genetic syndromes, seizure disorder, hydrocephalus, cerebral palsy, failure to thrive, head trauma, meningitis, craniosynostosis, and microcephaly. The authors tested 169 children with the iScreen®, including 37 who were developmentally-at-risk, and compared the test results with a clinical evaluation. The sensitivity of the test in the developmentally delayed group was 89%, compared to 84% in the developmentally normal group ($p = 0.53$). The specificity for the delayed group was 100%, compared to 80% for the normal group. Sensitivity of the iScreen® in previous studies has been found to be as high as 92.4%, but subjects in these studies were older and/or developmentally normal. The authors concluded that the presence of developmentally-at-risk factors did not reduce the efficacy of the iScreen®, and that this instrument may be useful in screening patients with developmental delays.

Can a Photoscreener Help Us Remotely Evaluate and Manage Amblyopia?

Noelle S. Matta, C.O., C.R.C., C.O.T., Robert W. Arnold, M.D., Eric L Singman, M.D., Ph.D., David I. Silbert, M.D., F.A.A.P. *Am Orthopt J* Fall 2011; 61: 124 – 127. (s12)

This retrospective study combined the results of best-corrected optotype visual acuity testing with the plusoptiX® S04 photoscreener results in 103 patients with known amblyopia or amblyopia risk factors. Both the visual acuity measurement and the photoscreening were performed by a certified orthoptist or technician. The photoscreening was done with optical correction in place. The purpose was to determine if this combination of acuity and photoscreening tests would be adequate to monitor amblyopia treatment. The plusoptiX® device is an autorefractor, that can also provide some information on eye alignment. Sensitivity and specificity of the plusoptiX® alone, visual acuity alone, and the combination of the two tests were reported. The most effective regimen was the combination of tests, yielding a sensitivity of 97%, and a specificity of 89%. The authors feel that visual acuity testing and plusoptiX® S04 could be used easily and accurately by a lay screener in developing countries, with results being interpreted by a pediatric ophthalmologist using telemedicine.

Smooth pursuit in infants: maturation and the influence of stimulation

Christina Pieh,¹ Frank Proudlock,² Irene Gottlob *Br J Ophthalmol* January 2012;96:73-77 (s12)

Purpose To investigate the development of smooth pursuit in infants and to assess the influence of different stimulus characteristics.

Methods A total of 131 eye movement recordings were obtained from 71 infants between 1 and 18 months of age using infrared photo-oculography. Smooth pursuit eye movements (SPEM) were stimulated using targets of different sizes (1.28 and 4.78 of visual angle) and velocities (7.58/s, 158/s and 308/s).

Results Smooth pursuit maturation peaked between 2 and 6 months of age with smooth pursuit gain showing a steep rise for all stimulus velocities and target sizes within this age range ($p < 0.0001$). Higher stimulus velocities were associated with shorter durations of the longest smooth pursuit ($p < 0.0001$) and higher saccadic frequencies ($p < 0.0001$). A larger stimulus size led to an increased saccadic frequency ($p = 0.035$). Tracking time was highest when the larger stimulus of 4.78 of visual angle was applied ($p = 0.022$) and when it moved at a medium stimulus velocity of 158/s ($p = 0.0002$). The choice between a schematic face and a scrambled face did not influence the quality of the infants' smooth pursuit.

Conclusion SPEM show an intensive maturation between 2 and 6 months of life. By 6 months of age SPEM have already reached an almost adult-like gain of 0.8 or higher. Further maturation is slow and still incomplete by the age of 18 months. Stimulus velocity and size have an important impact on the smooth pursuit quality, which should be considered in smooth pursuit testing in infants

The Bruckner Transillumination Test: Limited Detection of Small Angle Esotropia

Michael Graf, MD, Qasem Alhammouri, MD, Christian Vieregge, Birgit Lorenz
Ophthalmology. December 2011; 118:2594-2509 (s12)

Single-blinded evaluation of the Bruckner test to evaluate its sensitivity in detecting esotropia of 2-10 degrees by interocular asymmetry of the red fundus reflex. The Bruckner red reflex was not suitable for detecting small angles of strabismus. Research performed at the Department of Ophthalmology, Justus-Liebig University, Giessen, Germany

Comment: Lots of "how to" pictures included for those interested in verifying or duplicating the study.

III. Refractive Error

The Child Self-Refracton Study

Results from Urban Chinese Children in Guangzhou

Mingguang He, MD, PhD, Nathan Congdon, MD, MPH, Graeme MacKenzie, Dphil, Yangfa Zeng, MD, et. al. *Ophthalmology*, Volume 118 Number 6, June 2011 (f11)

Type of Study

Cross-sectional study involving Chinese school children from age 12 to 17 years. Children with uncorrected visual acuity in either eye underwent measurement of the logarithm of the minimum angle of resolution (logMar) visual acuity, habitual correction, self-refraction without cycloplegia, auto-refraction with and without cycloplegia and subjective refraction with cycloplegia. All of these modalities were compared.

Study Objectives and Design

The purpose of the study was to compare visual and refractive outcomes between self-refracting spectacles (Adaptive Eye Care, Limited, Oxford, UK) with non-cycloplegic auto-refraction and cycloplegic subjective refraction. The purpose of this study was to determine the value of self-refracting spectacles developed by Adaptive Eyewear in the United Kingdom as part of a global mission to meet the requirements of the World Health Organization to eliminate blindness by the year 2020. This is a joint initiative with the World Health Organization and the International Agency for the Prevention of Blindness.

Ninety-four percent of those children living in Sub-Saharan Africa do not have access to corrective eye wear or to centers to provide corrective eye wear.

Study Objectives and Design

Five-hundred and fifty-four children with an uncorrected visual acuity of less than 6/12 in at least 1 eye underwent measurement of lensometry, self-refraction with special spectacles used and manufactured by Adspecs, Adaptive Eyecare, Limited, Oxford and UK containing 2 fluid filled lenses each consisting of 2 membranes 23 micrometers thick sealed at a circular perimeter with a diameter of 42mm that is secured by a frame.

Spherical refractive power ranging from -6.0 to $+6.0$ diopters is obtainable although no cylindrical correction is possible. The lens may be sealed and the adjustment mechanism removed after the desired power is obtained. All refractions were monitored by the teacher of each participating class. All teachers participated in 1-2 hour training workshops where the protocol was reviewed and practiced.

All of the children participating in this study also underwent auto-refraction with the KR8800, Topcon instrument. Cycloplegic subjective refraction with 1% Cyclopentolate and media and fundus examination including direct and indirect ophthalmoscopy after pupillary dilatation.

Key Study Conclusions

Refraction seems to be less prone to accommodative inaccuracy than non-cycloplegic auto-refraction. Self refraction seems to be very appropriate for use in areas where access to eye care providers is limited. Visual results between self-refraction, auto-refraction with and without cycloplegia and subjective cycloplegic refraction were comparable. *High astigmatism could not be corrected or identified with the adjustable glasses.*

Pearls

This study validates the concept of self-refraction in children 13 to 15 years of age.

Furthermore, it presents a potential solution to the world wide problem of uncorrected refractive error, which currently is the second most common cause of treatable blindness in the world after cataract according to the World Health Organization publication in 2001.

Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children

Nicola S Anstice, BOptom, PhD, John R Phillips, MCOptom, Ph.D.

Ophthalmology Volume 118, Number 6, June 2011 (f11)

Prospective, randomized, paired-eye control, investigator-masked trial with cross-over involving 40 children ages 11 to 14 years of age with a mean spherical equivalent refraction (SER) of -2.71 diopters. This study was done in the Department of Optometry and Vision Science, New Zealand National Eye Centre, The University of Auckland, New Zealand.

Study Objectives and Design

The purpose of the study is to test the efficacy of experimental dual-focus (DF) soft contact lens in reducing myopia progression. The Dual-focus Inhibition of Myopia Evaluation in New Zealand (DIMENZ) study was a prospective, randomized, paired-eye comparison that was conducted with 40 children. The experimental DF soft contact lens was worn in 1 eye while single vision distance contact lens (SVD) was worn in the contralateral eye as control (the concept of paired-eye design).

The aim of this paired-eye design was to measure the efficacy of the dual-focus lens in slowing myopia progression by comparing progression in 2 eyes of each subject. To avoid the potential for any significant anisometropia developing, the lens allocation was crossed over between the eyes at the end of the first 10 months. This paired-eye design with crossover allowed 2 types of analysis to be conducted. In group 1 within subject, between eye comparison using data from periods 1 and 2 separately and group 2 more conventional crossover analysis (within subject, within eye comparison) comparing myopic progression between periods 1 and 2. Both types of analysis have the advantage of using within-subject comparison.

Key Study Conclusions

In 70% of the children studied myopia progression was reduced by 30% or more in the eye wearing the dual-focused lens relative to the eye wearing the single vision distance lens. Similar reductions in myopia progression and axial elongation were also observed with a dual-focused lens during period 2. Accommodation to a target at 40cm was driven through the central distance correction zone of the dual-focused lens.

Visual acuity and contrast sensitivity with dual-focused lens were not significantly different from visual acuity and contrast sensitivity noted with single vision distance soft contact lens. Dual-focused lenses provide normal acuity and contrast sensitivity and allowed accommodation to near targets. Myopia progression and eye elongation were reduced significantly in eyes wearing dual-focused lenses. This study suggests that sustained myopic defocus, even when presented to the retina simultaneously with a clear image, can act to slow myopia progression without compromising visual function.

Pearls

This study represents another attempt to reduce myopia progression utilizing a dual-focus soft contact lens and comparing it in a very sophisticated, well-defined, randomized, paired-eye control, clinical trial with crossover to prevent development of anisometropia. The long-term results of this modality needs to be corroborated by other studies.

The value of the dual-focus soft contact lens may be compromised by its cost and impracticality (concepts of crossover and paired-eye usage). Furthermore, the effect in reduction of myopia needs to be compared to establish modalities such as cycloplegic refraction with the use of progressive bifocals.

Hypo-accommodation responses in hypermetropic infants and children.

Anna M Horwood and Patricia M Riddell *Br J Ophthalmol* February 2011, 95: 231-237 (f11)

Aims Accommodation to overcome hypermetropia is implicated in emmetropisation. This study recorded accommodation responses in a wide range of emmetropising infants and older children with clinically significant hypermetropia to assess

common characteristics and differences.

Methods A PlusoptiXSO4 photorefractor in a laboratory setting was used to collect binocular accommodation data from participants viewing a detailed picture target moving between 33 cm and 2 m. 38 typically developing infants were studied between 6 and 26 weeks of age and were compared with cross-sectional data from children 5-9 y of age with clinically significant hypermetropia (n1/415), corrected fully accommodative strabismus (n1/414) and 27 age-matched controls.

Results: Hypermetropes of all ages under accommodated compared to controls at all distances, whether corrected or not ($p < 0.00001$) and lag related to manifest refraction. Emmetropising infants underaccommodated most in the distance, while the hypermetropic patient groups under-accommodated most for near.

Conclusions Better accommodation for near than distance is demonstrated in those hypermetropic children who go on to emmetropise. This supports the approach of avoiding refractive correction in such children. In contrast, hypermetropic children referred for treatment for reduced distance visual acuity are not likely to habitually accommodate to overcome residual hypermetropia left by an under-correction.

Are We Doing Enough for the Patients With Myopia? A Literature Review.

Parker M; Oconnor AR. Brit Ir Orthopt J. 2011; 8: 3-9. Brit Ir Orthopt J. 2011; 8: 10-16. (s12)

This well-researched review article discusses the current treatments available to slow the progression of myopia and determine whether it is possible to predict future high myopia in which the eye is at increased risk for diseases such as glaucoma, retinal detachment and cataract.

There is no universally effective treatment to "cure" myopia or slow its progression but the authors give a detailed review of its classification and etiology and describe the process of progressive myopia. They discuss the influence of accommodation and near work and state that there is ample evidence against accommodation as the main factor in myopic development. The authors compare optical treatment methods such as bifocals, and progressive addition lenses with pharmaceutical treatment methods including atropine and pirenzapine. [74 REFS]

Spectrum of visual impairment among urban female school students of Surat

Basu M, Das P, Pal R, Kar S, Desai VK, Kavishwar A. Indian J Ophthalmol 2011;59:475-9 (Nov-Dec) (s12)

A population-based cross-sectional study was undertaken among 3002 urban girl students of Surat in Gujarat, India. Overall prevalence of refractive error was found to be 15.22%; myopia affected 91.47%, hyperopia 4.60%, and astigmatism 0.04%. Of all spectacle users, in 29.73% cases the eyesight was not found to be with the best possible corrections. Refractive error was observed to be higher among the general caste (50.98%) and among Muslims (54.05%). Still, among those with problems of eyesight, 75.93% students had good academic performance. **Conclusion** : This study highlighted the load of eye morbidities of adolescent Indian urban girls, and the need for vision screening because a significant percentage of the students with refractive errors were asymptomatic. **Comment** This study provides a birds eye

view of refractive error distribution in a population of students. However some of the statistical analysis is flawed. For example, the study reports that more than 50% of those with refractive errors were Muslim, but this is because the study population was 50% Muslim.

The Influence of Unilateral Uncorrected Astigmatism on Binocular Vision and Fixation Disparity

April Nisson, Maria Nilsson, Scott B Stevenson, Rune L. Brautaset, *Strabismus*, 19(4), 138-141, December 2011 (s12)

Approximately 45% of soft contact lenses wearers have -0.75 D of cylinder or more, yet only 20-28% of patients are fit for toric contact lenses. The others are fit with a lens in their spherical equivalent power, this is the accepted practice for patients with lower amounts of astigmatism. This allows for an easier fit with less chair time and fewer follow ups. This study evaluated how a monocular astigmatic blur affects a patient's binocular visual function. The study found that monocular stigmatism blur in the amounts of -0.75 to -1.25 D did not have a significant effect on binocular visual function concluding that for low amounts of astigmatism, spherical equivalent contact lenses are a viable option.

A Randomized Trial Using Progressive Addition Lenses to Evaluate Theories of Myopia Progression in Children with a High Lag of Accommodation.

David A. Berntsen, Loraine T. Sinnott, Donald O. Mutti, and Karla Zadnik. (ClinicalTrials.gov number, NCT00335049.) (*Invest Ophthalmol Vis Sci*. February 2012; 53:640–649) DOI:10.1167/iovs.11-7769 (s12)

PURPOSE. To compare the effect of wearing, then ceasing to wear, progressive addition lenses (PALs) versus single vision lenses (SVLs) on myopia progression in children with high accommodative lag to evaluate accommodative lag and mechanical tension as theories of myopia progression. **METHODS.** Eighty-five children (age range, 6–11 years) with spherical equivalent (SE) cycloplegic autorefractometry between - 0.75 D and - 4.50 D were randomly assigned to wear SVLs or PALs for 1 year; all children wore SVLs a second year. Children had high accommodative lag and also had near esophoria if their myopia was greater than - 2.25 D SE. The primary outcome after each year was the previous year's change in SE. **RESULTS.** When the children were randomly assigned to SVLs or PALs, the adjusted 1-year changes in SE were - 0.52 D (SVL group) and - 0.35 D (PAL group; treatment effect = 0.18 D; $P = 0.01$). When all children wore SVLs the second year, there was no difference in myopia progression between SVL and former PAL wearers (0.06 D; $P = 0.50$). Accommodative lag was not associated with myopia progression. **CONCLUSIONS.** The statistically significant, but clinically small, PAL effect suggests that treatments aimed at reducing foveal defocus may not be as effective as previously thought in myopic children with high accommodative lag. Finding no evidence of treatment loss after discontinuing PAL wear supports hyperopic defocus-based theories such as accommodative lag; however, not finding an association between accommodative lag and myopia progression is inconsistent with the PAL effect being due to decreased foveal blur during near work.

Although progressive addition lenses (PALs) have generally yielded modest reductions in myopia progression that were not clinically meaningful, subgroup analyses from a previous large, well executed clinical trial found that PALs may be more effective in children with high lag of accommodation. Positive results from PAL treatment in children with high lag of accommodation could provide insight into the mechanism responsible for juvenile-onset myopia progression.

These results confirm the presence of a small but statistically significant treatment effect when children with high accommodative lag wear PALs. Although these results provide additional evidence that PALs slightly reduce myopia progression, the 1-year effect of 0.18 D is not clinically meaningful.

Decrease in Rate of Myopia Progression with a Contact Lens Designed to Reduce Relative Peripheral Hyperopia: One-Year Results

Padmaja Sankaridurg, Brien Holden, Earl Smith III, Thomas Naduvilath, Xiang Chen, Percy Lazon de la Jara, Aldo Martinez, Judy Kwan, Arthur Ho, Kevin Frick, and Jian Ge (*Invest Ophthalmol Vis Sci. December 2011;52:9362–9367*) DOI:10.1167/iovs.11-7260 (s12)

PURPOSE. To determine whether a novel optical treatment using contact lenses to reduce relative peripheral hyperopia can slow the rate of progress of myopia.

METHODS. Chinese children, aged 7 to 14 years, with baseline myopia from sphere -0.75 to -3.50 D and cylinder ≤ 1.00 D, were fitted with novel contact lenses ($n = 45$) and followed up for 12 months, and their progress was compared with that of a group ($n = 40$) matched for age, sex, refractive error, axial

length, and parental myopia wearing normal, single-vision, spherocylindrical spectacles.

RESULTS. On adjusting for parental myopia, sex, age, baseline spherical equivalent (SphE) values, and compliance, the estimated progression in SphE at 12 months was 34% less, at -0.57 D, with the novel contact lenses (95% confidence interval [CI], -0.45 -0.69 D) than at -0.86 D, with spectacle lenses (95% CI, -0.74 to -0.99 D). For an average baseline age of 11.2 years, baseline SphE of -2.10 D, a baseline axial length of 24.6 mm, and 320 days of compliant lens wear, the estimated increase in axial length (AL) was 33% less at 0.27 mm (95% CI, 0.22– 0.32 mm) than at 0.40 mm (95% CI, 0.35– 0.45 mm) for the contact lens and spectacle lens groups, respectively. **CONCLUSIONS.** The 12-month data support the hypothesis that reducing peripheral hyperopia can alter central refractive development and reduce the rate of progress of myopia.

The authors tested the peripheral hyperopia reduction hypothesis using novel contact lenses. These novel contact lenses were designed not only to correct central vision with a central zone that corrected for the central refractive error but also to produce a peripheral hyperopia-reducing effect by greater reduction in the degree of relative peripheral hyperopia, shifting in the effective peripheral treatment zone closer to the visual axis, and a more prevailing consistent stimulus because contact lenses largely remained aligned with the eyes when they moved.

Contact lenses that decrease the relative degree of peripheral hyperopia while maintaining clear vision demonstrate promise as a strategy for reducing myopia progression in children.

Clearly, larger and longer studies are needed using these lens designs to ensure the longevity of these effects on myopia progression and to maximize the benefits for individual children.

Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1% and 0.01% Doses (Atropine for the Treatment of Myopia 2)

Audrey Chia, Wei-Han Chua, Yin-Bun Cheung, Wan-Ling Wong, Anushia Lingam, Alan Fong, *Ophthalmology* 2012 February;119:347-354 (s12)

Follow up study for the treatment of myopia with atropine by means of a single-center double-masked, randomized study involving 400 children aged 6-12 years of age with at least -2.0 diopters of myopia. The children were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1% and 0.01% atropine to be administered once nightly to both eyes for two years. Cycloplegic refraction, axial length, accommodation amplitude, pupil diameter and visual acuity were noted at baseline, 2 weeks and then every four months for two years.

Atropine 0.01% had a negligible effect on accommodation and pupil size and no effect on near visual acuity.

Atropine 0.01% had minimal side effects when compared to atropine 0.5% and 0.1% and retained comparable efficacy in controlling myopic progression.

This study was performed at the Singapore National Eye Center, Singapore

COMMENT: Significant study that shows that 0.01% atropine accomplished the same effect in slowing the progression of myopia as the more conventional concentrations of atropine without the usual side effects. This may be a worthwhile approach for use of atropine in the treatment of amblyopia.

Risk Factors for Astigmatism in Preschool Children: The Multi-Ethnic Pediatric Eye Disease and Baltimore Pediatric Eye Disease Studies.

Roberta McKean- Cowdin, Rohit Varma, Susan Cotter, Kristina Tarczy- Hornoch, Mark S. Borchert, et al. the Joint Writing Committee for the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study Groups, *Ophthalmology* 2011; 118:1974-1981 (October) (s12)

Population-based cross-sectional study of two pediatric eye disease study groups with diverse ethnic and geographic constituency to evaluate risk factors for astigmatism in a sample of school age children.

Hispanic and African-American ancestry, infancy and maternal smoking during infancy are associated with a higher risk of having astigmatism. Other risk factors include myopia and hyperopia.

Study performed in Los Angeles, California and Baltimore, Maryland by respective study groups.

COMMENT: This study selects out geographic and ethnicity bias that is seen in other less diverse studies .

IV. VISUAL IMPAIRMENT

Capturing Children and Young People's Perspectives to Identify the Content for a Novel Vision-Related Quality of Life Instrument

Jugnoo S Rahi, PhD, FRCOphth, Valerie Tadic, MSc, PhD, Sarah Keeley, BSc, et. al.
Ophthalmology Volume 118, Number 5, May 2011 (F11)

Type of Study

Health questionnaire designed by the medical research council center of epidemiology for child health at the University College of London, United Kingdom, with contributions from the Institute of Ophthalmology at the University College of London and the School of Health and Social Studies at the University of Warwick Coventry, United Kingdom.

A stratified random patient sample of children and young people with visual impairment and blindness (Snellen acuity better than 6/18) as the result of any visual disorder, but in the absence of any other significant impairment in 49 children age 10-15 years. The second group included 29 school-based sample of children and young people with visual impairment/blindness age 10-17 years.

Study Objectives and Design

This study describes a child-centered approach to identifying content for a novel, self-reported questionnaire for assessing vision-related quality of life of visually impaired or blind children in young people. After multiple interviews with children in the age group of 10 to 17 years of age, a 47 question draft instrument was developed. The draft instrument included questions and social relations, social acceptance, participation, independence and autonomy, psychological and emotional well being, future aspirations and future fears, functioning at home, school and leisure and treatment of eye condition.

Key Study Conclusions

The questionnaire evaluation demonstrated that a child-centered approach to identifying the content for a

self-report, vision-related quality of life questionnaire is feasible. The authors suggest that this approach is critical to accurately capturing children and young peoples subjective perspectives on the impact of living with impaired vision.

Importance for Pediatric Ophthalmologists

This is the first investigative child-centered approach to identifying content for a self-reported questionnaire assessing vision-related quality of life in visually impaired and blind children.

Pearls

Ophthalmologists are frequently centered on the visually impaired child's visual acuity and refractive error. This study emphasizes the importance of considering social relations, public and family acceptance, participation activities, independence autonomy and preference for developing a self-sustaining and economically rewarding future.

Irlen Colored Overlays Do not Alleviate Reading Difficulties

Ritchie SJ, Della Sala S, McIntosh RD *Pediatrics* October 2011; 128(4): 392-8. (s12)

This prospective study was performed to test the efficacy of Irlen colored overlays for alleviating reading difficulties ostensibly caused by Irlen syndrome, a proposed perceptual disorder with controversial diagnostic status. Sixty-one schoolchildren (aged 7–12 years) with reading difficulties were assessed by an Irlen diagnostician. A within-subject study design to examine differences in reading rate across 3 conditions: using an overlay of a prescribed color; using an overlay of a nonprescribed color; and using no overlay. In a subset of 44 children, all of whom had a diagnosis of Irlen syndrome, a between-group design to test the effects of Irlen colored overlays on a global reading measure was performed. The report detailed that an Irlen diagnostician diagnosed Irlen syndrome in 77% of the poor readers. There was no evidence found for any immediate benefit of Irlen colored overlays as measured by the reading-rate test or the global reading measure. The authors concluded that Irlen colored overlays do not have any demonstrable immediate effect on reading in children with reading difficulties. This paper is important for counseling patients and parents regarding the use of colored lens overlay for treatment of reading disorders. This research provides scientific evidence for the lack of efficacy of this treatment.

The Richard G. Scobee Memorial Lecture: Why Do Children with Down Syndrome Have Subnormal Vision?

Gail V. Morton, C.O. *Am Orthopt J* Fall 2011; 61: 60 – 70. (s12)

The author begins with a review of the history of what has become known as Down syndrome. The common physical and ocular features of the syndrome are also listed. A review of the literature revealed that subnormal visual acuity is common in Down syndrome. VEP studies show that visual acuity improves at a slower rate than normal from birth to approximately age 12 – 24 months, where it levels off and remains subnormal. Many of the cases with reduced visual acuity could not be explained by the most obvious causes of decreased vision in this population. These causes include significant refractive error, amblyopia, nystagmus, hypoaccommodation, cataract, and foveal hypoplasia. In addition, the brain of the Down syndrome patient varies from the age-matched normal. Although similar in shape and size to controls in the neonatal period, after 3 to 5 months of age, brain growth and development slows, stops, and then may even regress in the Down syndrome patient. Many of the documented changes involve the visual cortex. The author hypothesizes that the lack of development and changes in brain morphology over the first two years of life may be the cause of reduced visual acuity potential in these patients.

Prevalence and Causes of Blindness in Children in Vietnam

Hans Limburg, Clare Gilbert, Do Nhu Hon, Nguyen Chi Dung,

Ophthalmology 2012 February; 119: 355-361 (s12)

Population- based study that sampled children from 16 Vietnamese provinces, aged 0-16 including 569 children from 28 blind schools and 28,800 children from the general school age population. Blindness was defined as vision less than 3/60 in the better eye.

16,400 children were blind from all causes with 36% from uncorrected refractive error. The findings of the study reflect improving socioeconomic changes and a decreased infant mortality in Vietnam this includes but is not limited to reduced incidences of retinopathy of prematurity, measles and vitamin A deficiency.

Eye care services for children should now focus on refractive errors, cataract and control of ROP

Study produced from the International Centre for Eye Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

COMMENT: Study involved general and pediatric ophthalmologists.

V NEURO

Editorial: On the Use of “Stem Cells” for Optic Nerve Hypoplasia

Authors

American Association for Pediatric Ophthalmology & Strabismus (AAPOS) Research Committee
Ophthalmology Volume 118, Number 5, May 2011 (f11)

Introduction

This editorial on the use of stem cells for treatment of optic nerve hypoplasia is in response to an explosion of knowledge about the future of cell based therapies for numerous diseases including blinding disease in children. In general these potential therapies are centered around stem cells which can be divided into 3 categories. One, pluripotent embryonic stem cells (PES) derived from human embryos, 2) induced pluripotent stem cells, in which differentiated cells, such as skin fibroblasts, are reprogrammed to differentiate and 3) somatic stem cells (SSC), derived from tissues such as umbilical cord blood and bone marrow. With the exception of limbal stem cell transplantation in corneal opacification, the use of various forms of stem cells, for the treatment of eye disease has only been studied systematically in animal models.

Market based practices coming from China are advertising the use of peripherally administered stem cells to improve vision secondary to optic nerve hypoplasia. The authors go through the highly implausible activation of peripherally administered stem cells passing through the circulation and arriving at the ganglion cells of the retina and then causing the development of visual tracks from the ganglion cell layer through the optic nerve, geniculate body, and then to the cerebral cortex.

The editorial stresses optimism about cell based therapies which will eventually have a role in treating blinding disease of adults in children. The burden of proof, however, remains in those opposing such treatment and the burden of proof should involve

peer-reviewed animal studies which would precede the use of treatment in humans. Once the treatment in humans is recommended, these programs should be followed by a well-designed clinical study with appropriate data and safety monitoring and ultimately randomized clinical trials.

Monocular Elevation Deficiency (“Double Elevator” Palsy): A Cautionary Note.

Brodsky MC, Karlsson V. J Neuro-ophthalmol 2011; (Mar) 31:(1) 56-57. (f11)

In this clinical observation, the authors note that the buckling of the lower eyelid sometimes seen in unilateral monocular elevation deficiency may give a misleading pseudo-hypertropia in the affected eye on downgaze. This is due to asymmetry from the differing position of the eyelids caused by inferior rectus contracture. Good photographs illustrate this point. The authors caution clinicians to assess alignment and binocular function on downgaze in these patients as the misleading appearance could lead to unnecessary neuro-diagnostic evaluation. [4 refs]

Unusual Monocular Pendular Nystagmus in Multiple Sclerosis.

Jasse L, Vighetto A, Vulusic S, Pelisson D, Tilikete C. J Neuro-ophthalmol 2011; (Mar) 31:(1) 38-41. (f11)

The authors of this original contribution (Université Lyon, France), present two unusual cases of monocular pendular nystagmus in patients with multiple sclerosis. Both patients complained of oscillopsia. The nystagmus was not present in primary gaze, but was elicited in the first patient on right gaze, appearing in the abducting eye, which also showed a slight abduction paresis. The movement was pendular, not jerk as seen in classic abducting nystagmus.

In the second patient a mild internuclear ophthalmoplegia was noted on right gaze but the nystagmus appeared in the adducting left eye. Again the movement was pendular, not jerk nystagmus.

Monocular adduction pendular nystagmus has been reported in cases of multiple sclerosis, but only on convergence. These two patients demonstrated monocular pendular nystagmus only on eccentric gaze. The authors show eye movement recordings in both patients. They theorize that abnormal delays in motor feedback loops that control eye stability may explain the pendular nystagmus. However, this does not explain the why the nystagmus is triggered in an eccentric gaze position. Another hypothesis suggests that instability in motor feedback could involve the ocular motor neural integrator, which could lead to triggering of nystagmus with eccentric gaze. Nystagmus occurring during convergence, as in the second case, also supports the concept of instability in motor feedback loops involving the vergence system. Adaptive changes taking place in a neural network affected by demyelination and instability in feedback loops may have triggered monocular eye-position-dependent pendular nystagmus. [11 refs.]

Functional Constriction of the Ocular Motor Field: Description and Preliminary Evaluation of a New Technique to Help distinguish Organic from Nonorganic Visual Field Loss.

Nadeem Ali. J Neuro-ophthalmol 2011; (Jun) 31:(2) 131-134. (f11)

At first glance, this article appears to be about testing visual fields to assess patients with functional vision loss. In fact, it describes a unique method of testing the uniocular field of fixation (motor field) while the patient is seated at the Goldmann perimeter. The perimeter provides the opportunity to switch from a visual (sensory) task using kinetic perimetry in the standard manner, to a motor task (the patient follows the target) without changing the testing environment.

First, a standard visual field is plotted using a V4e target moved in random order toward the center along the eight cardinal meridia while the patient is instructed to view the central spot. The second step begins immediately and the patient is instructed to follow the target from the center as it moves outward. The patient is led to believe that the second step is another visual field task when it is, in fact, a test of ocular motility using the fovea.

The study divided ten patients with normal ocular movements but constricted visual fields into two groups, five with suspected functional vision loss and five with organic field loss. In the organic group the motor field was larger than the visual field, as would be expected. In the non-organic group, the motor field was markedly constricted, similar to the visual field.

The paper discusses the various techniques used to “trick” a patient so that the examiner can prove there is sight in a blind field. The goal of this test is to document additional functional behavior, showing restriction of ocular ductions where none exists.

The author concludes that this test may help identify patients with functional vision loss as the motor field should not be constricted. Patients believe that they are still undergoing a vision test. A skilled perimetrist is needed to perform this test in a continuous and convincing manner. [11 refs]

Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders.

Oystreck DT, Engle EC, Bosley TM. J Neuro-ophthalmol 2011; (Mar) 31:(1) 69-77. (f11)

This State-of-the-Art review provides a comprehensive update of the entities encompassed in the term Congenital Cranial Dysinnervation Disorder (CCDD.) In 2002, the new term was proposed as a substitute for the more general term “congenital fibrosis of the extraocular muscles” (CFEOM) assumed to be caused by a muscle abnormality. Mounting scientific evidence from genetic, neuropathologic and imaging research indicates that a more profound primary neurologic maldevelopment is the cause.

The article describes each entity in detail with its unique ophthalmologic findings and includes the systemic disorders associated with each syndrome as well as its genetic basis. The most well known syndromes described are Duane retraction syndrome, Möbius syndrome, and CFEOM types 1-3. A few entities with normal ocular movement exist, and all of these are closely related.

The authors comment that although some of these syndromes are rare and others occur only in certain parts of the world, with international travel knowing few boundaries, these patients may present in ophthalmology or neurology clinics anywhere in the world. [44 refs]

Pediatric optic neuritis and risk of multiple sclerosis: Meta-analysis of observational Studies

Waldman AT, Stull LB, Galetta SL, Balcer LJ, Liu GT. J AAPOS. 2011 Oct;15(5):441-6 (s12)

The authors performed a systematic review of the literature to determine whether age is a risk factor for unilateral versus bilateral simultaneous optic neuritis in children with idiopathic optic neuritis. 14 studies met the inclusion criteria. Of 223 children with optic neuritis 51% of cases were unilateral. 72% of children <10 displayed bilateral optic neuritis, but bilateral optic neuritis was only seen in 30% of children ≥ 10 years of age. For every 1-year increase in age, the odds of unilateral optic neuritis increased by 25%. Over the duration of the studies, 29% of children whose data was available, converted to MS. Although unilateral optic neuritis cases had a higher likelihood of converting to MS, this relationship was no longer significant after adjusting for age. The presence of MRI abnormalities outside the visual system was associated with an increased risk of MS. For every 1-year increase in age, the odds of developing MS after optic neuritis increased by 32%, adjusted for the presence of MRI lesions. Different methodologies and study designs across different papers limit these findings, however this is expected in a meta-analysis. Non-English articles were excluded. Publication bias must also be considered. Finally 58% of the children did not have available MRI data, but children with and without MRI data showed the same rates of MS development.

Radiation-Induced Ocular Motor Cranial Nerve Palsies in Patients with Pituitary Tumor. Vaphiades MS; Spencer SA; Riley K; Francis C; Deitz L; Kline LB. J Neuro-ophthalmol. Sept 2011; 31: 210-213. (s12)

The onset of diplopia following treatment of pituitary tumor raises concern of tumor recurrence, but in this study the cause of the diplopia was found to be radiation-induced ocular motor nerve neuropathy following radiotherapy for pituitary tumor.

In a group of 181 patients receiving radiation therapy for pituitary tumor, six patients with pituitary adenoma developed diplopia following transsphenoidal resection and subsequent radiation therapy. Five of these developed sixth nerve palsies; 3 unilateral and 2 bilateral, one of whom had a fourth nerve palsy preceding the sixth nerve involvement. The remaining patient had a pupil-involving third nerve palsy.

Five of the 6 patients has growth hormone-secreting tumors and developed acromegaly requiring more aggressive radiation treatment. Multiple radiotherapy sessions may put these patients at risk for radiation damage to the ocular motor nerves. [17 REFS]

Early Diagnosis of Horner Syndrome Using Topical Apraclonidine. Cooper-Knock J; Pepper I; Hodgson T; Sharrack B. J Neuro-ophthalmol. Sept 2011; 31: 214-216. (s12)

In older patients, physiological anisocoria and involitional ptosis can mimic Horner Syndrome so confirmation of the diagnosis of HS with early recognition and intervention can be lifesaving. Traditionally this diagnosis has been made with topical cocaine drops but increasingly apraclonidine has been reported as an alternative agent. The response to this adrenergic drug is a reversal of the anisocoria after bilateral instillation of the drops. However, some questions persisted regarding its sensitivity in the acute stage of HS.

The authors describe a 43-year-old man who presented with a 3-hour history of blurred vision and neck ache. He had been involved in a motor vehicle accident 4 days previously. HS secondary to a carotid dissection was diagnosed when the anisocoria tested positive after administration of apraclonidine. This suggests that the test is sensitive in the acute setting. [22 REFS]

Clinical Course of Patients with Ophthalmoplegia Caused by Radiographically Detectable Brainstem Demyelination Occurring as a Clinically Isolated Demyelinating Syndrome. Pula JH; Brock K; Kattah JC. J Neuro-ophthalmol. Sept 2011; 31: 234-238. (s12)

This study reviewed 327 consecutive cases presenting to the neuro-ophthalmology clinic with diplopia as the first manifestation of a clinically isolated demyelinating syndrome.

Ten patients met the criteria. Ocular movement disorders included sixth nerve palsies (6), internuclear ophthalmoplegia (3), and one-and-a-half syndrome (1). None had skew deviation. Treatment was given according to the clinical course of each patient.

The course and recovery in these patients was recorded over 43.9 months (median 28; range 10-122 months.) There was a high rate of improvement in all patients. The authors recommend prismatic correction during this recover period with well-documented stability before considering surgical correction of any residual ocular deviation. [19 REFS]

Use of the Cogan Lid Twitch to Identify Myasthenia Gravis. Singman EL; Matta NS; Silbert DI. J Neuro-ophthalmol. Sept 2011; 31: 239-240. (s12)

In this prospective pilot study, 117 randomly-selected adult patients referred to the neuro-ophthalmology service were evaluated. The purpose of the study was to evaluate the usefulness of the Cogan Lid Twitch test in identifying myasthenia gravis without preselection bias. In a previous paper by van Stavern, the CLT test was used in the differential diagnosis of ptosis to determine whether it was due to MG or not. Results of that study found that a positive CLT was not particularly common in patients with ptosis.

The authors describe how to perform the Cogan Lid Twitch test and discuss the innervation of the eyelids in ptosis. They also discuss eyelid retraction in dysthyroid patients. MG patients display a greater frequency of antithyroid antibodies than the general population.

The authors recommend further study to evaluate whether the presence of CLT in patients with MG varies depending on the concurrent presence of antithyroid antibodies and to observe the timing of the diagnosis of MG with the appearance of a positive CLT. This should be tested on patients with and without ptosis. They conclude that the CLT test appears to be a sensitive (75 percent) and specific (99 percent) test for the diagnosis of MG. [7 REFS]

Bilateral Pupil-Sparing Third Nerve Palsies as the Presenting Sign of Multiple Sclerosis.

Seery LS; Hurliman E; Erie JC; Leavitt JA. J Neuro-ophthalmol. Sept 2011; 31: 241-243. (s12)

The authors present a rare case of bilateral pupil-sparing involvement of the third cranial nerves as a presenting sign of demyelinating disease.

A 30-year-old man presented with a 3-week history of blurred vision and difficulty tracking objects, especially downward. He also noted slight ptosis of his left upper eyelid. His family history was significant for a sister and a great-great aunt with MS. His medical history was significant for alcohol abuse.

MRI with FLAIR documented midbrain fascicular lesions affecting both third nerves. Despite profound bilateral inferior rectus dysfunction, both pupils were spared. The cranial neuropathies and MRI abnormalities resolved following treatment with intravenous methylprednisolone. [11 REFS]

Periodic Unilateral Eyelid Retraction in a Pediatric Patient.

Gandhi NG; Rogers GM; Kardon RH; Allen RC. J Neuro-ophthalmol. Dec 2011; 31: 350-352. (s12)

The family of an 11-year-old girl reported right upper eyelid retraction since birth. The eyelid closed normally during sleep and no change or variability in eyelid position was noted over time while awake or sleeping.

A 2.5mm palpebral fissure difference was present on examination. Ductions, versions and pupillary responses were normal. A right levator recession was planned. After induction of general anesthesia, and before administration of local anesthetic, the patient displayed periodic spasms of right upper eyelid retraction occurring in exactly 48-second intervals. No fasciculations, change in pupil size or eye position was noted during these episodes. The left eye was unaffected. This phenomenon was observed for 10 minutes.

At a post-operative visit 3.5 months later, improvement in right upper eyelid position was seen. No cyclic behavior was noted. It was proposed that this phenomenon was similar to cyclic oculomotor palsy, but is distinct from all previously described cases. There was no involvement of the extraocular muscles or the intrinsic muscles of the affected eye. The possibility that was an effect of inhaled sevoflurane was considered. [19 REFS]

Neuro-Ophthalmology and Pregnancy: What does a Neuro-Ophthalmologist Need to Know? [Jacobsen Lecture] Digre KB. *J Neuro-ophthalmol.* Dec 2011; 31: 381-387. (s12)

Pregnancy offers a unique condition in clinical medicine as both the mother and her developing child must be considered in any treatment plan. In her memorial lecture honoring Dan Jacobson, Dr Digre gives a comprehensive review of the normal changes in pregnancy that affect the eye and the brain and also discusses neuro-ophthalmic conditions and their evaluation and treatment during pregnancy and the post-partum period.

Common problems include vascular complications, papilledema, pre-eclampsia and eclampsia, and cranial neuropathy. The most common cranial neuropathy is Bell palsy, two-thirds of which occur in the third trimester. Sixth and fourth nerve involvement are the next most common complication. Horner syndrome has been reported following epidural analgesia. Management of any neuro-ophthalmic complications in pregnancy follows the edict that whatever is best for the mother generally will be best for the baby too. [90 REFS]

Clinical characteristics of optic neuritis in Taiwanese children.

Sun MH, Wang HS, Chen KJ, Su WW, et al *Eye (Lond)*. November 2011;25(11):1457-64. (s12)

The authors documented the clinical characteristics of optic neuritis in a cohort of 24 children (38 eyes) at a Taiwanese Hospital. The study entailed a retrospective review of medical records over a ten year period.

Overall, 14 patients (58.3%) were female and 10 patients (41.7%) were male. 14 patients (58.3%) had bilateral involvement, and 10 patients (41.7%) had unilateral involvement. Out of 38 eyes, 24 (63.2%) had disc swelling. Out of 24 patients, 21 (87.5%) underwent intravenous steroid therapy followed by an oral taper. Out of 24 patients, 20 (83.3%) achieved final visual acuity (VA) of 20/40 or better. Poor visual acuity at presentation was not predictive of poor final visual acuity. However, pale disc at presentation ($P=0.002$) and age older than 10 years ($P=0.012$) were correlated with a final visual acuity of less than 20/40. Five patients were diagnosed with acute disseminated encephalomyelitis (21%), and three patients were diagnosed with multiple sclerosis (12.5%).

The authors conclude that although visual recovery from optic neuritis is largely favorable, pale disc and older age (>10 years) at presentations are associated with a poor visual outcome.

Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus.

Strupp M, Thurtell MJ, Shaikh AG, Brandt T, Zee DS, Leigh RJ.

J Neurol. 2011 Apr 2. (s12)

We review current pharmacological treatments for peripheral and central vestibular disorders, and ocular motor disorders that impair vision, especially pathological nystagmus. The

prerequisites for successful pharmacotherapy of vertigo, dizziness, and abnormal eye movements are the "4 D's": correct diagnosis, correct drug, appropriate dosage, and sufficient duration. There are seven groups of drugs (the "7 A's") that can be used: antiemetics; anti-inflammatory, anti-Ménière's, and anti-migrainous medications; anti-depressants, anti-convulsants, and aminopyridines. A recovery from acute vestibular neuritis can be promoted by treatment with oral corticosteroids. Betahistine may reduce the frequency of attacks of Ménière's disease. The aminopyridines constitute a novel treatment approach for downbeat and upbeat nystagmus, as well as episodic ataxia type 2 (EA 2); these drugs may restore normal "pacemaker" activity to the Purkinje cells that govern vestibular and cerebellar nuclei. A limited number of trials indicate that baclofen improves periodic alternating nystagmus, and that gabapentin and memantine improve acquired pendular and infantile (congenital) nystagmus. Preliminary reports suggest suppression of square-wave saccadic intrusions by memantine, and ocular flutter by beta-blockers. Thus, although progress has been made in the treatment of vestibular neuritis, some forms of pathological nystagmus, and EA 2, controlled, masked trials are still needed to evaluate treatments for many vestibular and ocular motor disorders, including betahistine for Ménière's disease, oxcarbazepine for vestibular paroxysmia, or metoprolol for vestibular migraine.

Comment: There are many pharmacologic options for treating nystagmus. Clinical trials are needed. Nystagmus is a difficult issue for many pediatric patients; families can be told that many medical treatments are being examined for efficacy.

Bilateral Abducens Nerve Palsy by Compression from Bilateral Anterior Inferior Cerebellar Artery. Taniguchi A; Yuichiro I; Kobayashi H. J Neurol Dec 2011; 258: 2271-2273. (s12)

Bilateral cases of isolated abducens palsy are rare. Depending on the study, the main causes are trauma, vascular lesions and brain tumor. Taniguchi et al present a case of a 75-year-old man with complete right, and moderate left abducens palsies. There were no abnormalities in pupillary function or vertical eye movements. MR imaging with contrast showed no abnormalities. MR angiography (see great figure) revealed dolichoectasia (elongation and distension with displacement) of the basilar and left vertebral arteries. This caused stretching of the right abducens nerve by the anterior inferior cerebellar artery (AICA) and compression of the left abducens nerve as it exited by the left AICA.

An anatomical study by Marinkovic in 1994 showed that the ventral surface of the abducens nerve was crossed by the AICA in 75 percent of autopsied brains and almost all nerves were in contact with the artery. [18 REFS]

The Tullio Phenomenon: A Neurologically Neglected Presentation. Kaski D; Davies R; Luxon L; Bronstein AM; Rudge P. J Neurol Jan 2012; 259: 4-21. (s12)

The Tullio phenomenon refers to sound-induced disequilibrium or oscillopsia. Patients may describe vertigo, postural sway, and tilting or movement of the environment in response to a sudden loud noise or change in pressure. In this review article, the authors describe the phenomenon, its clinical presentation and management. They examined 28 cases. The

condition was particularly bothersome for several patients who played wind instruments as both sound, and pressure from the Valsalva maneuver triggered the symptoms.

High resolution CT scanning has identified dehiscence of the superior semicircular canal on the affected side as the cause. Ocular symptoms are common. Patients often describe tilting of the environment, and oscillopsia, usually vertical. One patient could hear her eyes moving! Objective findings include horizontal and torsional nystagmus, downbeat nystagmus, skew deviation, and ocular tilt reaction.

The authors suggest observing eye movements during exposure to a loud sound stimulus, while performing a Valsalva maneuver, or by applying pressure to a closed external auditory canal (Hennebert's sign) in anyone describing these symptoms. [68 REFS]

Can Fast-Component of Nystagmus on Caloric Vestibulo-Ocular Responses Predict Emergence from Vegetative State in ICU? Weiss N; Tadie J-M; Faugeras F; Diehl J-L; Fagon J-I; Guerot E. *J Neurol* Jan 2012; 259: 70-76. (s12)

Vegetative state (VS) is characterized as a wakeful unconscious state. The early detection in the ICU of signs of consciousness is crucial for prognosis and for end-of-life decisions. Neurological assessment can be difficult in the ICU setting where the patient may have orotracheal intubation or motor impairment. Technology such as fMRI, EEG, or PET scans could provide evidence of conscious thought but these tests are cumbersome to perform in mechanically-ventilated, non-transportable, critically ill patients.

The purpose of this study was to determine if bedside caloric VOR responses could predict recovery of consciousness in VS patients. Twenty-six severely brain injured patients underwent cold caloric stimulation of the external auditory canal and the VOR responses were observed. Thirteen patients ultimately recovered consciousness. All 13 demonstrated a slow-component nystagmus response during VOR testing, as did 11 in the group that remained unconscious. However, all 13 that recovered also showed a fast-component of nystagmus compared to only one of the 11 that remained unconscious.

Preliminary data suggest that the presence of a fast-component at VOR testing could predict accurately, during the acute phase in the ICU, which clinical VS patients will emerge from unconsciousness. [24 REFS]

Characteristics and appearance of the normal optic nerve head in 6-year-old children Chameen Samarawickrama, Amy Pai, Yasser Tariq, Paul R Healey, et al *Br J Ophthalmol* January 2012;96:68- 72 (s12)

Aim To document planimetric measures of normal optic nerve head parameters in 6-year-old children and to report prevalence and associations of common optic nerve signs.

Methods The Sydney Childhood Eye Study examined 1765 children aged 6 years. Complete retinal photographs were available for 1225 participants, captured using a digital camera. Optical coherence tomography optic-disc measurements were acquired using the 'fast' optic-disc protocol. Statistical analyses were conducted using SAS version 9.1.3.

Results The mean (95% CIs) planimetric optic-disc area was 2.29 mm² (2.27 to 2.32), mean cup area 0.48 mm² (0.47 to 0.50), mean vertical disc diameter 1.81 mm (1.80 to 1.82) and mean vertical cup diameter 0.72 mm (0.71 to 0.73), resulting in a mean vertical cup/disc ratio of 0.40 (0.39 to 0.40). Similarities existed between vertical, horizontal and area cup/disc ratios ($p>0.05$) measured by planimetry and optical coherence tomography, but only for vertical disc diameters between 1.75 and 1.96 mm. Visible lamina cribrosa pores were present in 4.9%. This sign was associated with larger optic nerve parameters. The prevalence of optic disc tilt and cyclotorsion was 1.6% and 8.7%, respectively, and the prevalence of **a**- and **b**-peripapillary atrophy was 43.3% and 20.2%, respectively. Neither sign was associated with myopia, after adjusting for age, sex and ethnicity, although eyes with **b**-peripapillary atrophy had a longer mean axial length ($p=0.04$). Cilioretinal arteries were present in 27% and tended to be located temporally.

Conclusions The mean vertical cup/disc ratio was 0.4 in this 6-year-old sample. Planimetric optic nerve head measures and population prevalence findings for optic disc signs in this population could be regarded as normative data for ophthalmologists in clinical settings

Comments: Very good population based study. The other good part the age factor will not affect the disc parameter, as they have taken only one age group of patients. There are no other confounding variables as well.

Electrophysical Evaluation of Retinal Function in Children Receiving

Vigabatrin Medication Ulrika Kjellstrom, Sten Andreasson, Vesna Ponjavic, Journal of Pediatric Ophthalmology and Strabismus November 2011; 48: 357-365 (s12)

Vigabatrin is an antiepileptic drug that is used as an add-on therapy in patients with seizures that are resistance to other drugs. Vigabatrin has also been found to be effective in the management of infantile spasms. Patients on vigabatrin treatment had full field electroretinography (ffERG) and the entire group showed reduced amplitudes for the b-waves of the isolated rod response, the combined rod-cone response and the 30Hz flicker cone response. There was also a prolonged b-wave implicit time for the 30 Hz flicker cone response and the a-wave implicit time for the combined rod-cone response. Use of ffERG helps to confirm that children are also sensitive to the retinal side effects of vigabatrin which has been difficult to establish with visual field testing as children cannot cooperate with visual field as well as adults. Therefore, routine ophthalmic follow-up for children on vigabatrin is just as important as it is for adults.

Initial Visual Field as a Predictor of Recurrence and Postoperative Visual Outcome in Children with Craniopharyngioma

Min Joung Lee, Jeong-Min Hwang, Journal of Pediatric Ophthalmology and Strabismus January 2012; 49: 38-42 (s12)

Craniopharyngioma is the most frequent nonglial suprasellar tumor in Children. Younger age and visual symptoms at presentation are known to be related to a poorer visual outcome. The parameters previously studied relate to preoperative and postoperative visual acuity, however, there has been no studies related to visual field defects as a predictor of recurrence and postoperative visual outcomes in children with craniopharyngioma. Visual field defects include bitemporal hemianopsia, unilateral hemifield defects, homonymous

defect, unilateral loss of central visual function, anterior junction syndrome and inferonasal island. A retrospective study of 32 patients found that children with a normal visual field at presentation were more likely to preserve better vision in both eyes and a normal visual field postoperatively. Regardless of tumor size, preoperative visual field was found to be a prognostic indicator of postoperative visual field and recurrence; therefore, when an abnormal preoperative visual field is found, more meticulous control of tumor during surgery should be undertaken and physicians should be aware of the higher rate of recurrence so they can coordinate follow up care accordingly.

Magnetic resonance diffusion tensor imaging (MRDTI) of the optic nerve and optic radiations at 3T in children with neurofibromatosis type I (NF-1)

Christopher G. Filippi, Aaron Bos, Joshua P. Nickerson, Michael B. Salmela, Chris J. Koski and Keith A. Cauley, *Pediatric Radiology*. February 2012;42(2):168-174 (s12)

Optic pathway glioma (OPG) is a characteristic hallmark of neurofibromatosis type I (NF-I). The National Institutes of Health NF-I Optic Nerve Task Force recommends ophthalmological examination of children newly diagnosed with NF-I along with yearly ophthalmological exams until age 6 followed by longer intervals after age 6. Neuroimaging is recommended only when clinically indicated. However, optic pathway gliomas might be present prior to onset of clinical symptoms, and vision loss can be difficult to accurately detect in young children. Thus, the role of neuroimaging in children with NF-I is sometimes considered controversial despite these guidelines. The inability to differentiate or predict progressive from non-progressive optic pathway tumors in children with NF-I remains problematic even with increasingly sophisticated MR imaging.

This was a prospective series in 9 children with NF-1 (7 boys, 2 girls, average age 7.8 years, range 3-17 years) without any clinical findings of optic pathway glioma or visual symptoms. Comparison was made with 44 age matched controls. Two NF-I patients had bilateral optic nerve gliomas, three had chiasmatic gliomas and four had unidentified neurofibromatosis objects (UNOs) along the optic nerve pathways. The authors concluded that MRDTI can evaluate the optic pathways in children with NF-I and that statistically significant abnormalities were detected. Further longitudinal research is needed to determine whether abnormalities detected on MRDTI correlate quantitatively with long-term clinical outcome or can predict tumor progression tumor or UNO development.

Paediatric MRI under sedation: is it necessary? What is the evidence for the alternatives?

Andrea D. Edwards and Owen J. Arthurs. *Pediatric Radiology*. November 2011;41(11):1353-1364 (s12)

High-quality imaging is increasingly being used to aid diagnosis and treatment options and to monitor treatment response. Cross-sectional imaging such as CT and MRI has seen a huge increase in demand over recent years. However, despite the impressive speed of CT, it is inherently limited in pediatric imaging by the ionizing radiation dose administered to the patient.

MRI provides excellent image quality, superior soft-tissue resolution and does not impart ionizing radiation, and is therefore well-suited for pediatric patients. MR uses rapidly changing magnetic field gradients and electromagnetic radiofrequency pulses to provide high-

resolution images predominantly based on proton spin characteristics within the body. MR is now the imaging modality of choice in many pediatric circumstances.

To achieve high-quality diagnostic images during MRI examinations, small children need to lie still to avoid movement artifact. Thus, MRI of infants is frequently carried out under sedation or general anesthesia. However, this is not without risk and expense. Many other techniques are available for preparing children for MRI, which have not been fully evaluated. Here, the authors evaluate the advantages and disadvantages of sedation and anesthesia for MRI. They then describe various alternatives, including neonatal comforting techniques, sleep manipulation, and appropriate adaptation of the physical environment. Factors which influence choice of imaging preparation are discussed. The choice of approach to pediatric MRI is multi-factorial, with limited scientific evidence for many of the current approaches. Further investigation is encouraged on an individual or study basis to compare the alternatives to standard sedation and anesthesia for pediatric imaging.

Radiology update in neuro-ophthalmology Pula, John H.; Daily, Jennifer; DeSanto, Jeffrey .Current Opinion in Ophthalmology. November 2011;22(6):451-457 (s12)

Radiologic imaging is indispensable for the diagnosis and management of many neuro-ophthalmologic conditions. Many recent advances mean there is a constant stream of new information for the clinician. Functional MRI, diffusion tensor MRI, magnetization transfer imaging, and magnetic resonance spectroscopy are examples of nonstandard radiographic techniques, which have expanded the knowledge of neuro-ophthalmologic conditions. Studies using conventional MRI have also led to advances in understanding optic neuropathies, the ocular motor system, pseudotumor cerebri, posterior reversible encephalopathy syndrome and migraine.

This article discusses recent radiologic advances relevant to neuro-ophthalmology. It also compares various imaging modalities for different conditions along with the advantages and disadvantages. Although practicing clinicians are not expected to possess the knowledge of a radiologist with regards to imaging modalities used in neuro-ophthalmologic conditions, it is important that they remain up to date on both conventional and nonconventional radiographic techniques.

Review of the limits and advantages of imaging allows the ophthalmologist to make informed choices about when to order imaging, which type of scan to order, and how to interpret the results.

Cerebral venous sinus system and stenting in pseudotumor cerebri Dykhuizen, Matthew J.; Hall, Jennifer. Current Opinion in Ophthalmology. November 2011;22(6):458-462 (s12)

The pathogenesis and treatment paradigm for idiopathic intracranial hypertension (IIH) is controversial. This article reviews the current literature on a relatively new and controversial therapeutic approach for a subset of IIH patients: dural venous sinus stenting. Currently there is no consensus whether transverse sinus stenosis is a primary or secondary process relative to raised intracranial pressure (ICP). Transverse sinus stenosis is seen in the majority of patients with IIH and appears to play some role in the disease process.

Up to 18–22% of IIH cases are nonresponsive to maximal medical therapy and weight-loss regimens. Often, patients who have intractable headaches or vision loss undergo surgical procedures such as cerebrospinal fluid (CSF) shunting procedures or optic nerve sheath fenestrations (ONSF). However, what if these measures also fail? Recent case reports and case series that looked at patients treated with venous sinus stents show encouraging results in decreasing ICP and its related signs and symptoms. Venous sinus stenting could be a treatment option for many patients with IIH. Exactly where venous sinus stenting fits into the treatment paradigm is unclear, but many currently advocate stenting for refractory cases or cases in which a known high-pressure gradient exists across a transverse sinus stenosis. Venous stenting may be the last option or an alternative to more traditional surgical options for many patients. Additional work, preferably controlled prospective studies, are needed to evaluate its safety and efficacy. Finally, venous sinus stenting should be compared in head-to-head trials with ONSF and CSF diversion surgeries.

Neuroimaging yield in isolated Horner syndrome Al-Moosa, Ashref; Eggenberger, Eric. *Current Opinion in Ophthalmology*. November 2011;22(6);468-471 (s12)

This article reviews the yield of imaging in isolated cases of Horner syndrome in order to better understand if and when imaging will ultimately be beneficial. Imaging in Horner syndrome is commonly performed, however, imaging yield in isolated Horner syndrome has not been extensively studied. A few studies have tried to look into the yield of imaging in such cases and derive conclusions from their findings. With limited evidence-based data, the general recommendation for evaluation in pediatric cases of isolated Horner syndrome is physical examination, urinary catecholamines and imaging. In adults, it may be possible to hold-off on imaging of isolated Horner syndrome especially if evidence exists establishing chronic duration.

VI. NYSTAGMUS

Effects of Topical Brinzolamide on Infantile Nystagmus Syndrome Waveforms: Eyedrops for Nystagmus. Dell'Osso LF; Hertle RW; Leigh RJ; Jacobs JB; King S; Yaniglos S. *J Neuro-ophthalmol*. Sept 2011; 31: 228-233. (s12)

Therapeutic methods to damp the oscillations in infantile nystagmus waveforms and improve foveation include optical, surgical, and pharmaceutical approaches. Several of these authors previously studied the effects of systemic acetazolamide on the waveforms in one patient and compared these effects with those of contact lenses and induced convergence. They also discuss the estimated effects of tenotomy and reattachment eye muscle surgery.

In this study, the same patient was reevaluated after the administration of topical brinzolamide eye drops. The results provide evidence for the hypothesis that a topical eyedrop-based therapy may be effective in infantile nystagmus.

The results with brinzolamide showed better effects than other treatment methods except for convergence. The latter provided a greater improvement in peak visual acuity. Brinzolamide

eye drops may provide a viable addition to other treatment modalities and offer positive therapeutic effects that can avoid surgery or the side effects of systemic medications. [37 REFS]

Comparison of 10-mg Doses of 4-Aminopyridine and 3, 4-Diaminopyridine for the Treatment of Downbeat Nystagmus. Kalla R; Spiegel R; Claassen J; Bardins S; Hahn A; Schneider E; Rettinger N; Glasauer S; Brandt T; Strupp M. *J Neuroophthalmol.* Dec 2011; 31: 320-325. (s12)

The effects of equivalent doses of 4-aminopyridine and 3, 4-diaminopyridine on the slow-phase velocity of downbeat nystagmus were compared in this prospective, double-blind, crossover study. Aminopyridines increase the resting activity and excitability of the Purkinje cells in the cerebellar flocculus.

Eight patients with DBN were included in the study. Etiologies included cerebellar degeneration (1), bilateral vestibulopathy (1), Chiari I malformation with cerebellar ataxia (1) and cryptogenic cerebellar ataxia (4).

Patients were given a single 10 mg capsule of either 4-AP or 3, 4-DAP. Six days elapsed and the opposite substance was given. 3-D videoculography recorded eye position with patients seated upright before, 45 and 90 minutes after each drug administration.

With the exception of mild transient parasthesias in all 8 patients, no other side effects were noted. Results showed that 10 mg doses of 4-AP gave a more pronounced decrease in the slow-phase velocity of DBN than equivalent doses of 3, 4-DAP. The paper discusses the mechanisms causing DBN and the pharmacokinetics of aminopyridines. [36 REFS]

Improvement in Visual Acuity Following Surgery for Correction of Head Posture in infantile Nystagmus Syndrome

Anand Kumar, Shashikant Shetty, P. Vijayalakshmi, Richard W. Hertle, *Journal of Pediatric Ophthalmology and Strabismus* November 2011, 48: 341-346 (s12)

Infantile Nystagmus Syndrome (INS) is an ocular motility disorder occurring at birth or early infancy. Clinically it is characterized by horizontal, jerky, involuntary oscillations of the eyes. Approximately 20-70% of patients with INS have an abnormal head position which allows the child to improve vision or visual function. Improvement of abnormal head position has been reported to improve visual acuity and/or function. A prospective non-randomized, interventional study was conducted on 28 patients who underwent the Anderson-Kestenbaum procedure or the modified Anderson procedure. Best corrected vision was checked before surgery and one month after surgical intervention. An improvement in visual acuity was noted in this study

Neural Circuit Involved in Idiopathic Infantile Nystagmus Syndrome Based on fMRI

Lawrence E. Leguire, Nasser H Kashou, Nick Fogt et. Al Journal of Pediatric Ophthalmology and Strabismus November 2011; 48: 347-356 (s12)

Infantile Nystagmus Syndrome (INS) describes periodic involuntary ocular oscillations detected within the first six months of life. The current study uses functional magnetic resonance imaging (fMRI) to localize the anatomical correlates for INS. fMRI compares two states – off and on, when neural activity is minimal and when its maximal, respectively. By linking the two states, the brain site(s) related to the INS was revealed. The preliminary data reveal that the declive of the cerebellum is related to the nystagmus associated with INS.

Nystagmus and Reduced Visual Acuity Secondary to Drug Exposure in Utero: Long Term Follow-up

Manish Gupta, Glas; Alan O. Mulvihill, Gerassimos Lascaratos, et. Al Journal of Pediatric Ophthalmology and Strabismus January 2012; 49: 58-63 (s12)

Drug use during pregnancy is known to be associated with congenital abnormalities in the developing embryo and fetus. The study describes 25 children with visual system problems secondary to drug exposure in utero. All children with nystagmus and a history of maternal opiate and/or benzodiazepine use in pregnancy were studied. Patients who may have other forms of nystagmus were excluded from the study. The study demonstrated that nystagmus secondary to opiate/benzodiazepine use exposure in utero does not resolve, but may improve in some. The study also found decreased vision in children exposed to opiates and benzodiazepines. This is likely due to central nervous system insult rather than an abnormality in the visual system.

Reading Strategies in Infantile Nystagmus Syndrome.

Mervyn G. Thomas, Irene Gottlob, Rebecca J. McLean, Gail Maconachie, Anil Kumar, and Frank A. Proudlock (Invest Ophthalmol Vis Sci. October 2011;52:8156–8165)
DOI:10.1167/iovs.10-6645. (s12)

PURPOSE. The adaptive strategies adopted by individuals with infantile nystagmus syndrome (INS) during reading are not clearly understood. Eye movement recordings were used to identify ocular motor strategies used by patients with INS during reading. **METHODS.** Eye movements were recorded at 500 Hz in 25 volunteers with INS and 7 controls when reading paragraphs of

text centered at horizontal gaze angles of -20°, -10°, 0°, 10°, and 20°. At each location, reading speeds were measured, along with logMAR visual acuity and nystagmus during gazeholding.

Adaptive strategies were identified from slow and quick-phase patterns in the nystagmus waveform. **RESULTS.** Median reading speeds were 204.3 words per minute in individuals with INS and 273.6 words per minute in controls. Adaptive strategies included (1)

suppression of corrective quick phases allowing involuntary slow phases to achieve the desired goal, (2) voluntarily changing the character of the involuntary slow phases using quick phases, and (3) correction of involuntary slow phases using quick phases. Several individuals with INS read

more rapidly than healthy control volunteers. **CONCLUSIONS.** These findings demonstrate that volunteers with INS learn to manipulate their nystagmus using a range of strategies to acquire visual information from the text. These strategies include taking advantage of the stereotypical and periodic nature of involuntary eye movements to allow the involuntary eye movements to achieve the desired goal. The versatility of these adaptations yields reading speeds in those with

nystagmus that are often much better than might be expected, given the degree of foveal and ocular motor deficits.

The authors investigated reading strategies in 25 volunteers with INS (10 albinotic and 15 nonalbinotic or unassociated) and 7 healthy controls while they read paragraphs of text. They compared reading at five different gaze angles (-20°, -10°, 0°, 10°, and 20°), to induce a variety of nystagmus waveforms, and at two distances (33 and 120 cm), since nystagmus amplitude is known to decrease with convergence in individuals with good binocularity. For each reading task they also compared visual acuity and the nystagmus characteristics during gaze-holding.

This study provides insights into adaptation to involuntary eye movement disorders caused through pathology. It is demonstrated that in the ocular motor system, humans take advantage of involuntary movement to achieved desired goals, presumably through prior learning of the expected behavior of their eyes through skills that may have been acquired over many years during visual development.

VII. ROP

Masked trial of topical anesthesia for retinopathy of prematurity eye examinations.

Cogen MS, Parker JS, Sleep TE, et al. J AAPOS February 2011;15:45-48. (f11)

This study was randomized, masked and placebo-controlled. The study observed the effects of proparacaine 0.5% on pain and corneal clarity in premature infants undergoing eye examinations for ROP. Topical anesthetic was used for 22 examinations and saline solution for 17. The PIPP (premature infant pain profile) scale was lower but did not reach statistical significance, when topical anesthetic was used for the overall exam and during scleral depression. There was no difference in corneal clarity. A larger sample of patients is needed to make definite conclusions. Corneal clarity was measured subjectively. Topical anesthetic can blunt the bradycardia induced by scleral depression. This may have falsely elevated PIPP scores in the anesthetized group (masking a larger pain difference between the groups), because heart rate elevation is a pain indicator on the PIPP scale.

Predictive Value of Pre-plus Disease in Retinopathy of Prematurity.

David K. Wallace, MD, MPH; Sharon F. Freedman, MD; M. E. Hartnett, MD; Graham E. Quinn, MD, MSCE. Arch Ophthalmol. May 2011;129(5):591-596. (f11)

The goal of this study was to investigate prospectively whether the presence of pre-plus disease predicts progression to severe retinopathy of prematurity (ROP) requiring laser treatment. In this study, posterior retinal video recordings were obtained during 710 indirect ophthalmoscopy examinations of 214 premature infants over a period of 5 years. Two masked experts reviewed short video recordings and determined whether there was plus disease, pre-plus disease, or neither. The primary analysis included results of one examination of the right eye at 33 to 34 weeks' postmenstrual age. The primary outcome was a comparison of the proportion of eyes subsequently requiring laser treatment between the group graded as having pre-plus disease vs the group graded as having neither plus disease nor pre-plus disease. Of 10 eyes with pre-plus disease at 33 to 34 weeks' postmenstrual age, 7 (70%) subsequently required laser treatment; of 154 eyes without pre-plus disease or plus disease at 33 to 34 weeks' postmenstrual age, 14 (9%) subsequently required laser treatment (risk ratio, 7.7; 95% confidence interval, 4.1-14.8; $P < .001$). The mean time between the examination diagnosing pre-plus disease and laser treatment was 1.6 weeks (range, 1.0-2.4 weeks). When adjusting for birth weight, gestational age, ROP location (zone), and ROP severity (stage), the presence of pre-plus disease at 33 to 34 weeks' postmenstrual age independently predicted the need for laser treatment (adjusted odds ratio, 7.6; 95% confidence interval, 1.4-42.3; $P = .02$). The authors concluded that pre-plus disease observed early during the course of ROP is strongly associated with the development of severe ROP requiring laser treatment. The diagnosis of pre-plus disease has prognostic value beyond that already provided by birth weight, gestational age, ROP zone, and ROP stage. This paper suggests that eyes with pre-plus disease should be closely observed to allow optimal timing of intervention.

Grating Visual Acuity Results in the Early Treatment for Retinopathy of Prematurity Study

The Early Treatment for Retinopathy of Prematurity Cooperative Group*
Arch Ophthalmol. July. 2011;129(7):840-846. (f11)

This study compares grating (resolution) visual acuity at 6 years of age in eyes that received early treatment (ET) for high-risk prethreshold retinopathy of prematurity (ROP) with that in eyes that underwent conventional management (CM). In a randomized clinical trial, infants with bilateral, high-risk prethreshold ROP ($n = 317$) had one eye undergo ET and the other eye undergo CM, with treatment only if ROP progressed to threshold severity. For asymmetric cases ($n = 84$), the high-risk prethreshold eye was randomized to ET or CM. The study used as its main outcome measure grating visual acuity measured at 6 years of age by masked testers using Teller acuity cards. Monocular grating acuity results were obtained from 317 of 370 surviving children (85.6%). Analysis of grating acuity results for all study participants with high-risk prethreshold ROP showed no statistically significant overall benefit of ET (18.1% vs 22.8% unfavorable outcomes; $P = .08$). When the 6-year grating acuity results were analyzed according to a clinical algorithm (high-risk types 1 and 2 prethreshold ROP), a benefit was seen in type 1 eyes (16.4% vs 25.2%; $P = .004$) undergoing ET, but not

in type 2 eyes (21.3% vs 15.9%; $P = .29$). The authors concluded that early treatment of eyes with type 1 ROP improves grating acuity outcomes, but ET for eyes with type 2 ROP does not.

A clinical prediction model to stratify retinopathy of prematurity risk using postnatal weight gain.

Binenbaum G, Ying GS, Quinn GE, Dreiseitl S, Karp K, Roberts RS, Kirpalani H; Premature Infants in Need of Transfusion Study Group. *Pediatrics*. 2011 Mar;127(3) (f11)

The authors sought to develop an efficient clinical prediction model that includes postnatal weight gain to identify infants at risk of developing severe retinopathy of prematurity (ROP). Under current birth weight (BW) and gestational age (GA) screening criteria, <5% of infants examined in countries with advanced neonatal care require treatment. This study was a secondary analysis of prospective data from the Premature Infants in Need of Transfusion Study, which enrolled 451 infants with a BW < 1000 g at 10 centers. There were 367 infants who remained after excluding deaths (82) and missing weights (2). Multivariate logistic regression was used to predict severe ROP (stage 3 or treatment). Median BW was 800 g (445-995). There were 67 (18.3%) infants who had severe ROP. The model included GA, BW, and daily weight gain rate. Run weekly, an alarm that indicated a need for eye examinations occurred when the predicted probability of severe ROP was >0.085. This alarm identified 66 of 67 severe ROP infants (sensitivity of 99%), and all 33 infants requiring treatment. Median alarm-to-outcome time was 10.8 weeks (range: 1.9-17.6). There were 110 (30%) infants who had no alarm. Nomograms were developed to determine risk of severe ROP by BW, GA, and postnatal weight gain. The authors conclude that in this high-risk cohort, a BW-GA-weight-gain model could have reduced the need for examinations by 30%, while still identifying all infants requiring laser surgery. Additional studies are required to determine whether including larger-BW, lower-risk infants would reduce unnecessary examinations further and to validate the prediction model and nomograms.

Thrombocytopenia and retinopathy of prematurity

Jensen AK, Ying G, Huang J, et al *J AAPOS*. 2011 Feb 1;15(1) (f11)

Platelets store, regulate and transport VEGF. Therefore thrombocytopenia may have an association with severe ROP. The authors present a 1:1 matched case-control study to determine the association between thrombocytopenia and the development of any type 1 ROP. Cases were only included if platelet data were available within 1 week before surgery. 91 eligible cases and 91 controls matched for birth weight and gestational age were included for analysis. Thrombocytopenia was seen in 23/91 (25.3%) of infants with Type 1 ROP versus 12/91 (13.2%) of controls. A strong association between zone 1 type 1 ROP and thrombocytopenia was found, but this was not the case with zone 2 type 1 ROP. These findings do not establish a causal relationship

Prevalence and course of strabismus through age 6 years in participants of the Early Treatment for Retinopathy of Prematurity randomized trial

VanderVeen DK, Bremer DL, Fellows RR, et al. J AAPOS. 2011 Dec;15(6):536-40 (s12)

The authors present strabismus data collected prospectively from 342 infants with high-risk ROP surviving to 9 months corrected age who were enrolled in ETROP. The prevalence of strabismus gradually increased from 30% at 9 months' corrected to 42.2% at 6 years. Strabismus rates were the same for children with Type 1 or Type 2 ROP. However, strabismus rates were much higher in children with an unfavorable structural outcome from ROP,, abnormal fixation in one or both eyes, or unfavorable visual acuity in one or both eyes.. Rates of strabismus were also higher if amblyopia was diagnosed, anisometropia was ever present or if there was a history of seizures or cerebrospinal fluid shunt placement. 53 children underwent strabismus surgery.

Accuracy of retinopathy of prematurity image-based diagnosis by pediatric ophthalmology fellows: Implications for training

Myung JS, Chan RVP, Espiritu MJ, et al J AAPOS. 2011 Dec;15(6):573-8 (s12)

Based on a Web-based survey, up to 25% of ROP examinations are being performed by retina or pediatric ophthalmology fellows without supervision by an attending physician. This study evaluated how well pediatric ophthalmology fellows perform image-based ROP diagnosis. Images from consecutive infants whose parents provided informed consent were captured. Fellows were oriented to the diagnostic classification of ROP used in this study with a 1-page guide developed by the authors. All 5 fellows who participated in this study were in the first 6 months of their fellowship and had minimal or no ROP screening experience during residency training. Fellows showed high specificity for image-based detection of mild levels of ROP but showed lower diagnostic sensitivity for detecting clinically significant levels of disease. Mean sensitivities for detecting type 2 and treatment-requiring ROP were approximately 50%. There was a general tendency to undercall clinically significant levels of disease. Expert retinal specialists were more likely to agree with the expert reference standard diagnosis. The number of subjects in this study was small and these findings were based on interpreting a set of standard retinal images, not bedside indirect ophthalmoscopy.

ere was a history of seizures or cerebrospinal fluid shunt placement. 53 children underwent strabismus surgery.

Serum Concentrations of Bevacizumab (Avastin) and Vascular Endothelial Growth Factor in Infants With Retinopathy of Prematurity Sato T, Wada K, Arahori H, et al. Am J Ophthalmol February 2012; 153(2): 327-33. (s12)

This prospective case series was performed to determine the serum concentrations of bevacizumab and vascular endothelial growth factor (VEGF) in infants with retinopathy of prematurity (ROP) who received intravitreal bevacizumab, and to determine whether the changes in the serum concentration of bevacizumab were significantly correlated with the serum concentration of VEGF after intravitreal bevacizumab. Eleven infants (4 girls and 7

boys) with ROP were studied. They received 0.25 mg or 0.5 mg of intravitreal bevacizumab to either 1 eye (unilateral cases) or both eyes (bilateral cases) with vascularly active ROP. Serum samples were collected before and 1 day, 1 week, and 2 weeks after the intravitreal bevacizumab. The serum concentrations of bevacizumab and VEGF were measured by enzyme-linked immunosorbent assay, and the correlation in the serum levels between the 2 was determined.

The serum concentration of bevacizumab before and 1 day, 1 week, and 2 weeks after a total of 0.5 mg of intravitreal bevacizumab was 0 ng/mL, 195 ± 324 ng/mL, 946 ± 680 ng/mL, and 1214 ± 351 ng/mL, respectively. The serum bevacizumab level before and 1 day and 1 week after a total 1.0 mg of intravitreal bevacizumab was 0 ng/mL, 248 ± 174 ng/mL, and 548 ± 89 ng/mL, respectively. The serum concentration of VEGF before and 1 day, 1 week, and 2 weeks after a total of 0.5 mg intravitreal bevacizumab was 1628 ± 929 pg/mL, 427 ± 140 pg/mL, 246 ± 110 pg/mL, and 269 ± 157 pg/mL, respectively. There was a significant negative correlation ($r = -0.575$, $P = .0125$) between the serum concentration of bevacizumab and VEGF when a total of 0.25 mg or 0.5 mg of bevacizumab was injected. Based on these findings, the authors concluded that bevacizumab can escape from the eye into the systemic circulation and reduce the serum level of VEGF in infants with ROP. Continued extensive evaluations of infants are warranted for possible effects after intravitreal bevacizumab in ROP patients.

This paper is important for those clinicians who are treating ROP with or without the use of bevacizumab. When counseling patients, the effect of systemic bevacizumab and lower serum VEGF levels on the developing organ systems will need to be discussed.

A co-twin study of the relative effect of birth weight and gestational age on retinopathy of prematurity.

Woo SJ, Park KH, Ahn J, Oh KJ, Lee SY, Jeong EH, Park KH. *Eye (Lond)*. 2011 Nov;25(11):1478-83. (s12)

Low gestational age (maturity) and low birth weight (intrauterine growth) are the strongest and most consistently identified risk factors of prematurity. The study attempted to assess the relative importance of these two risk factors by analyzing twins in terms of ROP risk.

This study was a retrospective cohort study from South Korea of 55 consecutive twin pairs of 110 infants of gestational age ≤ 33 weeks. The outcomes of ROP including occurrence (any stage), severe ROP (stage 3 or more), and clinically significant ROP requiring laser treatment were compared between twins with the lower birth weight from each pair and their co-twins with the higher birth weight. No significant differences in ROP between larger and smaller infants were observed in the twin-paired analysis. In both the larger and smaller infant groups, gestational age of < 28 weeks was significantly associated with ROP outcomes.

The twin twin study suggests that gestational age (maturity) is more important in the pathogenesis of ROP than birth weight (intrauterine growth).

Understanding Clinically Undetected Macular Changes in Early Retinopathy of Prematurity on Spectral Domain Optical Coherence Tomography

Anand Vinekar, Kavitha Avadhani, Munusamy Sivakumar, Padmamalini Mahendradas,
Invest Ophthalmol Vis Sci. 2011 Jul 15;52(8):5183-8 (f11)

Purpose. To investigate macular changes in acute retinopathy of prematurity (ROP).

Methods. Fifty-four premature infants with ROP and 20 controls underwent routine ROP screening with indirect ophthalmoscopy and imaging. A tabletop spectral domain optical coherence tomography (SD-OCT) scanner (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was converted into a handheld device to image infants in the office sans sedation.

Results. SD-OCT images were obtained in all infants in the office. On SD-OCT, 23 of 79 eyes (29.1%) with stage 2 ROP showed abnormal foveal changes despite clinically normal foveae. Of the 23 eyes, 2 distinct patterns of foveal involvement were observed: "pattern A," which was characterized by dome-shaped foveal elevation and cystoid spaces with highly reflective intervening vertical septae, and "pattern B," which was characterized by preservation of the foveal depression with fewer intraretinal cystoid spaces. These patterns were seen in 12 (52.2%) and 11 (47.8%) eyes, respectively. All eyes (100%) belonging to stage 1 ROP (27) and the normal group (40) had no abnormal SD-OCT changes. The mean central foveal thickness was $156.9 \pm 28.3 \mu\text{m}$, $206.5 \pm 98.7 \mu\text{m}$, and $135.9 \pm 17.6 \mu\text{m}$ for stage 1, 2, and normal eyes, respectively ($P < 0.001$). Nineteen of the 23 eyes underwent serial imaging at 52 weeks' postmenstrual age (PMA), and all of them revealed normalization of foveal contours at this visit.

Conclusions. SD-OCT changes of the macula in mild ROP have not been previously described. Our method reveals that infants may be imaged supine and unanesthetized in the office. We hypothesize that these transient foveal changes at the critical time of fovealization in premature infants may influence their visual acuity in the adult life.

Comment: The authors modified a Heidelberg desktop OCT to image the foveas of premature babies. They found that many of these infants develop cysts in the fovea that then resolve. This may be related to the decreased best corrected vision in some former premature children.

The temporal and nasal retinal arteriolar and venular angles in preterm infants

Karen Wong, Jeffrey Ng, Anna Ells, Alistair R Fielder, Clare M Wilson
Br J Ophthalmol December 2011;95:1723e1727. (s12)

Aim To determine the angle between the temporal or nasal retinal vessels in preterm infants and to determine the relationship of these angles to birthweight (BW), gestational age (GA) and retinopathy of prematurity (ROP) status.

Methods Colour digital images were acquired during ROP screening examinations in infants born with a range of BWs and GAs between 33 and 42 weeks postmenstrual age. Four retinal vessel angles were measured: temporal venular angle, temporal arteriolar angle (tAA),

nasal venular angle and nasal arteriolar angle. Measurements were performed by Computer-Aided Image Analysis of the Retina, a validated semi-automated computer software program. The relationship of each of four angles to BW and also to GA was determined using Mann-Whitney test and Spearman's rho, respectively.

Results tAA was significantly narrower in infants with ROP and correlated positively with BW and GA. The other vessel angles, temporal venular angle, nasal arteriolar angle and nasal venular angle, showed no significant correlation with BW, GA or ROP status.

Conclusion The retinal vessel angles can be quantified in a simple repeatable manner. tAA correlated positively with BW and GA, and was significantly narrower in infants with stage 3 ROP than in those without ROP or with mild disease.

Outcome of Eyes Developing Retinal Detachment During the Early Treatment for Retinopathy of Prematurity Study

Michael X. Repka, MD; Betty Tung, MS; William V. Good, MD; Antonio Capone Jr, MD; Michael J. Shapiro, MD *Arch Ophthalmol.* September 2011;129(9):1175-1179. (s12)

This paper describes the structural and visual outcomes at age 6 years of retinal detachment (RD) from retinopathy of prematurity (ROP) in the Early Treatment for Retinopathy of Prematurity (ETROP) study. ETROP is a prospective multicenter nonrandomized series of infants with high-risk prethreshold ROP who developed an RD by 6 months corrected age treated with observation or vitreoretinal surgery. Of 401 patients, 63 (89 eyes) experienced RD. Follow-up at age 6 years was available for 70 eyes (79%) of 49 surviving patients. The RDs were stage 4A in 28 eyes (40%), stage 4B in 14 (20%), stage 5 in 13 (19%), and not classified in 15 (21%). The macula was attached in 17 of 50 eyes (34%) after vitrectomy with or without scleral buckle, in 6 of 9 (67%) after scleral buckle only, and in 2 of 11 eyes (18%) observed. An attached macula at age 6 years after vitreoretinal surgery was present in 5 of 16 eyes (31%) with stage 4A, 6 of 10 (60%) with stage 4B, and 0 of 10 with stage 5. Favorable visual acuity (>20/200) was found in 6 of 70 eyes (9%); 5 had stage 4A, and 1 was not classified. In summary, macular attachment was achieved in approximately one-third of eyes with RD and favorable visual acuity in some eyes with stage 4A.

Modified 23-Gauge Vitrectomy System for Stage 4 Retinopathy of Prematurity

Wei-Chi Wu, MD, PhD; Chi-Chun Lai, MD; Rey-In Lin, MD; Nan-Kai Wang, MD; An-Ning Chao, MD; Kuan-Jen Chen, MD; Tun-Lu Chen, MD; Yih-Shiou Hwang, MD

Arch Ophthalmol. October 2011;129(10):1326-1331. (s12)

The purpose of this paper was to evaluate the outcome of a novel, modified 23-gauge vitrectomy system in the treatment of stage 4 retinal detachment in retinopathy of prematurity. Consecutive patients with stage 4 retinopathy of prematurity treated with modified 23-gauge vitrectomy were included in this medical record review. Major novel modifications included the use of a small infusion cannula, a 20-gauge blade for the creation of sclerotomies in the pars plicata, and a 23-gauge endoilluminator and vitreous cutter. Conjunctival dissection and suturing of sclerotomies were performed using this modified 3-port, 23-gauge vitrectomy technique. Anatomic success and surgical complications were analyzed. A total of twenty-six eyes of 17 patients were included and analyzed. The mean (SD) gestational age was 28.0 (2.5) weeks, and the mean birth weight was 1199 (449) g. Mean postmenstrual age at the time of vitrectomy was 40.5 (3.0) weeks. Overall, 20 eyes (77%) achieved retinal attachment

in a single operation, and 23 eyes (88%) achieved retinal attachment after multiple procedures. Postoperative complications included disc dragging (5 eyes [19%]), cataracts (4 [15%]), glaucoma (2 [8%]), persistent vitreous hemorrhage (1 [4%]), and posterior synechia (1 [4%]). The authors feel that this 23-gauge vitrectomy system seems to be a safe and effective approach for treatment of stage 4 retinopathy of prematurity. This modified system combines the benefits of 20- and 23-gauge vitrectomy and offers safer insertion of infusion cannulas in smaller eyes, more working space in pediatric eyes, a cutting port that is closer to the retina, and a faster cutting speed with less vitreous traction during the operation.

Spectral-Domain Optical Coherence Tomographic Assessment of Severity of Cystoid Macular Edema in Retinopathy of Prematurity

Ramiro S. Maldonado, MD; Rachele O'Connell, BS; Simon B. Ascher, BS; Neeru Sarin, MD; Sharon F. Freedman, MD; David K. Wallace, MD, MPH; Stephanie J. Chiu, BSE; Sina Farsiou, PhD; Michael Cotten, MD; Cynthia A. Toth, MD Arch Ophthalmol. Published online January 9, 2012. (s12)

The goal was to investigate whether the severity of cystoid macular edema (CME) in neonates who were 31 to 36 weeks' postmenstrual age, as viewed by spectral-domain optical coherence tomography (SD-OCT) imaging, predicts the severity of retinopathy of prematurity (ROP) or is related to systemic health. Of 62 prematurely born neonates in a prospective institutional review board–approved study, 42 met the following inclusion criteria: at least 1 SD-OCT imaging session prior to 37 weeks' postmenstrual age and prior to ROP laser treatment, if a laser treatment was performed, and an ophthalmic ROP examination at or after 41 weeks' postmenstrual age, evidence of complete retinal vascularization in zone III, or documentation through telephone report of such information after transfer of care. Measures of CME severity, including central foveal thickness, retinal layer thicknesses, and foveal-to-parafoveal thickness ratio in 1 eye per subject, were compared with ROP outcomes: laser treatment, maximum plus disease, and maximum ROP stage. Systemic health factors were also correlated. Cystoid macular edema was present in 50% of neonates. Multiple elongated cystoid structures within the inner nuclear layer were most common. The presence of CME was not associated with ROP outcomes. The central foveal thickness, the thickness of the inner retinal layers, and the foveal-to-parafoveal thickness ratio were higher in eyes that required laser treatment or that developed plus disease or ROP stage 3. Cystoid macular edema was not clearly associated with systemic factors. Cystoid macular edema is common in premature infants screened for ROP before 37 weeks' postmenstrual age, with the most common SD-OCT phenotype of a bulging fovea from multiple elongated cystoid spaces. Detection of CME is not associated with ROP severity; however, tomographic thickness measurements could potentially predict a higher risk of requiring laser treatment or developing plus disease or ROP stage 3. Systemic health factors are probably not related to the development of CME.

Use of intravitreal anti-VEGF: Retinopathy of prematurity surgeons' in Hamlet's dilemma?.

Azad R.

Indian J Ophthalmol 2011;59:421-2 (Nov-Dec) (s12)

This editorial reviews the questions surrounding intravitreal anti-VEGF agents for ROP in light of recent clinical trials. The main question is whether these agents should be used as monotherapy or rescue therapy for patients not responding to the standard-of-care laser treatment. Other considerations are safety of anti-VEGF agents in preterm neonatal patients, unknown effects of anti-VEGF agents on the developing brain and other organs, late recurrence of ROP in patients treated with anti-VEGF agents as monotherapy, and optimal timing and dose of the drug.

Structural sequelae and refractive outcome 1 year after laser treatment for type 1 prethreshold retinopathy of prematurity in Asian Indian eyes

Katoch D, Sanghi G, Dogra MR, Beke N, Gupta A. Indian J Ophthalmol 2011;59:423-6 (Nov-Dec) (s12)

A retrospective chart review of infants with Type 1 prethreshold ROP (defined according to the Early Treatment for Retinopathy of Prematurity study) undergoing laser treatment at a tertiary center between January 2004 and December 2008 was done. **Results** None of the eyes developed retinal structural sequelae. On cycloplegic retinoscopy, 59.4% eyes had nonsignificant hyperopia [spherical equivalent (SE) ≤ 4 D], 14.5% eyes had no refractive error (SE 0 D), 24.7% eyes had low myopia (SE < 5 D), and 1.4% eyes had high myopia (SE > 5.0 D). Eyes developing myopia were associated with a greater number of clock hours of ROP, greater number of laser spots used, and a longer time to disease regression. Two infants (5.6%) had esotropia and one (2.8%) had exotropia. **Comment** Limitations of the study include a cohort of babies that were heavier and older than the ETROP cohort, and so the disease profile and outcomes in these infants are likely to be different from smaller and younger premature infants in the ETROP cohort. The low rate of strabismus in the present study (compared with ETROP cohort) may be attributed to short follow-up duration, predominant symmetric presentation, and regression without sequelae in both the eyes of the infants.

Prevailing clinical practices regarding screening for retinopathy of prematurity among pediatricians in India: A pilot survey

Patwardhan SD, Azad R, Gogia V, Chandra P, Gupta S. Indian J Ophthalmol 2011;59:427-30 (Nov-Dec) (s12)

Pediatricians registered with Indian Academy of Pediatrics from six states of India were selected randomly and were telephonically interviewed in accordance with a preformed questionnaire which comprised of questions regarding demographic factors, number of premature children seen per month, awareness and referral scheme to ophthalmologist; responses thus obtained were analyzed. **Results** Hundred percent knowledge about ROP and need for screening in premature babies was observed among the respondents. However, only 135 (58%) pediatricians always referred for ROP screening, 19 (8%) referred only

sometimes and 80 (34%) did not refer at all. Consistent referral protocols taking into account all plausible risk factors for ROP were followed by only 25% of those who always referred. Major deterrent in ROP screening was perceived as non-availability of trained ophthalmologists. **Conclusion** Only 14.5% of total pediatricians contacted were following international recommendations for ROP referral. Screening for ROP remains dismal as observed in this pilot survey as a consequence of non-availability of trained ophthalmologists as well as inconsistent screening guidelines. **Comment** The authors recommend a larger nationwide survey to evaluate the causes for poor screening of high-risk premature babies, recruiting more trained ophthalmologists especially in rural areas and the need to organise a network among the fellow physicians, paramedical staff and parents, for early detection and effective treatment of ROP.

Screening for Retinopathy of Prematurity in a Tertiary Hospital in Istanbul: Incidence and Risk Factors

Aylin Ardagil Akcakaya, Sevil Ari Yaylali, Hasan Hasbi Erbil, et al. *Journal of Pediatric Ophthalmology and Strabismus* January 2012; 49: 21-25 (s12)

Retinopathy of Prematurity (ROP) remains a major visual threat in countries with low or moderate levels of development. Premature infants born in Istanbul, Turkey were identified and risk factors associated with ROP, number of premature infants at risk, current screening practices for ROP and findings in this population was evaluated. There was a statistically significant difference between infants with ROP and those without when looking at gestational age, birth weight and length of oxygen treatment. There was also a significant relationship between ROP and blood transfusions, sepsis, respiratory distress and mechanical ventilation. These five variables were identified as significant independent risk factors for ROP. Guidelines for infant care in the neonatal Intensive care unit of these moderately developed countries need to be addressed with tighter control and monitoring of oxygen treatment to decrease the incidence of severe ROP. In addition, there needs to be increased education to the general population to ensure improved compliance when follow up or treatment is needed.

Placenta Microbiology and Histology and the Risk for Severe Retinopathy of Prematurity

Minghua L. Chen, Elizabeth N. Allred, Jonathan L. Hecht, Andrew Onderdonk, Deborah VanderVeen, David K. Wallace, for the ELGAN Study (*Invest Ophthalmol Vis Sci*. September 2011;52:7052–7058) DOI:10.1167/iovs.11-7380 (s12)

PURPOSE. To test the hypothesis that the presence of bacteria and/or histologic inflammation in the placenta of infants born preterm is associated with an increased risk for severe retinopathy of prematurity (ROP). **METHODS.** This was a prospective cohort study. Exploratory and multivariable data analyses were used, including logistic regression models with interaction terms. Main outcomes were four definitions of severe ROP: stage 3 or higher, any ROP in zone I, prethreshold/threshold, and plus disease. **RESULTS.** Individually, placenta bacteria and histologic inflammation were not associated with severe ROP in

univariable analyses among 1064 infants with gestational age <28 weeks or among 715 infants with gestational age <27 weeks (we excluded infants with a gestational age of 27 weeks because of the very small number of ROP cases). However, the co-occurrence of bacteria and inflammation was associated with an increased risk for ROP in zone I (odds ratio, 3.1; 95% confidence interval, 1.02–9.5). Among 339 infants with any placental bacteria, the co-occurrence of (1) inflammation and a gestational age of 23 to 24 weeks and (2) inflammation and hyperoxia were associated with prominent increases in risk for all definitions of severe ROP. **CONCLUSIONS.** While antenatal exposure to infection or inflammation alone does not appear to convey risk information for severe ROP, their co-occurrence does. This finding supports the hypothesis that a fetal inflammatory response to antenatal infection might be part of the etiology of severe ROP.

The authors suggest that ROP's etiology and pathogenesis might begin *in utero* and hypothesize that both recovery of organisms from the placenta and histologic indicators of inflammation are associated with an increased risk of ROP. They report results of an exploration of associations between antenatal infection/inflammation and ROP in the Extremely Low Gestational Age Newborn (ELGAN) study. Particular emphasis is on interaction analysis and multivariable modeling. In conclusion, very preterm infants who were exposed to multiple pro-inflammatory stimuli appear to be at increased risk for severe ROP. Future studies of ROP should consider such interaction patterns.

CRITICAL PERIOD FOR FOVEAL FINE STRUCTURE IN CHILDREN WITH REGRESSED RETINOPATHY OF PREMATURITY

Wang, Jingyun, Spencer, Rand, Leffler, Joel N, Birch, Eileen E, Retina. February 2011; 32(2):330-339 (s12)

Midgestation (24 to 28 weeks) is a critical period in the formation of the foveal avascular zone. Previous studies using time-domain optical coherence tomography (OCT) have shown that children with regressed retinopathy of prematurity (ROP) have greater total foveal thickness than full-term control children. Limitations of time-domain OCT precluded quantitative analysis of whether all retinal layers or only specific retinal layers were responsible for this thickening. In this study the authors evaluated the effects of preterm birth on foveal structure in children with regressed ROP using frequency-domain OCT.

Children with regressed ROP and normal-appearing posterior poles ($n = 26$) were compared with full-term control children ($n = 56$). Total thickness of the fovea in the ROP group ($287.7 \pm 47.6 \mu\text{m}$) was greater than that in the control group ($230.1 \pm 18.2 \mu\text{m}$). Although all retinal layers were significantly thicker in the ROP group, inner retinal layers contributed to the difference in thickness more than outer layers. This was due to a failure of the inner retinal layers to migrate away from the fovea. Further analysis was performed to examine the relationship between total foveal thickness and gestational age. Before 28 weeks, foveal thickness decreased with gestational age ($14.3 \mu\text{m}/\text{week}$); after 28 weeks, foveal thickness decreased only slightly ($2.73 \mu\text{m}/\text{week}$). Foveal thickness was correlated with gestational age at birth but not with visual acuity or refractive error.

VIII PREMATURITY

Preterm Birth: The Ophthalmic Consequences. O'Connor, AR. *Brit Ir Orthopt J.* 2011; 8: 3-9. (s12)

In this major review, the author provides an evidence-based update on the ophthalmic outcomes following premature birth. The review focuses on publications in the past 3 years.

Although preterm births account for 1.5 percent of all live births in the United States, this small population requires a disproportionate amount of health care resources, both in terms of neonatal and long term care. Increased survival rates are usually accompanied by increased disability but this trend may be declining. These disabilities encompass all areas of development including the visual system. Factors include ROP, refractive errors and amblyopia but neurological deficits are harder to detect in preterm children with developmental delay or cognitive disorders.

Improved imaging techniques allow more detailed analysis of the visual pathways. VEP testing can be undertaken at an early age. The use of anti-VEGF drugs such as Avastin is a new advance in the treatment of ROP but no long term data are yet available. [92 REFS]

Dynamics of Human Foveal Development after Premature Birth

Ramiro S. Maldonado, Rachelle V. O'Connell, Neeru Sarin, MD, Sharon F. Freedman, MD et. al. *Ophthalmology* December 2011; 118: 2315-2325 (s12)

This study provides the first view into the development of the living cellular layers of the human retina, utilizing portable spectral domain OCT. It has some excellent color and black & white OCT images outlining the layers of the immature versus mature retina (p2316). There is also a nice map of regional changes in human foveal development extending from 31 weeks post menstrual age to adulthood. (p2320). The paper establishes baseline information, not previously published, of the timeline of human foveal development and how it relates to early disease detection as well as improve our understanding of integral relationships between the foveal and visual cortical differentiation.

Study prepared by the Departments of Ophthalmology, Pediatrics and Biomedical Engineering at Duke University, Durham, North Carolina

COMMENT: A must read for anyone interested in retinal and visual-retinal development.

IX. STRABISMUS

Repair of Strabismus and Binocular Fusion in Children with Cerebral Palsy: Gross Motor Function Classification Scale

Fatema Ghasia, Janice Brunstrom-Hernandez, and Lawrence Tychsen *Invest Ophthalmol Vis Sci.* September 2011;52:7664–7671) DOI:10.1167/iovs.10-6906. (s12)

PURPOSE. Children with cerebral palsy (CP) tend to be either excluded from studies of strabismus repair or pooled with children who have other neurologic disorders. The authors limited this study to children with defined CP to determine the success or failure of restoring eye alignment and fusion. **METHODS.** An observational, cross-sectional, prospective study was conducted on a representative cohort of 50 children. CP severity ranged from Gross Motor Function Classification System (GMFCS) level 1 (least severe) to 5 (most severe). Mean age at entrance and surgery was 3.5 years, and mean follow-up was 4.1 years (minimum 1 year).

RESULTS. The predominant form of strabismus was infantile onset: esotropia in 54%, exotropia in 26%, and dyskinesia in 10%. Sixty-six percent of esotropic children and 61% of exotropic children achieved optimal (microtropic) alignment after an average of 2 and 1.8 surgical procedures, respectively. The likelihood of optimal alignment was similar in children with mild (GMFCS level 1–2) versus severe (GMFCS level 3–5) CP ($P = 0.7$; χ^2). Irrespective of GMFCS severity, 46% of children gained binocular fusion/stereopsis, but the quality of fusion gained was greater in children with mild CP ($P < 0.05$). Earlier surgery was more likely to be successful ($P < 0.05$). **CONCLUSIONS.** Restoration of binocular alignment and a degree

of fusion is a realistic goal in the majority of strabismic CP children. Repair may be achieved in children at both the mild and the severe ends of the GMFCS spectrum, without undue concern about treatment futility or excessive reoperation.

Children with CP have strabismus at rates exceeding those detected in neurologically normal (NN) children. The most common form is infantile-onset, which is prevalent at each level of GMFCS severity. The first goal of their study was to determine whether CP children, at different levels of GMFCS, differ in their motor outcomes or need for reoperation after attempted strabismus repair. The second goal was to determine whether repair of sensorial binocular fusion is achievable. Their results indicate that the restoration of binocular alignment and a degree of fusion is a realistic goal in the majority of strabismic CP children. Earlier surgery yielded greater rates of success. Repair may be achieved in children at both the mild and the severe ends of the GMFCS spectrum without undue concern about treatment futility or excessive reoperation.

Astigmatism Progression in the Early Treatment for Retinopathy of Prematurity Study to Six Years of Age

Bradley V. Davitt, MD, Graham E. Quinn, MD, MSCE, David K. Wallace, MD, MPH, Velma Dobson, PhD et.al. *Ophthalmology* December 2011: 118:2326-2329 (s12)

This study examines the prevalence of astigmatism at six years of age for children enrolled in the Early Treatment of Retinopathy of Prematurity Study (ETROP). In children with high-risk prethreshold ROP, astigmatism greater than 1.00 D or more, occurred in more than 50% of eyes and astigmatism greater than 2.0D occurred in more than 25% of eyes. Most of the astigmatism was with-the rule. Type 2 ROP eyes had a greater incidence of astigmatism than Type 1 ROP eyes by 6 years of age.

These findings support the need to follow children with prethreshold ROP through the early grade school years.

Study produced by multiple authors from many institutions who were involved in the Early Treatment Retinopathy of Prematurity Cooperative Group.

COMMENT: Important epidemiologic study regarding refractive error development in premature children. No controls provided to compare 6 year data on non-premature children.

The Long-Term Follow-up of Accommodative Esotropia in a Population-based Cohort of Children Brian G Mohny, MD, Chrystia C Lilley, BS, Amy E Green-Simms, MD, Nancy N Diehl, BS Ophthalmology Volume 118, Number 3, March 2011 (f11)

Retrospective population-based cohort study evaluating pediatric patients less than 19 years of age diagnosed with accommodative esotropia in Olmsted County, Minnesota, between January 1, 1975, and December 31, 1994. Medical records were identified by the Rochester Epidemiology Project and reviewed for spectacle and surgical management.

Study Objectives and Design

The purpose of the study was to report refractive and surgical outcomes in a cohort of children with accommodative esotropia. Three hundred and six children were diagnosed with accommodative esotropia during the study years of January 1, 1975, to December 31, 1994. Two hundred and forty-four out of 306 children (80%) had fully accommodative esotropia (FAET). Sixty-two out of 306 (20%) had partial accommodative esotropia (PAET or what is also called mixed mechanism esotropia). The Kaplan-Meier rate of discontinuing spectacles for strabismus in this population was 8% by 5 years after diagnosis, 20% by 10 years after diagnosis and 37% by 20 years after diagnosis.

Children born prematurely or with greater initial farsighted refractive error were significantly less likely to become spectacle free during follow-up. During the follow-up of 9.8 years 33 of the 244 subjects (13.5%) with fully accommodative esotropia eventually underwent strabismus surgery. The risk factors for higher likelihood of surgery included male gender and earlier age of onset in the diagnosis of fully accommodative esotropia.

Importance for Pediatric Ophthalmologists

The majority of children with accommodative esotropia in this population continue to require spectacle correction into their second decade of life. 13.5% of the children with fully accommodative esotropia required surgical intervention which is more likely to occur among boys and those with an earlier age of onset and diagnosis of convergent strabismus.

Pearls/Comments

Despite the robust conclusions of this study, the population is biased to the relatively homogenous/single race constituents of Olmsted County, Minnesota. This is the third Olmsted County Epidemiologic Study done by Dr. Mohny and his colleagues at the Mayo Clinic. One study was on the incidence of childhood ptosis and a second study was performed on Acquired Nonaccommodative Esotropia. Both of these studies were published in the June issue of Ophthalmology.

Long-term Follow-up of Acquired Nonaccommodative Esotropia in a Population-based Cohort

Sarah M Jacobs, MD, Amy Green-Simms, MD, Nancy N. Diehl, BS, Brian G Mohny, MD. Ophthalmology.2011. June (f11).

Retrospective chart review of patients residing in Olmstead County, Minnesota, who were diagnosed with acquired nonaccommodative esotropia from January 1, 1965, to December 31, 1994 (over 30 year cohort).

Potential cases of acquired nonaccommodative esotropia (ANAET) were identified by using the resources of the Rochester Epidemiology Project, medical records linkage system designed to capture data on any patient-physician encounter in Olmstead County, Minnesota.

Study Objectives and Design

Clinical characteristics and long-term motor and sensory outcome in children with acquired nonaccommodative esotropia.

Key Study Conclusions

The frequency of acquired nonaccommodative esotropia was much higher than previous studies have reported. This study occurred in 1 out of 287 children. The condition was more prominent in male children. Diplopia was a common presenting symptom in many cases. None of the children were found to have intracranial malignancy.

Most patients achieved good motor and sensory outcome with the best results among those with a later onset of the deviation. No patients had amblyopia.

The majority of patients in this study underwent a single surgery and after a mean follow-up of 1 decade, two-thirds of the patients were within 10PD of orthophoria and had measurable stereopsis. The best sensory outcomes occurred among those with an older age at onset and no amblyopia.

Importance for Pediatric Ophthalmologists

Increased awareness of this as a common diagnosis in childhood strabismus.

Pearls

Children with acquired nonaccommodative esotropia seldom have neurologic comorbidities and do well with surgery.

Strabismus Precipitated by Monovision

Pollard ZF, Greenberg MF, Bordenca M, Elliott J, Hsu V
Am J Ophthalmol. 2011 Jun 11. (f11)

Purpose

To present patients who had the onset of strabismus or the recurrence of strabismus after converting to a monovision system of seeing.

Design

Retrospective interventional case series.

Methods

Clinical records of 12 patients from the private practice of the corresponding author of this paper (Z.F.P.) were reviewed. Patients obtaining monovision via contact lenses, LASIK, and cataract surgery with posterior chamber intraocular lenses were studied if their monovision produced a new strabismus or was related to the recurrence of a previous strabismus.

Results

All patients were first treated by converting the monofixing near eye to distance vision and then using reading glasses for near work. Of the 12 patients, 7 regained their fusion by doing away with monovision and 5 required surgery to reestablish motor or sensory control. All of the surgery patients obtained an excellent alignment but 1 did not regain sensory fusion.

Conclusion

Monovision is successful for the far majority of patients who try it. However, in patients with a previous history of strabismus or those with significant phorias, caution should be used in recommending monovision, and if monovision is elected, keeping the anisometropia to small levels such as 1.25 to 1.50 diopters (D) might lessen the chance of producing strabismus post monovision. The majority of our patients developed strabismus after 2 years of monovision, telling us that while a trial of monovision with a contact lens prior to surgery may suggest that the patient could tolerate monovision, it is not a guarantee.

Reviewer Comment

Surgeons should spend extra time counseling patients who opt for monovision, particularly those with a history of strabismus.

Distance stereotest using a 3-dimensional monitor for adult subjects

Kim J, Yang HK, Kim Y, Lee B, Hwang JM.
Am J Ophthalmol. 2011 Jun;151(6):1081-1086. (f11)

Purpose

To evaluate the validity and test–retest reliability of a contour-based 3-dimensional (3-D) monitor distance stereotest (distance 3-D stereotest) and to measure the maximum horizontal disparity that can be fused with disparity vergence for determining the largest measurable disparity of true stereopsis.

Design

Observational case series.

Methods

Sixty-four normal adult subjects (age range, 23 to 39 years) were recruited. Contour-based circles (crossed disparity, 5000 to 20 seconds of arc; Microsoft Visual Studio C++ 6.0; Microsoft, Inc, Seattle, Washington, USA) were generated on a 3-D monitor (46-inch

stereoscopic display) using polarization glasses and were presented to subjects with normal binocularity at 3 m. While the position of the stimulus changed among 4 possible locations, the subjects were instructed to press the corresponding position of the stimulus on a keypad. The results with the new distance 3-D stereotest were compared with those from the distance Randot stereotest.

Results

The results of the distance 3-D stereotest and the distance Randot stereotests were identical in 64% and within 1 disparity level in 97% of normal adults. Scores obtained with the 2 tests showed a statistically significant correlation ($r = 0.324$, $P = .009$). The half-width of the 95% limit of agreement was 0.47 log seconds of arc (1.55 octaves) using the distance 3-D stereotest—similar to or better than that obtained with conventional distance stereotests. The maximum binocular disparity that can be fused with vergence was 1828 ± 794 seconds of arc (range, 4000 to 500).

Conclusions

The distance 3-D stereotest showed good concordance with the distance Randot stereotest and relatively good test–retest reliability, supporting the validity of the distance 3-D stereotest. The normative data set obtained from the present study can serve as a useful reference for quantitative assessment of a wide range of binocular sensory abnormalities.

Reviewer Comment

Here is another option for testing distance stereoacuity, which may be particularly useful in following patients with intermittent exotropia.

Biomechanical analysis of x-pattern exotropia

Brandner M, Buchberger M, Kaltofen T, Haslwanter T, Hoerantner R, Langmann A.
Am J Ophthalmol. 2011 Jul;152(1):141-6 (f11)

Purpose

To simulate and check the plausibility of the proposed mechanisms of X-pattern exotropia and to determine the least invasive surgical method that can be used to treat the disorder.

Design

Computational supported analysis and retrospective study.

Methods

The oculomotor model SEE++ was used to simulate the effects of the different causes that have been proposed for the X-phenomenon. In addition, a retrospective study was conducted using preoperative and postoperative measurements of 10 patients with X-pattern exotropia. Eye movements and surgery of these patients were simulated and analyzed statistically.

Results

Our computer-based simulations showed that only 1 of the 4 proposed theories can account successfully for the observed X-patterns: an overaction of all 4 oblique muscles can induce divergent exotropia in upgaze and downgaze, and an alteration of horizontal muscles can cause the additional divergence in all gaze positions. The simulation of eye muscle surgery

confirmed that a sufficient correction of the divergent deviation in all gazes already can be achieved by a recession and resection of 2 horizontal eye muscles.

Conclusions

In case of X-pattern exotropia, recession and resection of 2 horizontal muscles can be used as a first-line therapy, leading to a simplification of the therapy.

Reviewer Comment

It will be interesting to see if the conclusions drawn from computer-based simulations prove to be true when these treatments are applied to human subjects.

Fusional convergence in childhood intermittent exotropia

Hatt SR, Leske DA, Mohny BG, Brodsky MC, Holmes JM.

Am J Ophthalmol. 2011 Aug;152(2):314-9. (f11)

Purpose

To evaluate fusional convergence and associations with control in children with intermittent exotropia (XT).

Design

Retrospective case series.

Methods

Sixty-four children (median age 7 years) with intermittent XT were identified with measures of angle of deviation, control (using a previously reported 0-to-5-point scale), and fusional convergence at a single examination. Total convergence was defined as the sum of the angle of deviation plus additional convergence in reserve. Mean values were compared with published normals. A fusion reserve ratio was calculated as "convergence reserve divided by angle of deviation." Relationships of control score with total amplitude, reserve, recovery, and fusion reserve ratio were assessed using Spearman rank correlations.

Results

Convergence differed from normals in children with intermittent XT: total convergence was higher at distance (33 prism diopters [pd] vs 17 pd, $P < .0001$) and near (38 pd vs 18 pd, $P < .0001$) whereas convergence reserve was lower at distance (7 pd vs 17 pd; $P < .0001$). There was a strong correlation between fusion reserve ratio and control score at distance ($R = -0.75$, $P < .0001$) and near ($R = -0.66$, $P < .0001$).

Conclusions

Children with intermittent XT have subnormal convergence reserves at distance. The fusion reserve ratio correlates well with control and may be useful in grading the severity of intermittent XT.

Reviewer Comment

One of the challenges to following intermittent exotropia is assessing the control of the deviation, which can change minute-to-minute. The fusion reserve ratio may be particularly valuable to help assess control of the deviation.

Health-related quality of life in parents of children with intermittent exotropia.

Yamada T, Hatt SR, Leske DA, and Holmes JM. J AAPOS April 2011 (f11)

The Intermittent Exotropia Quality of Life Questionnaire (IXTQ) has three components: 1.child self-report questionnaire, 2.proxy parent-report questionnaire, 3.parent self-report questionnaire. The Parent IXTQ was compared as a health-related quality of life (HRQOL) instrument with the Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM). Prospectively, parents of 59 children with intermittent exotropia, and parents of 29 normal subjects, were recruited to complete both instruments. Median scores on the parent IXTQ were worse if the child had intermittent exotropia compared to normal controls. However, this difference was not found with the PedsQL FIM. Results were not affected by the age of the child. The parent IXTQ instrument may be helpful in identifying parents who are especially worried about their child's eye condition. Mothers filled out the forms in over 75% of subjects in both groups. Also the normal subject group had a much higher incidence of spectacle wear.

Treatment of symptomatic convergence insufficiency with a home-based computer orthoptic exercise program. Serna A, Rogers DL, McGregor ML, et al. Feb. J AAPOS 2011;15:140-143
This retrospective chart review evaluated the effectiveness of home-based computer orthoptic exercises in the treatment of children with convergence insufficiency. 42 children were treated for 3 to 30 weeks. Near point of convergence decreased from a mean of 24.2 cm to 5.6 cm. Treatment effect on positive fusional vergence was also highly significant. Mean exodeviation at near decreased from 10.1 PD to 6.3 PD. All patients reported improvement in symptoms and almost 2/3 had resolution of symptoms. Almost 1/3 of these patients also displayed accommodative insufficiency. This study was retrospective and did not have a placebo group of sham exercises. The authors feel home-based therapy can successfully treat patients with convergence insufficiency.

Enhanced Vertical Rectus Contractility by Magnetic Resonance Imaging in Superior Oblique Palsy.

Robert A. Clark, MD; Joseph L. Demer, MD, PhD. Arch Ophthalmol. July 2011;129(7):904-908. (f11)

The purpose of this study was to seek evidence for causative secondary changes in extraocular muscle volume, cross-sectional area, and contractility in superior oblique (SO) palsy using magnetic resonance imaging, given that vertical deviations in SO palsy greatly exceed those explained by loss of SO vertical action alone. High-resolution, quasi-coronal orbital magnetic resonance images in target-controlled central gaze, supraduction, and infraduction were obtained in 12 patients with chronic unilateral SO palsy and 36 age-matched healthy volunteers using an 8-cm field of view and 2-mm slice thickness. Digital image analysis was used to quantify rectus extraocular muscle and SO cross-sectional areas and volumes. Measurements were compared with those of controls in central gaze to detect hypertrophy or atrophy and during vertical gaze changes to detect excess contractility. The results showed: In central gaze, the paretic SO was significantly atrophic ($P < .001$) and the contralesional superior rectus (SR) was significantly hypertrophic ($P = .02$). Across the range of vertical duction from supraduction to infraduction, both the contralesional SR ($P = .04$) and

inferior rectus ($P = .001$) exhibited significantly supernormal contractile changes in maximum cross-sectional area. Contractile changes in the ipsilesional SR and inferior rectus exhibited a similar but insignificant trend ($.08 < P < .12$). The authors concluded that central gaze hypertrophy of the contralesional SR may be secondary to chronic excess innervation to compensate for relative hypotropia of this eye. Supernormal contralesional SR and inferior rectus contractility suggests that dynamic patterns of abnormal innervation to vertical rectus extraocular muscles may contribute to large hypertropias often observed in SO palsy. type 2, completely noncalcified remnant; type 3, partially calcified remnant; and type 4, atrophic chorioretinal flat scar). Evolution of these regression patterns was observed over time. Immediately following 6 cycles of chemoreduction, types 0 (2%), 1 (30%), 2 (3%), 3 (33%), and 4 (32%) regression patterns were found. During a mean follow-up period of 56 months (median, 48 months; range, 18-145 months), there was no change in regression patterns classified as type 0, 1, or 4. However, there was evolution of regression pattern types 2 and 3. Over time, type 2 tumor scars either remained stable (41%) or evolved to type 4 (41%), 3 (9%), or 1 (9%) scars. Type 3 tumor scars remained stable (74%) or evolved to type 1 (26%) scars. In conclusion, following chemoreduction and tumor consolidation therapy, retinoblastoma regression patterns types 2 and 3 can slowly evolve over time into a slightly different appearance, even without additional treatment.

Validity and ease of use of a computerized Hess chart

Watts P, Nayak H, Lim MK, et al J AAPOS. 2011 Oct;15(5):451-4 (s12)

The Hess chart is used to diagnose mechanical and paralytic ocular deviations, providing a reliable and repeatable record. This study prospectively compared the agreement between a computerized system (OMA) and the gold standard conventional Lees screen for analyzing ocular motility in adult patients. Completion times and subjective ease of each method were also compared. 65 patients were included in the study. OMA overestimated conventional scores for horizontal right and left eyes. OMA underestimated conventional scores for vertical scores in the left eye only. There was no significant difference in completion times. Testing times overall, were weakly linked to patient age. OMA testing was found to be easier for patients. The results of the two testing methods were not found to be interchangeable. The shorter working distance for OMA may have effected accommodation and therefore horizontal displacements.

Stereoacuity in children with anisometropic amblyopia

Wallace DK, Lazar EL, Melia M, et al J AAPOS. 2011 Oct;15(5):455-61. (s12)

The Pediatric Eye Disease Investigator Group (PEDIG) has enrolled more than 3,000 amblyopic patients into treatment trials. Stereoacuity data is available. Data was pooled from seven randomized clinical trials of subjects 3 to <18 years. The mean baseline stereoacuity was 2.7 log arcsec (between 400" and 800") overall and 2.3 log arcsec (approx. 200") for those with measurable baseline stereoacuity. 236/633 (37%) had no measurable baseline stereoacuity. Better baseline acuity was associated with 5 to <10 age group, better baseline amblyopic eye acuity, less anisometropia, and anisometropia due to astigmatism alone. 248 subjects were included in the cohort for the analyses of outcome stereopsis. The mean

stereoacuity at outcome after treatment was 2.4 log arcsec (between 200" and 400"). 154/248 (62%) achieved at least 200" of stereoacuity and 63/248 (25%) achieved at least 60" of stereoacuity. Better outcome stereoacuity was associated with better baseline stereoacuity and better amblyopic eye acuity at outcome, adjusting for baseline amblyopic eye acuity. Of 48 subjects who achieved 20/25 or better amblyopic eye acuity, 26 (54%) had a Randot Preschool Stereoacuity score of 60 arcsec or better.

Stability of near stereoacuity in childhood intermittent exotropia

Holmes JM, Leske DA, Hatt SR, et al J AAPOS. 2011 Oct;15(5):462-7. (s12)

The functional importance of near stereoacuity has been established as a measure of intermittent exotropia. The present study evaluated the course of near stereoacuity in a cohort of children with intermittent exotropia. This was a retrospective study of children with basic exotropia, or divergence-excess (pseudo or true) exotropia. Primary deterioration of stereoacuity was defined as a drop of 3 or more octaves from the previous measure. Secondary analyses with less stringent criteria were also evaluated. Ninety-five children with intermittent exotropia were identified and followed for a median duration of 15 months. Children with no stereopsis were excluded from deterioration evaluation. The primary deterioration criteria were problematic because not all subjects started with sufficient stereoacuity to allow that degree of deterioration. Of the 75 potential subjects, 2 (3%) showed deterioration during the course of follow-up. Rates were slightly higher with the less stringent criteria. Many of the subjects who deteriorated had improvement on subsequent measurements without any intervening treatment, which brings up a concern of misclassification. The definition of deterioration is fraught with problems. The primary deterioration criteria required a large drop in stereoacuity which immediately excluded those patients with poorer stereoacuity at baseline. Also the low rates of deterioration may be indistinguishable from chance rates alone. However, a more liberal approach increases the chance of misclassification. Stereoacuity can vary from visit to visit, and even over the course of one day. This reinforces the need to retest stereoacuity on the same clinic visit if there is a concern of deterioration. Finally, intermittent exotropia often takes years to decompensate and this study may not have had a long enough follow-up period.

Characteristics of divergence excess type intermittent exotropia in Asian children

Lim Z, Seenyen L, and Quah BL J AAPOS. 2011 Oct;15(5):468-72 (s12)

This study evaluates the distance-near relationships and AC/A ratios for Asian children with divergence excess type intermittent exotropia. Forty-two children were included. One hour of monocular occlusion increased strabismus measurements, except in the pseudo-divergence group. -2.0 D lens decreased distance deviations and +3.0 D lens increased near deviations. The distance-near mean difference dropped from 19 PD +/- 6 PD to 3 PD +/- 4 PD in the pseudodivergence excess group after occlusion. The true divergence excess group only showed a reduction from 24 PD +/- 10 PD to 20 PD +/- 7 PD. Results obtained with the -2.0 D lens gradient method were not always comparable with those using the +3.0 D lens gradient method after occlusion. The patients in this study were all from the office of a single practitioner and there was no matched control group.

Changes in binocular function in anisometric nonstrabismic children with optical correction and occlusion therapy

Awadein A and Fakhry MA J AAPOS. 2011 Dec;15(6):545-50 (s12)

Anisometropia can cause subnormal binocular function and decreased stereoacuity, even in the absence of amblyopia. This study enrolled children aged 4 to 11 with anisometropia. Data from 118 patients was evaluated. Spectacles improved the acuity of the more ametropic eye 2.6 +/- 2.3 lines by 1-year of follow-up. Half of this improvement occurred by 3 months and then the other half occurred over the remaining 9 months. Initially 63/118 (53%) displayed amblyopia, but with patching treatment only 21/118 (18%) had amblyopia after 1 year. Improvement in acuity was not related to age or type of anisometropia, but was related to smaller interocular acuity difference, small difference in refractive error, and better baseline best-corrected visual acuity. Positive 4 base-out prism testing (to test for bifoveal fixation), improved from 47% at baseline to 79% at the end of one year. Worth-4-dot testing displayed distance fusion in 37% at baseline and this increased to 66% at the end of one year. Measurable stereopsis improved from 59% to 80% over the same time period. >4 diopters of anisometropia was associated with reduced binocular function after completion of treatment.

Success of Prisms in the Management of Diplopia Due to Fourth Nerve Palsy. Tamhankar MA; Ying G; Volpe NJ. J Neuro-ophthalmol. Sept 2011; 31: 206-209. (s12)

This retrospective analysis studied 83 patients who were given prisms to alleviate diplopia due to fourth nerve palsy. Sixty-nine of these patients had congenital fourth nerve palsies and 14 were acquired. The authors excluded patients who declined prism therapy due to prior dissatisfaction with prism use, those who preferred eye muscle surgery or wanted to avoid the expense of incorporated prisms. Therefore they tested prism acceptance on a preselected group of patients likely to respond to prisms. They also lumped together congenital and acquired cases but did not refer to the state of incomitance. The paper gives an extended description of the basic methods of correcting diplopia with prisms, which are well known to most clinicians dealing with vertical deviations. This reviewer did not think it added much new information.[13 REFS]

The Effect of Luminance on Visual Acuity with Fresnel Prisms.

Knight R; Griffiths HJ. Brit Ir Orthopt J. 2011; 8: 29-32. (s12)

This short article reports a study on 12 subjects with normal visual acuity and binocular single vision. The purpose of the study was to determine the effect on visual acuity under photopic versus mesopic luminance conditions while wearing Fresnel prisms. The authors postulate that lowering luminance can affect visual function, making driving more dangerous, especially at night.

The results show that Fresnel prisms do decrease visual acuity under photopic conditions and moreso under mesopic conditions. This applied to prism strengths greater than 5 diopters and showed a progressive decline with increasing prism strength. The authors state

that patients should be warned about these findings, especially if Fresnel prisms are to be worn bilaterally. (Reviewer note: Adult patients should rarely, if ever be given Fresnel prisms bilaterally.) [24 REFS]

Chromostereopsis and Stereograms. Summersgill KL; Keating PD.

Brit Ir Orthopt J. 2011; 8: 50-53. (s12)

Chromostereopsis or color stereoscopy is used in this experiment to explore the effect that color has on the fusion range. It is based on the principle that red and blue stimuli have different wavelengths and create effects due to chromatic aberration. The authors tested their hypothesis that color acts as a depth cue and can complement or conflict with disparity cues in a stereogram.

Using a Synoptophore and specially designed slides resembling the well known "bucket" slides produced by Clement Clarke, one set of slides was altered to display a red inner circle and a blue outer one; the design on the other set of slides was reversed so the blue became the inner circle and red the outer one. Fusional amplitudes were tested in the usual manner.

Results showed that total fusion may increase when using complementing chromostereoscopic cues and may decrease with conflicting cues. They conclude that chromostereopsis does have an effect on the binocular control of a stereogram. [6 REFS]

Prevalence and Characteristics of Abnormal Head Posture in Children with Down Syndrome A 20-Year Retrospective, Descriptive Review.

Dumitrescu AV, Moga DC, Longmuir SQ, Olson RJ, Drack AV.

Ophthalmology.2011 Sep;118(9):1859-64. (s12)

PURPOSE:

To characterize the abnormal head posture (AHP) in children with Down syndrome (DS). The study had 3 aims: to estimate the prevalence of AHP, to describe the distribution of different causes for AHP, and to evaluate the long-term outcomes of AHP in children with DS evaluated at the University of Iowa Hospitals and Clinics between 1989 and 2009.

DESIGN:

Retrospective chart review.

PARTICIPANTS:

Two hundred fifty-nine patient records.

METHODS:

The study data were analyzed using chi-square tests (the Fisher exact test when appropriate) to describe the relationship between the outcome of interest and each study covariate. A predictive logistic regression model for AHP was constructed including all the significant covariates.

RESULTS:

Over the study period, 259 records of patients with DS were identified. Of these, 64 (24.7%) patients had AHP. The most frequent cause of AHP was incomitant strabismus in 17 (26.6%)

of 64 patients. The second most frequent cause of AHP was nystagmus, in 14 (21.8%) of 64 patients. For a substantial number of patients with AHP, the cause could not be determined. They represented 12 (18.8%) of all the patients with AHP in this study and 12 (4.6%) of all patients with DS examined. When compared with patients with AHP from a determined cause, this subgroup has a statistically significantly ($P = 0.027$, Fisher exact test) higher percentage of atlantoaxial instability. In the study population, 9 (14.1%) of 64 patients with AHP had more than 1 cause for AHP. Refractive errors, ptosis, unilateral hearing loss, and neck and spine musculoskeletal abnormalities were responsible for AHP in a small percentage of patients. Of all the patients with AHP, 23 (35.9%) improved their head posture with treatment (glasses or surgery). An additional 6 (9.4%) patients improved their posture spontaneously, over time and without treatment.

CONCLUSIONS:

The prevalence of AHP in the children with DS evaluated was 24.7%. From this analysis, having strabismus of any kind and particularly incomitant strabismus, nystagmus, or both is highly correlated with the development of an AHP. Almost 19% of DS patients with AHP had no definitive cause that could be determined.

Comment: Almost 25% of patients with Down Syndrome seen in this University pediatric eye clinic had some type of abnormal head posture, and despite many years of follow up and full evaluations, about 19% of these patients could never have an etiology for the abnormal head posture found. Only about 9% of patients with abnormal head posture had spontaneous improvement. In the children with unknown cause, a higher percentage had atlantoaxial instability than in the normal head posture group, but it is not known if this is related. Parents of children with Down syndrome should be told that abnormal head posture is not uncommon and in 1/5 cases in this series, no ocular or other cause could be found.

Congenital innervation dysgenesis syndrome (CID)/congenital cranial dysinnervation disorders (CCDDs).

Assaf AA. *Eye (Lond)*. October 2011; 25(10):1251-61. (s12)

Congenital loss of innervation to the extra-ocular muscles (EOMs) can have a profound effect on the target muscle. This has been well recognized in Duane's retraction syndrome. However, it has been less emphasized in other congenital oculo-motor disorders. Other disorders include congenital fibrosis of EOMs, congenital ptosis, monocular elevation defect, Möbius syndrome, and horizontal gaze palsy progressive scoliosis. Loss of innervation to motor muscles can be unified as a defined clinical entity, which can be labeled as congenital innervation dysgenesis syndrome (CID). The term CID, coined by the author Assaf, is similar to the term congenital cranial dysinnervation disorder, coined by others. The author describes the clinical features, genetics and neuroimaging of several of the CID/CCDDs: Duane's syndrome, CFEOM and Möbius syndrome.

Situational Restriction: Using Your Physical Exam to Differentiate Pulley Abnormalities from Other Vertical Deviations Secondary to Restrictive Conditions

Steven E. Rosenberg, M.D., Sara Shippman, C.O. *Am Orthopt J* 2011; 61: 13 – 18. (S12)

The authors describe a simple clinical method to detect strabismus secondary to a pulley anomaly, for use by those without access to dynamic MRI. The authors review, in detail, the clinical tests currently utilized to evaluate limitations in ocular rotations. The term, situational restriction, is used to describe a limitation that may disappear if the order of rotational movement is changed. In other words, if the patient appears to have a limitation in a tertiary position of gaze, rather than having the patient adopt that position of gaze by rotation around an oblique axis on Listing's Plane, the muscle function should be evaluated by having the patient rotate the eyes about the X-axis of Fick followed by the Z-axis of Fick, and compared to the result of rotation about the Z-axis first, followed by the X-axis. If the final position of the globe is the same, regardless of the path the eye took to get there, then the eye movement is commutative. Incomitant strabismus secondary to palsy or restriction typically reveals a limitation that is commutative. In a situational restriction, however, the eye movements are noncommutative, meaning that the final position of the globe is different depending on the path it took to get there. Noncommutative movements violate Listing's Law. Strabismus secondary to pulley abnormalities tend to result in noncommutative eye movements. Therefore checking versions using more than one path of motion can be helpful in determining the cause of strabismus associated with limitation of movement.

Facts, Opinions, and Unknowns The John Pratt-Johnson Annual Lecture: Intermittent Exotropia:.

Kenneth G. Romanchuk, M.D., F.R.C.S.C. *Am Orthopt J* Fall 2011; 61: 71 – 87.(S12)

The author compares his own experience with intermittent exotropia to that which has been reported in published studies. Literature on the typical presentation, age of onset, symptomatology, and natural history of the condition is reviewed and compared. The author discusses evidence of the natural variability in size of the angle, control of the angle, and stereoacuity in these patients. The sometimes contradictory recommendations regarding deterioration and timing of surgical management are emphasized. The author concludes that objectively judging deterioration, whether based on increasing frequency of the deviation, increasing angle of deviation, or loss of binocular vision, is difficult and prone to bias. Increasing parental concern over cosmesis and social interaction appears to be just as valid a measure of deterioration as the results of sensory and motor tests. He also notes that there is no consensus as to when surgical treatment should be offered, what procedure should be performed and for what target angle of deviation.

The 11th Bielschowsky Lecture: Incomitant Strabismus: Does Extraocular Muscle Form Denote Function?

Burton J. Kushner, M.D. *Am Orthopt J* Fall 2011; 61: 88 – 102. (s12)

This article is based on the Bielschowsky Lecture, given at the 2010 meeting of the International Strabismological Association in Istanbul, Turkey. The common terms used to describe clinical observation of muscle function are misleading because they may imply a specific pathophysiology. The strength of a muscle is determined by several factors such as the path of the muscle, the lever arm of the muscle, interactions with extraocular muscles in

the same and the fellow eye, patterns of innervation, muscle fiber type and distribution, and total force of the muscle. The total force of an extraocular muscle is the sum of its elastic force and its contractile force. Muscle function will be altered with abnormalities or changes in any of these categories. For this reason, a muscle that is judged clinically to be over- or under-acting, may not necessarily show changes in length or cross-section. The author concludes that extraocular muscle form does not always denote function.

Conservative Management of Intermittent Distance Exotropia: A Review

Marianne Piano, B.Sc. (Hons.), Anna R. O'Connor, Ph.D., B. Med.Sci. (Hons.) *Am Orthopt J* Fall 2011; 61: 103 – 116. (s12)

The authors reviewed the English language literature from 1950 to present to determine the outcome of non-surgical management of intermittent exotropia. Because the natural history of the condition is variable, with no strong tendency toward improvement, stability, or deterioration, many clinicians choose conservative management initially. "Conservative" management techniques include minus lens therapy, occlusion, orthoptic exercises, prisms, and observation. Published studies on each of these are reviewed and discussed in the article. The authors found that conservative management was reported to reduce the angle of deviation, promote binocular vision, and in some cases, lead to better sensory and motor outcomes following strabismus surgery. They recommend further research into these treatments.

Factors Contributing to the Outcome of Sensory Testing in Patients with Anomalous Binocular Correspondence

Kyle Arnoldi, C.O. *Am Orthopt J* Fall 2011; 61: 128 – 136. (s12)

Previous publications have emphasized the effect of image dissociation on outcome of sensory testing. The author compared the results of two different tests of sensory fusion, one highly dissociating and one mildly dissociating, using two different techniques (fovea-to-fovea presentation vs. fovea-to-deviation point presentation) in 74 patients with strabismus and previously diagnosed anomalous correspondence in order to determine what effect the choice of retinal element examined may have on the test results. Subjects were tested with the Worth 4-dot test at near fixation, the Worth 4-dot test with prism offset of the deviation at near, the Bagolini glass test at near, and the Bagolini glass test with prism offset of the deviation at near in random order. The study confirmed the results of earlier publications, showing that a fusion response is more likely on a mildly dissociating test, regardless of presentation type. However, the test presentation also had a significant impact on results. Interestingly, study subjects with a horizontal deviation between ET 15 Δ and XT 10 Δ reported fusion on the fovea-to-deviation point presentation regardless of level of image dissociation, but tended to show suppression or normal correspondence on the fovea-to-fovea presentation. Study subjects with ET \geq 20 Δ and XT \geq 15 Δ reported suppression on the fovea-to-deviation point presentation, but reported paradoxical diplopia on the fovea-to-fovea presentation. These results suggest that the developing visual system adopts different strategies for sensory adaptation to manifest strabismus, based in part on the angle of deviation. The author briefly reviews what is known about the neurophysiology of binocular vision to provide a possible explanation for these results.

Comparison of subjective and objective torsion in patients with acquired unilateral superior oblique muscle palsy

Young-Rae Roh, Jeong-Min Hwang

Br J Ophthalmol November 2011;95:1583-1587 (s12)

Background To compare objective torsion, measured using fundus photography, and subjective torsion, measured with the Lancaster red-green test (LRGT) or double Maddox rod test (DMRT), in patients with acquired unilateral superior oblique palsy (SOP).

Methods Full ophthalmic examinations, including the alternate prism and cover test, ductions/versions, three-step test, LRGT, DMRT and fundus photography, were performed in 35 consecutive patients (28 men and 7 women) (mean age, 50.4±16.2 years) with acquired unilateral SOP. The correlation between the amount of torsion measured with fundus photography, the LRGT and DMRT was analysed using linear regression analyses.

Results The LRGT, DMRT and fundus photography revealed extorsion in 16 (46%), 21 (91%) and 35 eyes (100%), respectively. There were no significant correlations between the amounts of torsion measured with the LRGT, the DMRT and fundus photography. There was a statistically significant correlation between SOP duration and the amount of torsion only when measured by the LRGT (p.0.0006).

Conclusion Objective extorsion may be found in all patients with acquired unilateral SOP, whereas subjective extorsion may be found in most patients with acquired unilateral SOP; the latter was detected more frequently with the DMRT than with the LRGT.

Ability of an Upright-Supine Test to Differentiate Skew Deviation From Other Vertical Strabismus Causes

Agnes M. F. Wong, MD, PhD, FRCSC; Linda Colpa, OC(C); Manokaraanathan Chandrakumar, HBSoc

Arch Ophthalmol. December 2011;129(12):1570-1575. (s12)

The purpose of this paper was to determine the sensitivity and specificity of a new upright-supine test to differentiate skew deviation from trochlear nerve palsy and other causes of vertical strabismus in a large number of patients. The study consisted of 125 consecutive patients who sought treatment from January 1, 2008, through December 31, 2010, for vertical strabismus of various causes: skew deviation (25 patients), trochlear nerve palsy (58 patients), restrictive causes (14 patients), and other causes (eg, myasthenia gravis and childhood strabismus) (28 patients). Twenty healthy participants served as controls. The deviation was measured by the prism and alternate cover test using a near target at 40 cm in both the upright and supine positions. A vertical strabismus that decreased by 50% or more from the upright to supine position constituted a positive test result. The upright-supine test result was positive in 20 of 25 patients with skew deviation (sensitivity, 80%) but negative in all patients with trochlear nerve palsy, restrictive, or other causes (specificity, 100%). The authors feel that the upright-supine test is highly specific for differentiating skew deviation from other causes of vertical strabismus. This test could be added as a fourth step after the 3-step test, and if the result is positive, neuroimaging should be considered if indicated clinically.

Transient SO paresis after injection of BoTox for facial rejuvenation

Kothari M, Shukri N, Quayyum A.

Indian J Ophthalmol 2012;60:77-8 (Jan-Feb) (s12)

In this letter to the editor, the authors describe a patient who developed transient SO paresis following botox administration. There have been previous reports of transient IO paresis and LR paresis in this setting, but this is the first reported case of its kind. The resulting deviation was small, only 2 PD in primary gaze, but resulted in diplopia and a head tilt. The deviation resolved spontaneously 7 weeks following the BoTox administration. **Comment** The authors propose risk factors in this patient for development of the SO paresis were history of prior botox injections (increased intraorbital diffusion), proximity of needle tip to trochlea (faulty technique), and deep penetration of the needle into orbital septum (faulty technique).

Use of atropine to predict the accommodative component in esotropia with hypermetropia

Kothari M, Manurung F, Paralkar S . Indian J Ophthalmol 2011;59:487-90 (Nov-Dec) (s12)

This cohort study included children with esotropia and hypermetropia of $\geq +2.0$ diopters (D). The deviation was measured at presentation, under atropine cycloplegia and 3 months after full refractive correction. Eighteen (41%) had fully refractive accommodative esotropia (RAE), 10 (23%) had partial accommodative esotropia (PAE), and 5 (11%) had nonaccommodative esotropia (NAE). Eleven (25%) had convergence excess (CE). Under cycloplegia, all with RAE and RAE with CE had orthotropia. There was no significant change in the deviation in the patients with NAE. The deviation under cycloplegia and that with full refractive correction in PAE and PAE with CE (with +3.0 D addition) were not different. **Conclusion** Ocular deviation under cycloplegia can help to predict the accommodative component in esotropia with hypermetropia. **Comment** Although this seems to be a useful test, it is done with full atropine cycloplegia. The results may not be valid under partial or near-complete cycloplegia with in-office cycloplegic agents such as cyclopentolate. One should perform dynamic retinoscopy to check the completeness of cycloplegia following in-office cyclopentolate, before applying this test

Changes in Exodeviation Following Hyperopic Correction in Patients with Intermittent Exotropia

Seung Ah Chung, In Sik Kim, Wook Kyum Kim, Jong Bok Lee, Journal of Pediatric Ophthalmology and Strabismus, September 2011; 48: 278-284 (s12)

Hyperopic correction has traditionally been prescribed to patients with accommodative esotropia. Exodeviations are thought to be improved with giving a more minus prescription forcing one to accommodate and improving and exodeviation. However there have been reports of correction of exodeviations after correcting with a hyperopic prescription. The theory behind this is that correction of a refractive error allows for a clear retinal image that could improve fusional convergence with a subsequent improvement in the angle of exodeviation. The study found an improvement in the angle of deviation when there was hyperopic astigmatism or amblyopia rather than pure hyperopia because hyperopia reduces the need for accommodative convergence therefore increasing the angle of deviation.

Function Magnetic Resonance Imaging of Binocular Interactions in Visual Cortex in Strabismus

Vincent J. Chen, Kristina Tarczy-Hornoch, *Journal of Pediatric Ophthalmology and Strabismus* November 2011; 48: 366-374 (s12)

Strabismus, when it has its onset in childhood can cause the development of perceptual suppression which helps the child avoid diplopia and visual confusion. However, chronic suppression can lead to difficulty in depth perception. Using functional magnetic resonance imaging (fMRI), the study evaluated changes in cortical activity related to suppression of visual perception from one eye in the setting of strabismus. Other studies have demonstrated interocular suppression of cortical signals in patients with strabismus but none of these have been able to characterize the locus of neural suppression. Using fMRI in subjects with strabismus with and without amblyopia, the study was able to demonstrate modulation of neuronal activity in the primary visual cortex correlated with perception in the setting of strabismic subjects. The study also found that this modulation was less in amblyopic subjects than in nonamblyopic subjects and offers several hypotheses as to why this occurs.

Extraocular Muscle Dynamics in Diplopia from Enophthalmos

Michael K. Yoon, John R. Economides, Johnathan C. Horton, *Strabismus*, 19 (4), 142-146 December 2011 (s12)

Trauma related enophthalmos can cause diplopia due to a variety of reasons – fracture with secondary muscle entrapment, scarring, traumatic neuropathy or myopathy. If enophthalmos occurs secondary to enlargement of the orbit causing posterior displacement of the globe, diplopia may occur as well; however, the mechanism is unclear. This article reports a single case of a 55 year old man with binocular diplopia for 1 year in upgaze and lateral gaze and transient diplopia when returning to primary gaze. He had a left orbitozygomatic pterional craniotomy 2 years prior. After several months, he began experiencing diplopia. On examination, there was 8mm of enophthalmos in the left eye with limitation in elevation, adduction and abduction. Ct scan showed a large defect in the left zygomatic and sphenoid bones with a redundant loop of the lateral rectus muscle. The left medial rectus muscle was shorter than its right counterpart as was the left lateral rectus when compared to the right lateral rectus muscle. Postsurgical enophthalmos can occur following orbitozygomatic pterional craniotomy. If not properly reconstructed, there is a net increase in orbital volume causing posterior dislocation of the globe and the muscles shorten. This muscle shortening causes a weakening of the muscles in their field of action and causing diplopia in eccentric gaze, relatively sparing downgaze.

Congenital Esotropia and the Risk of Mental Illness by Early Adulthood

Joshua H. Olson, Curtis R. Louwage, Nancy N. Diehl, Brian G Mohny, *Ophthalmology* 2012 January; 119: 145-149 (s12)

Retrospective population- based cohort for patients less than 19 years of age, living in Olmsted County, Minnesota who developed congenital esotropia. All patients resided in Olmsted County between January 1, 1965 and December 31, 1994. All patients with congenital esotropia were matched 1 to 1 with non-strabismic birth and gender matched controls.

Patients with congenital esotropia, are 2.6 times more likely to develop mental illness than age matched controls. Similar findings have also have been reported for intermittent exotropia and convergence insufficiency.

Study performed by the Mayo Clinic Department of Ophthalmology, Rochester, Minnesota.

COMMENT: Hard to draw meaningful conclusions from this very select population cohort.

X. STRABISMUS SURGERY

Amniotic Membrane Transplantation for Restrictive Strabismus

Yi Ning J Strube, MD, FRCSC, Francisco Conte, MD, Claudia Faria, MD, Samuel Yiu, PhD, MD, Kenneth W Wright, MD
Ophthalmology Volume 118, Number 6, June 2011 (F11)

Type of Study

Retrospective, interventional case series. Chart review of 7 consecutive patients (8 eyes) who developed restrictive strabismus after periocular surgery and were treated with surgical removal of restrictive adhesions and placement of amniotic membrane transplant.

Study Objectives and Design

The purpose of this study was to report the use of amniotic membrane transplantations with restrictive strabismus. In this series, restrictive strabismus occurred after surgery for pterygium, retinal detachment, orbital floor fracture, dermoid cyst and dermatochalasis.

Restrictive strabismus occurred as a result of scarring of the conjunctiva, fat adherence or rectus muscle contracture after previous non-strabismus surgery. All patients developed postoperative scarring which failed additional standard surgery to remove the adhesions.

Results: Reoperation using amniotic membrane transplantation was associated with improvement of ocular motility in 6 of the 7 patients. One patient had recurrence of scarring with persistent diplopia. Six of 7 patients had no significant recurrence of scarring and extraocular motility remains stable during a follow-up period of 5 to 13 months.

Key Study Conclusions

Amniotic membrane transplantation seems to help prevent recurrence of adhesions in patients with restrictive strabismus caused by conjunctival scarring, fat adherence syndrome

or extraocular muscle contracture. All of the cases reported did not have previous strabismus surgery.

Use of an amniotic membrane transplant has been described for the repair of severe conjunctival dehiscence after strabismus surgery by Rahman et. al. in Eye (Lond) 2009. Two of the reported 7 patients required reoperations with amniotic membrane transplant. Two of the 7 patients also had previous surgery with Mitomycin C which was unsuccessful in controlling restrictive strabismus. Both of these patients did show improved ocular motility and decreased scarring with the use of amniotic membrane.

Pearls

Amniotic membrane transplantation may be a useful tool in the treatment of restrictive strabismus, particularly when restrictive strabismus is caused by conjunctival scarring from previous surgery. Conjunctival scarring with extraocular muscle contracture associated with previous surgery, fat adherence to the globe and eye muscle (with or without previous strabismus surgery) and contracture of the rectus muscle (of any cause).

Surgical management of adult onset age-related distance esotropia.

Mittelman D. JPOS 2011;48:214-216. (July-August) (s12)

Purpose: to study the effects of bilateral medial rectus muscle recession for the management of distance esotropia in adults who cannot be managed successfully with prism therapy.

Methods: ten patients with adult-onset distance esotropia measuring 14 prism diopters or greater underwent strabismus surgery to eliminate the need for prism glasses.

Results: in 13 of 14 patients the diplopia completely resolved post-operatively with a median residual deviation of 1 prism diopter esophoria for distance and 2 prism diopters exophoria at near.

Conclusion: bilateral medial rectus recession is a useful technique in managing adult-onset age-related distance esotropia that is not satisfactorily controlled with prism.

Comment: a good review of a common problem in adult strabismus. Reference is made to the previous term for this condition (divergence insufficiency) and suggests that this term no longer be used. Connective tissue changes within the orbit have been proposed as a possible cause in previous studies. Larger amounts of medial rectus muscle recession are required than typically used in standard strabismus surgery tables. Base-out prism remains the mainstay of therapy for most patients.

Globe perforation during strabismus surgery in an animal model: Treatment versus observation

Bagheri A, Erfanian-Salim R, Ahmadi H, et al. April J AAPOS 2011;15:144-147 (f11)

An animal model was used to assess different therapeutic modalities for the treatment of globe perforation during strabismus surgery. A full-thickness perforation of sclera was performed in each eye of 42 adult rex rabbits, 6 mm posterior to the rectus insertion. One eye was treated with either cryopexy or laser retinopexy, and the other eye was left

untreated. Retinal breaks occurred in 24/84 eyes and retinal tears occurred in 60/84 eyes. No cases of endophthalmitis or retinal detachment occurred, over a follow-up period of 1 to 7 months. Overall complication rates were not significantly different in the laser, cryo, or observation groups. The role of antibiotics were not addressed by this study. Also, applying results of this study to human eyes should be done with caution, because there are anatomical differences between the rabbit and human eye.

Long-term outcome of primary congenital glaucoma

De Silva DJ, Khaw PT, and Brookes JL. *Apr. J AAPOS* April 2011;15:148-152 (f11)

The goal of this paper was to evaluate the long-term outcome, acuity and risk of progression in patients with primary congenital glaucoma (PCG). Sixteen patients with at least 22 years of follow-up were included. Probability of stability was 90.3% at 1 year, 70.8% at 10 years, and under 50% at 40 years. Glaucomatous progression can occur many years after stability, highlighting the need for continued follow-up. These patients were followed over decades. Because of advances in surgery, medications, and diagnostic testing, the data from this paper is unlikely to be applicable to a patient who is newly diagnosed with PCG.

Surgical Management of Residual or Recurrent Esotropia Following Maximal Bilateral Medial Rectus Recession

David G. Morrison, MD; Matthew Emanuel, MD; Sean P. Donahue, MD, PhD. *Arch Ophthalmol.* February 2011;129(2):173-175. (f11)

The objective of this paper was to describe the effect of graded unilateral vs bilateral lateral rectus resection in the treatment of residual or recurrent esotropia after maximal medial rectus muscle recession. This was a retrospective case series of children with residual or recurrent esotropia. All children underwent initial eye muscle surgery for angles of 40 to 60 prism diopters (medial rectus recession of 5.5-6.5 mm; 11.0-11.5 mm from surgical limbus). If significant esotropia persisted or recurred, surgical results from graded lateral rectus resection were recorded. Thirty-eight children were identified for the study. Unilateral lateral rectus resection ranging from 4 to 7 mm resulted in mean esotropic corrections of 10.5 to 14.9 prism diopters. Differences in surgical response per millimeter of unilateral lateral rectus resection were not significant. Bilateral lateral rectus resection of 5, 6, and 7 mm resulted in a mean correction of 19.75, 28.75, and 33.5 prism diopters, respectively. The authors concluded that graded lateral rectus resection can produce highly variable results on a case-to-case basis, but mean values trend in the expected direction. Residual deviations larger than 15 prism diopters need to be addressed with bilateral surgery.

Dose-effect relationship of medial rectus muscle advancement for consecutive exotropia

Marcon GB and Pittino R *J AAPOS.* 2011 Dec;15(6):523-6 (s12)

The authors evaluated the dose-effect for medial rectus muscle advancement 6 months after surgery to correct a consecutive exotropia. This was a retrospective record review of consecutive patients treated for consecutive exotropia over a seventeen month period in a single-surgeon ophthalmic practice. Deviations <25 PD received one muscle surgery, while 2

muscle-surgery was performed on deviations >40 PD. For deviations measuring between 25 and 40 PD, one muscle was operated on, and then a second muscle was operated on 6 months later if necessary (but not included in data results). Preoperatively, the plan was to advance the medial rectus back to the original insertion, but intraoperatively the plan was modified based on the muscle stretch test. A dose-effect was calculated as the ratio between the change in deviation and the surgical dose.

Results from 24 patients (age range 18-60) were tabulated. A mean change of 2 PD was found for each mm of medial rectus advancement. A mean exodrift of 9 PD occurred during the follow-up period. A fairly linear, strong relationship was found between mm of medial rectus advancement and change in deviation. A larger preoperative angle also correlated with a greater change in the deviation for the same amount of advancement.

This study was small and retrospective. Also it is questionable whether advancing one medial rectus a certain number of mm is equivalent to advancing both medial recti half of that amount (ie. Does 6mm = 3mm + 3mm?). Finally, it is not known whether the amount of exodrift over time is the same if surgery is unilateral or bilateral.

Postoperative outcomes of patients initially overcorrected for intermittent exotropia

Pineles SL, Deitz LW and Velez FG J AAPOS. 2011 Dec;15(6):527-31 (s12)

Most clinicians agree that an esotropic overcorrection is the desired alignment immediately after strabismus surgery to correct intermittent exotropia. However, does the amount of initial overcorrection on postoperative day 1 help determine long-term stability? This paper is a retrospective review of one surgeons' cases over a twelve year period. 63 patients met inclusion criteria, which required the patient to be overcorrected on day 1 postoperatively. Of these patients, 26 (41%) still developed an intermittent exotropia of ≥ 8 PD at their last postoperative visit. Six patients (10%) had a monofixation range esotropia. There was a trend towards increased risk of recurrent exotropia in those with the smaller overcorrections on day 1 postop. The amount of esotropia on day 1 was not shown to correlate with long-term stability or successful alignment. This study is limited by its retrospective nature. Also non-surgical postoperative treatments, such as prisms or patching could have influenced results. True divergence excess patients were not differentiated from pseudo-divergence excess patients.

Anchored versus conventional hang-back bilateral lateral rectus muscle recession for exotropia

Nabie R, Azadeh M, Andalib D, and Mohammadlou FS J AAPOS. 2011 Dec;15(6):532-5 (s12)

Advantages of hang-back strabismus surgery include decreased operating times, better exposure, and a theoretical lower risk of scleral perforation. Potential disadvantages include muscle bowing, resulting in lower accuracy and reliability. The authors used an 'anchored' hang-back procedure, with a short superficial pass of a scleral suture adjacent to the muscle attachment site. This study compared results of conventional hang-back versus 'anchored'

hang-back for bilateral lateral rectus recessions. There was no significant difference in success rates or complications in the two groups over a minimum follow-up of 6 months. Based on this study, there does not seem to be any benefit of performing an 'anchored' hang-back procedure.

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The Long-Term Survival Analysis of Bilateral Lateral Rectus Recession Versus Unilateral Recession-Resection for Intermittent Exotropia."

Am Cho J, Chang JW, Kim SJ, Yu YS J Ophthalmol February 2012; 153(2):343-51. (s12)

This nonrandomized retrospective case series was conducted to form a comparison of the long-term surgical outcomes of bilateral lateral rectus recession (BLR) vs unilateral lateral rectus recession–medial rectus resection (RR) in treatment of intermittent exotropia.

Consecutive patients who underwent BLR or RR for treatment of intermittent exotropia with a minimum follow up of ≥ 2 years were compared, with the main outcome being overcorrection (esophoria/tropia $> 5 \Delta$), success (esophoria/tropia $\leq 5 \Delta$ to exophoria/tropia $\leq 10 \Delta$), or undercorrection/recurrence (exophoria/tropia $> 10 \Delta$) at postoperative 1 day, 1 month, 6 months, 1 year, and 2 years, and at the final examination. Of 128 patients, 55 underwent BLR and 73 underwent RR. The mean follow-up period was 44.2 months in the BLR group and 47.8 months in the RR group. At 1 day, 1 month, 6 months, 1 year, and 2 years after surgery, surgical outcomes in each group were not different ($P > .05$) However, the final outcome at a mean of 3.8 years was significantly different between the groups, demonstrating a higher success rate in the BLR group than in the RR group (58.2% vs 27.4%, $P < .01$). Cumulative probability of survival from recurrence was higher in the BLR group than in the RR group ($P = .01$, log-rank test). Recurrences were most common within 6 months from surgery; however, after that, recurrences occurred continuously in the RR group and rarely in the BLR group. The authors concluded that outcomes by 2 years after surgery for intermittent exotropia were not different between the BLR and RR groups but that final outcomes were better in the BLR group than in the RR group.

This paper is limited by its retrospective and non-randomized nature but is another interesting study that may aid clinicians managing intermittent exotropia. These findings will be tested further by the PEDIG randomized trial of BLR vs RR that is currently underway

Three horizontal muscle surgery for large-angle infantile esotropia: validation of a table of amounts of surgery.

Camuglia JE, Walsh MJ, Gole GA. *Eye (Lond)*. November 2011;25(11):1435-41. (s12)

The authors validate a table of amounts of three horizontal muscle surgery in patients with large-angle infantile esotropia (≥ 60 prism diopters, PD) in 51 patients. The table is for deviations of 60-85 PD, stratified by age $<$ or $>$ 12 months. The surgeon performs a bilateral medial rectus recession measured at 10 to 11 mm posterior to the limbus, and one lateral rectus muscle resection of 4 to 8 mm. The patients are followed for up to eight years postoperatively. The primary outcome measure is alignment within 10 PD of orthotropia.

The median preoperative deviation was 65 PD (range 60-80 PD) and median age at surgery was 11.8 months (range 5.1 months-3.6 years). Surgeries were performed between 1993 and 2009. Surgical success to orthotropia (± 10 PD) after one surgery was 100% at 2 months, 95.7% at 6 months, 91.3% at 12 months, 77.8% at 4 years, and 73.6% at 8 years. Postoperative failure requiring further horizontal surgery occurred in 17.6% (residual esotropia 4, consecutive exotropia 5).

The authors conclude that if the published table of surgical amounts is used, three horizontal muscle surgery in large-angle infantile esotropia (≥ 60 PD) appears to have a good long-term success rate. The authors do not report how many of the original 51 patients were analyzed at each of the postoperative time points, which raises the possibility that patients who were not followed to 8 years differ from those who were followed to 8 years.

The tendon width of lateral rectus muscle in predicting the effect of recession: is it just age-related artifact?

Yun CM, Kim SH. *Eye (Lond)*. October 2011;25(10):1356-9. (s12)

This study was conducted to investigate whether the tendon width of the lateral rectus would differ according to different age groups. The authors studied 133 patients ranging from 0 to 51 years of age who had undergone bilateral lateral rectus (BLR) recession for the basic type of intermittent exotropia. Under general anesthesia and before dissection of the muscle tendon from the sclera, the tendon width of the lateral rectus of both eyes near insertion was measured with calipers. Mean tendon widths of both eyes were 7.75 ± 0.34 in group 1 (age <2 years), 7.68 ± 0.42 in group 2 (age 2-5 years), 8.01 ± 0.39 in group 3 (age 5-13 years) and 8.06 ± 0.45 in group 4 (age 13-51 years). The difference of tendon width in both eyes was statistically significant in all four groups ($P < 0.01$).

This study shows that the anatomy of the extraocular muscles changes with age, as do other eye parameters. The authors believe that tendon width is clinically relevant because "it is known to be a useful indicator for estimation of the effect of lateral rectus recession in intermittent exotropia." The authors propose that tendon width be used to estimate the effect of lateral rectus recession in intermittent exotropia only in children ages 5 years and older, as the tendon is still growing in width in younger children.

Adjustable suture strabismus surgery.

Nihalani BR, Hunter DG. *Eye (Lond)*. October 2011; 25(10):1262-76. (s12)

Adjustable suture strabismus surgery has been available for decades as a tool to potentially enhance the surgical outcomes. Intellectually, it seems logical that having a second chance to improve the outcome of a strabismus procedure should increase the overall success rate and reduce the reoperation rate. Yet, adjustable suture surgery has not gained universal acceptance, partly because Level 1 evidence of its advantages is lacking, and partly because the learning curve for accurate decision making during suture adjustment may span a decade or more.

In this review, the authors describe the indications, anesthesia choices, surgical techniques, and special circumstances: adjustable suture use in children, adjustable superior and inferior oblique surgeries, adjustable posterior fixation sutures, semiadjustable sutures (primarily for the inferior rectus), and adjustable lower eyelid retractor positioning. Although no well controlled studies of adjustable suture use were found in the authors' literature review, they found that most published studies suggest a benefit of suture adjustment with an approximately 10% increase in success rates. The complications of adjustable sutures include symptoms related to suture adjustment: nausea, pain, and possible bradycardia due to the oculocardiac reflex; knot slippage; and abnormal conjunctival healing and inflammatory responses. The authors advocate that strabismus surgeons become facile in adjustable suture use.

Medial Rectus Recession After Vertical Rectus Transposition in Patients With Esotropic Duane Syndrome

Stacy L. Pineles, MD; Arthur L. Rosenbaum, MD; Ramesh Kekunnaya, MD; Federico G. Velez, MD

Arch Ophthalmol. September 2011;129(9):1195-1198. (s12)

This paper describes preoperative characteristics and postoperative results among patients with esotropic Duane syndrome who underwent vertical rectus transposition with vs without subsequent medial rectus recession (MRR). Clinical records were compared of patients with esotropic Duane syndrome who underwent vertical rectus transposition with (study group) vs without (control group) subsequent MRR. Twenty-three study group members and 26 control group members were identified. Preoperative characteristics that differed between groups were the mean (SD) primary position deviation (20 [7] prism diopters of esotropia [ET] for the study group vs 15 [9] ET for the control group, $P = .002$) and the mean (SD) adduction deviation (1.4 [4.0] ET for the study group vs 2.5 [4.0] exotropia for the control group, $P = .04$). Forced duction testing (FDT) revealed greater restriction to abduction (17 [7]° for the study group vs 23 [6]° for the control group, $P = .002$). After vertical rectus transposition, study group members had significantly greater mean (SD) ET (16 [7] ET vs 0.4 [0.6] ET for the control group, $P < .001$) and torticollis (10 [4]° vs 1 [5]° for the control group, $P < .001$) and significantly less mean (SD) abduction (−3.0 [−0.6] vs −2.0 [−0.7] for the control group, $P = .20$). After MRR, no significant difference was observed between groups in primary position deviation, but the study group had significantly less mean (SD) adduction (−1.0 [−0.8] vs −0.4 [−0.6] for the control group, $P < .003$). The authors conclude that the risk factors for requiring MRR after vertical rectus transposition include greater ET in the primary position and in the adducting field of gaze, as well as greater restriction to abduction on intraoperative FDT. Postoperative results of patients who required MRR were similar to those of patients who did not require MRR.

Superior Rectus Transposition and Medial Rectus Recession for Duane Syndrome and Sixth Nerve Palsy

Reshma A. Mehendale, MD; Linda R. Dagi, MD; Carolyn Wu, MD; Danielle Ledoux, MD; Suzanne Johnston, MD; David G. Hunter, MD, PhD

Arch Ophthalmol. February 2012;130(2):195-201 (s12)

The purpose of this paper was to describe our results using augmented temporal superior rectus transposition (SRT) with adjustable medial rectus muscle recession (MRc) for treatment of Duane syndrome and sixth nerve palsy. This was a retrospective surgical case review of patients undergoing SRT. Preoperative and postoperative orthoptic measurements were recorded. Minimum follow-up was 6 weeks. Main outcome measures included the angle of esotropia in the primary position and the angle of head turn. Secondary outcomes included duction limitation, stereopsis, and new vertical deviations. The review identified 17 patients: 10 with Duane syndrome and 7 with sixth nerve palsy. Combining SRT with MRc improved esotropia from 44 to 10 prism diopters ($P < .001$), reduced abduction limitation from −4.3 to −2.7 ($P < .001$), and improved compensatory head posture from 28° to 4° ($P < .001$). Stereopsis was recovered in 8 patients ($P = .03$). Three patients required a reoperation: 1 for overcorrection and 2 for undercorrection. A new primary position vertical deviation was observed in 2 patients with complex sixth nerve palsy and none with Duane syndrome. No patient described torsional diplopia. The authors feel that superior rectus transposition allows

for the option of simultaneous MRc in patients with severe abduction limitation who require transposition surgery. Combining SRT and MRc improved esotropia, head position, abduction limitation, and stereopsis without inducing torsional diplopia.

Management of diplopia in patients with blowout fractures

Ceylan OM, Uysal Y, Mutlu FM, Tuncer K, Altinsoy HI. Indian J Ophthalmol 2011;59:461-4 (Nov-Dec) (s12)

Data for 39 patients with diplopia due to orbital blowout fracture (inferior, medial, or both) were analyzed retrospectively. Strabismus surgery or prism correction was performed in required patients for the management of persistent diplopia. **Results:** Twenty-three (58.9%) patients with diplopia underwent surgical repair of blowout fracture. Diplopia was eliminated in 17 (73.9%) patients following orbital wall surgery. Of the 23 patients, three (7.6%) patients required prism glasses and another three (7.6%) patients required strabismus surgery for persistent diplopia. In four patients, strabismus surgery was performed without fracture repair. Twelve patients with negative forced duction test results were followed up without surgery. **Conclusions:** In this study 69.2% of patients with diplopia required surgical intervention. Primary gaze diplopia was eliminated in 73.9% of patients through orbital wall repair. The most frequently employed secondary surgery was adjustable inferior rectus recession and <17.8% of patients required additional strabismus surgery. **Comment** This retrospective analysis helps us consider (and discuss with patients) the possibility of a patient with diplopia from orbital wall fracture eventually needing prisms or surgery.

A Randomized Clinical Trial Comparing Myectomy and Recession in the Management of Inferior Oblique Muscle Overaction

Zhale Rajavi, Arman Molazadeh, Alireza Ramezani, Mehdi Yaseri, Journal of Pediatric Ophthalmology and Strabismus November 2011; 48: 375-380 (s12)

Inferior Oblique overaction often accompanies esotropia and exotropia causing a V-pattern. It can cause diplopia, asthenopia, hypertropia in adduction and in primary position, an abnormal head position as well as dissociated vertical deviation. The two main procedures used to weaken the inferior oblique are inferior oblique myectomy and inferior oblique recession. The goal of this study was to compare the effect of the two methods. The conclusion of the study was that both methods are effective in improving inferior oblique overaction and are comparable in achieving satisfactory results.

Conjunctival Cysts as a Complication After Strabismus Surgery

Ana Maria Guadilla, Pilar Gomez de Liano, Pilar Merino, Gema Franco, Journal of Pediatric Ophthalmology and Strabismus September 2011; 48:298-300 (s12)

Conjunctival cyst can occur as a complication after strabismus surgery. Clinically, a conjunctival cyst looks like a globular lesion with serous content and is attached to the sclera. The time of occurrence can vary up to years after the strabismus surgery. They can be observed or removed if irritating or are aesthetically displeasing. Conjunctival cysts were

found to have a low incidence after strabismus surgery (0.25% and there was a tendency (not statistically significant) for conjunctival cysts to appear following muscle recessions. A complete recession was recommended if surgical intervention is undertaken due to possible recurrence if another technique is used.

Underacting Inferior Oblique Muscle Following Myectomy or Recession for Unilateral Inferior Oblique Overaction

Sudipto Bhatta, Graham Auger, Tsiang Ung, John Burke, FRCS, *Journal of Pediatric Ophthalmology and Strabismus* January 2012; 49: 43-48 (s12)

The two most popular methods of treatment for inferior oblique overaction are an inferior oblique myectomy and an inferior oblique recession. The incidence, behavior and functional impact of postoperative inferior oblique under action following unilateral inferior oblique myectomy or recession was evaluated. Inferior oblique under action was found to be common. It was generally mild and asymptomatic six months after surgery. There were, however, a small number of patients (6.3%) that were symptomatic and required further surgery. The risk factors for symptomatic inferior oblique under action was a history of orbital and/or closed head trauma or a highly asymmetrical and masked bilateral superior oblique under action.

Postoperative Convergence After Recovery from General Anesthesia in Exotropia Surgery

Sukgyu Ha, Seung-Hyun Kim, *Journal of Pediatric Ophthalmology and Strabismus*, September 2011; 48: 305-310 (s12)

Eye position under general anesthesia is thought to be typically divergent. It is difficult to determine eye position immediately after surgery because of this fact. The study's aim is to evaluate eye position under general anesthesia following strabismus surgery and to evaluate if this is predictable of ocular motility findings on postoperative day one. Measurements taken under general anesthesia were taken using the Hirschberg method whereas on day one after surgery it was done using an alternate prism cover test. The study only looked at patients with exotropia who underwent either a bilateral rectus recession or a medial rectus resection and a lateral rectus recession. All patients that had bilateral lateral rectus recessions had approximately 10PD of convergence; those who had a resection of the MR and a recession of the LR muscle had a more predictable outcome following surgery, their immediate postoperative measurements under general anesthesia were similar to postoperative day one outcomes in the office.

Effects of Solid Hyaluronic Acid Film on Postoperative Fibrous Scar Formation After Strabismus Surgery in Animals

Kimio Takeuchi, Mitsuru Nakazawa, Tomomi Metoki, et. Al. *Journal of Pediatric Ophthalmology and Strabismus* September 2011, 48: 301-304 (s12)

Strabismus surgery typically has minimal scarring of the subconjunctival space. Extensive scarring, such that can occur with fat adherence syndrome can cause incurable adhesions between muscle, tenon's capsule and conjunctiva around the traumatized ocular surface. The article discusses the use of a film of solid hyaluronic acid and carboxymethyl cellulose in rabbit ocular tissues to evaluate the benefit of hyaluronic acid film in strabismus surgery. Formation of postoperative fibrous tissue was quantitatively less abundant in the film treated eyes than in control eyes. The hyaluronic acid film was easily inserted into the subconjunctival space. This may be a safe and effective procedure for preventing postoperative adhesions around surgical wounds in conjunctiva, subconjunctival space, sclera, and extraocular muscle.

Changes in the Interpupillary Distance Following General Anesthesia in Children with Intermittent Exotropia: A Predictor of Surgical Outcomes

Hyoungh Won Bae, Srung Ah Chung, Jin Sook Yoon, Jong Bok Lee, Journal of Pediatric Ophthalmology and Strabismus January 2012; 49: 49-53 (s12)

Adjustable sutures are not always practical in the pediatric population. Adjusting immediately after surgery while still under general anesthesia would be ideal. An objective indicator of ocular alignment during surgery is critical. This study evaluated whether changes in interpupillary distance following general anesthesia correlate with preoperative angle of deviation in children with intermittent exotropia and if this can predict surgical outcome. The study found that changes in anatomic interpupillary distance following general anesthesia was strongly correlated with preoperative angle of deviation. This could therefore predict surgical outcome in children with intermittent exotropia.

Superior Oblique Tuck: Its Success as a Single Muscle Treatment for Selected Cases of Superior Oblique Palsy

J.M. Durnian, I.B. Marsh, Strabismus, 19(4), 133-137, December 2011 (s12)

Superior Oblique Palsy (SOP) is the most common cycloversional palsy encountered. Surgical management aims to achieve motor fusion in the primary position. A superior oblique tuck (SOT) procedure for treatment of SOP is controversial. Some surgeons maintain that it should only be performed if a lax superior oblique tendon is noted. This study reports results of SOT for SOP over 17 years. All patients who underwent SOT did not have inferior oblique overaction (no overelevation in adduction). The study reported 75 cases and found success with a single SOT in 71% of cases. Twenty-nine percent of cases required further procedures – mostly contralateral inferior rectus recessions. Brown's syndrome occurred in 13% of cases – all were asymptomatic and not require treatment. The study concluded that SOT are a safe and effective procedure in selected cases. There was no correlation between the size of the tuck and change in deviation.

Surgery for Residual Convergence Excess Esotropia

Himanshu I. Patel, Emma Dawson, John Lee, Strabismus, 19 (4), 153-156 December 2011 (s12)

Convergence excess esotropia is when the patient is fully corrected for their hypermetropia and has a microtropia or an esophoria at distance. The treatment for this is typically bifocals or miotic drops. Surgery on the medial rectus muscle for the near deviation is an option but concerns regarding overcorrection arise. It is also an invasive procedure when a perfectly viable nonsurgical option is available. The current study reviewed a group of cases that had a secondary procedure for residual or recurrent convergence excess. The patients underwent either a bilateral medial rectus posterior fixation suture with or without a central tenotomy. All patients had an improvement in their deviation at near and non required bifocals after. Only one patient had an overcorrection at distance, however it was only an exophoria of 2 prism diopters. The study concluded that bilateral medial rectus posterior fixation sutures with or without a central tenotomy was a viable secondary procedure for residual convergence excess esotropia.

XI Cataract

The Infant Aphakia Treatment Study: Evaluation of cataract morphology in eyes with monocular cataracts

Wilson ME, Trivedi RH, Morrison DG, et al J AAPOS. 2011 Oct;15(5):421-6 (s12)

The Infant Aphakia Treatment Study (IATS) is a randomized multicenter clinical trial to compare IOL with contact lens correction in infants with a monocular cataract who have undergone surgery at 28 days to <7 months of age. The surgeries were videotaped. Nuclear cataracts were present in 45/83 eyes (54%). Nuclear cataract was associated with extension into the surrounding lens cortex in 41/45. All 45 had an associated posterior capsule plaque. Cortical cataract without nuclear involvement was seen in 21/83 eyes (25%). 16/21 also had a posterior capsule plaque. Evidence of PFV or persistent hyaloids stalk was seen in 18/83 eyes (22%). However this rate is artifactually low because severe PFV cases were excluded from this study. Posterior lentiglobus was seen in 4 of 83 eyes (5%). An isolated posterior capsule plaque was seen in 6/83 eyes (7%). A white cataract was present in 3/83 eyes (4%) and another 7/83 eyes (8%) had a partially resorbed lens. The most common single finding in this series was an opacity of the posterior capsule. Many of these would not have been noted on clinical examination alone. The results of this study support the contention that posterior capsule plaques and the associated opacities in the nucleus and cortex may occur as a result of a mild form of PFV. The results of this study should not be generalized to binocular cataracts or cataracts acquired later in life.

Infant Aphakia Treatment Study: Effects of persistent fetal vasculature on outcome at 1 year of age

Morrison DG, Wilson ME, Trivedi RH, et al J AAPOS. 2011 Oct;15(5):427-31 (s12)

The authors evaluated whether visual and structural outcomes in eyes with mild PFV differ from those of the overall IATS study group. 18/83 children in this study were determined to have evidence of PFV. Visual acuity at 1 year of age did not differ between these groups. Adverse effects occurred in the first year after surgery in 67% of children with PFV and in 46% of children without PFV. However this difference was not statistically significant. IATS was not powered to study differing causes of unilateral, infantile cataract. Also resolution acuity was tested, rather than recognition acuity.

Lenticular Abnormalities in Children

Sudarshan Khokhar, Tushar Agarwal, Gaurav Kumar, et. Al Journal of Pediatric Ophthalmology and Strabismus January 2012; 49: 32-37 (s12)

Lens abnormalities are an important cause of blindness in children. Cataracts can be congenital or acquired secondary to metabolic complexities or post traumatic complications. A retrospective collection of data over 2 years was collected at a hospital in New Dehli, India. Developmental cataracts were the most common type of cataract with a mean age of 4.53 years. Sixty seven percent were male and 44% had bilateral cataracts, 30 % of these cases had squint with esotropia more common than exotropia. Nystagmus was present in 15% of cases, typically when younger than 6 months of age and with total cataracts. The second most common type of cataract was post traumatic with a higher mean age of onset than developmental cataracts. Other types of cataracts are discussed as well as complications of cataract extraction. This study brings to light that given proper and timely care, these lenticular problems can be addressed and rehabilitated.

XII. CATARACT SURGERY

Axial Length Measurements by Contact and Immersion Techniques in Pediatric Eyes with Cataract

Rupal H Trivedi, MD, MSCR, M Edward Wilson, MD Ophthalmology Volume 118, Number 3, March 2011 (f11)

Prospective, comparative case series of 50 cataractous eyes of 50 children were studied at the Wilmer Eye Institute, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, and the Center on Aging and Health, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland. Axial length was measured by both contact and immersion techniques for all eyes, randomized as to which to perform first and to avoid measurement bias.

Study Objectives and Design

The purpose of the study is to compare axial length measurements by contact and immersion techniques in the pediatric cataractous eyes. The axial length measurement and the mean

age for cataract surgery was 3.87 ± 3.72 years. Axial length measurement by contact technique was significantly shorter as compared with immersion technique (21.36 versus 21.63). Axial length using the I-3 (Innovative Imaging Incorporated, Sacramento, California, Ophthalmic A-scan ultrasound). A Prager scleral immersion shell (Eye Surgical Instrument, Incorporated) was used to support the probe and normal saline was used as a coupling fluid.

Key Study Conclusions

A-scan measurements yield shorter axial length than immersion A-scan measurements. This difference was felt to be mainly a result of anterior chamber depth rather than lens thickness value. If the contact technique is used, intraocular lens power calculation will result in an average of 1 diopter stronger intraocular lens power than is actually required. This can lead to reduced myopia in the postoperative refraction.

Importance for Pediatric Ophthalmologists

This study supports the accuracy of the immersion technique in determining axial length in children. This usually needs to be done at the time cataract surgery is performed and is associated with careful examination under anesthesia.

Pearls

Even with the I-3 (Innovative Imaging, Incorporated) ultrasound utilizing the scleral immersion shell, cataractous eyes frequently have high degrees of variability. In our practice, we use the immersion technique performed immediately prior to cataract surgery, 5 readings of the axial length in each eye, compute the intraocular lens calculation based on the recommendations of the Holladay 1, SRK-T and the Hoffer-Q formulas.

The main clinical pearl from this study is that if axial length is measured with contact lens technique it will result in a stronger intraocular lens and is actually required. This may lead to induced myopia in the postoperative refraction.

Glaucoma following infantile cataract surgery.

Saltzman R, Weakley D, Aggarwal N, Whitson J. JPOS 2011;48:142-149. (May-June) (f11)

Purpose: to examine incidence, risk factors, and outcomes of glaucoma following cataract surgery in infants.

Methods: retrospective review of all patients undergoing cataract surgery from 1993 through 1996 at Children's Medical Center in Dallas.

Results: included 64 eyes of which 11 developed glaucoma with a mean follow-up of 65 months. Age younger than three months at cataract diagnosis/extraction and presence of anterior chamber anomalies were the only risk factors found to have statistical significance for the development of glaucoma. Eight of 11 eyes required at least one surgical intervention. Three of 10 eyes had final vision worse than 20/400 with another four eyes demonstrating some degree of amblyopia.

Conclusion: Despite modern techniques, infantile cataract surgery continues to pose a risk of secondary glaucoma. Most eyes required surgical management and visual outcomes remain poor.

Comment: confirms other studies demonstrating the high risk of glaucoma and poor visual outcomes in this infantile patient cohort, especially when cataract is diagnosed and/or extracted prior to three months of age.

Comparison of aphakic refraction formulas for secondary in-the-bag intraocular lens power estimation in children

Abdel-Hafez G, Trivedi RH, Wilson ME, and Bandyopadhyay D J AAPOS. 2011 Oct;15(5):432-4 (s12)

This paper evaluates the accuracy of aphakic refraction (AR) in determining IOL power compared to biometry in the setting of secondary in-the-bag IOL implantation. The absolute prediction error of two AR-based formulas (Hug's and Khan's) was compared with the biometry based Holiday I IOL formula. Records of all children who underwent secondary in-the-bag IOL implantation over a 14-year period were reviewed. 20 eyes of 16 patients were included. The mean of the absolute value of prediction error with both Hug's formula and Khan's formula was 2.4 +/- 2.0 D. The mean error with biometry was 1.6 +/- 1.4 D. The difference among the three methods was not statistically significant. The study is limited by its retrospective nature. In rare circumstances when there are biometry-related difficulties, or in the developing world where biometry is not available in the operating room, AR-based formulas can be used to estimate IOL power.

Secondary intraocular lens implantation after pediatric aphakia

Nihalani BR and Vanderveen DK J AAPOS. 2011 Oct;15(5):435-40 (s12)

The authors describe their technique for secondary in-the-bag IOL implantation and compare early clinical outcome measures with this technique versus sulcus implantation. A MVR blade was used to open the capsule 360' whenever possible and the residual cortical material between the anterior and posterior capsule leaflets was aspirated. 50 consecutive eyes of 32 patients who underwent secondary IOL implantation were evaluated. The mean age at secondary IOL implantation was 9.1 years. The mean follow-up was 12.3 months. 26 had in-the-bag IOLs and 24 had sulcus IOLs placed. Transient corneal edema was significantly more frequent in the sulcus IOL group (54% vs 19%). Early postoperative inflammation was also significantly greater in the sulcus group (92% vs 31%). No patients developed IOL decentration, retinal detachment, or opacification of the visual axis in either group. The greater postoperative inflammation in the sulcus group may represent a bias for more complicated cases in this group. The study was retrospective, with limited follow-up and a reasonably small sample size. Patients were not randomized because the aim was to implant an IOL in-the-bag whenever possible.

Refractive shift in pseudophakic eyes during the second decade of life.

Trivedi RH, Wilson ME, Bandyopadhyay D. J Cataract Refract Surg. January 2012;38(1):102-7. (s12)

The study evaluated the refractive shift in pseudophakic eyes of children after their 10th birthday. Both children who had had cataract surgery before age 10 and those who had it after age 10 years were included, and the study included bilateral pseudophakes (only one eye randomly selected for study inclusion) and unilateral pseudophakes. Two refractions performed at least one year apart after the child had attained age 10 were analyzed.

One hundred fourteen pseudophakic eyes were identified. The mean shift in refraction per year was -0.30 ± 0.38 D. 86.8% of eyes had a myopic shift in refraction, while 13.2% of eyes had a hyperopic shift in refraction. The refractive shift was significantly different between black patients and white [Caucasian] patients ($P=.006$), with black patients having a lesser myopic shift than white patients. The authors modeled that a white patient with emmetropia at age 10 years would be a -1.7 D myope at age 20, and a black patient with emmetropia at age 10 years would be a -0.8 D myope at age 20 years.

In unilateral cases, the mean refractive shift per year was similar between the operated and unoperated eyes.

A myopic shift in refraction continued in children after 10 years of age. The authors recommend targeting mild hyperopia when performing cataract surgery in the second decade of life, or, if aiming for emmetropia during the second decade of life, cautioning parents to expect mild myopia later on.

Clinical outcomes of cataract surgery after bag-in-the-lens intraocular lens implantation following ISO standard 11979-7:2006.

Tassignon MJ, Gobin L, Mathysen D, Van Looveren J, De Groot V.J *Cataract Refract Surg.* December 2011;37(12):2120-9. (s12)

This is a study from Belgium reporting clinical outcomes of bag-in-the-lens intraocular lens. This intraocular lens was designed to prevent posterior capsular opacification [see below]. The round has a groove along its side. The surgeon performs an anterior and posterior continuous curvilinear capsulorhexis (PCCC) equal in size to one another, and the optic is pushed into the central opening created by the two, with the groove sequestering proliferating lens epithelial cells peripherally, away from the central round optic.

The study enrolled 807 eyes of 547 patients, including 37 pediatric eyes (age less than 15 years.) The authors report on visual acuity outcomes and complications for the cohort as a whole over a mean follow-up of 26.1 ± 21.3 , and they find an acceptable rate of complications based on European international standards.

The report mentions that the bag in the lens IOL was implanted into 37 pediatric eyes ages <1 to 15 years, and these had 2 complications (5%). Three infant eyes required reoperation to remove residual proliferating lens epithelial cells because the lens was not appropriately positioned between the two capsular openings. It is unclear why only 2 complications rather than 3 are listed for the pediatric eyes, as reoperation was considered a complication.

This lens design is intriguing and may be applicable to pediatric cataract surgery, where capsular opacification and phimosis are common problems.

Comparing the astigmatic outcome after paediatric cataract surgery with different incisions

Amit Gupta, Muralidhar Ramappa, Ramesh Kekunnaya, Pravin K Vaddavalli, Et al Br J Ophthalmol March 2012;96:386 – 389 (s12)

Aims To compare astigmatism with clear corneal incision versus scleral tunnel incision following paediatric cataract surgery with primary intraocular lens implantation.

Methods Retrospective, comparative case series of 218 eyes of 138 children <12 years of age undergoing cataract extraction with intraocular lens implantation. The study cohorts were grouped into two categories based on incision location: group 1 comprising 108 eyes from 65 children with scleral incision; group 2 comprising 110 eyes from 73 children with clear corneal incision. Cycloplegic refraction was performed at 1, 3 and 6 months postoperatively.

Results The mean age in group 1 was 61.639 months and in group 2, 51.641 months. The mean postoperative astigmatism in group 1 was 1.2860.97 D, 1.4261.00 D and 1.3860.98 D at 1, 3 and 6 months respectively. The change in astigmatism between 1 and 6 months was non-significant (p.0.26). The mean astigmatism in group 2 was 1.3461.20 D, 1.1360.88 D and 1.0360.89 D at 1, 3 and 6 months respectively. Astigmatism in group 2 decreased significantly with time (p<0.001). The amount of astigmatism was comparable between the two groups at 1 month postsurgery (p.0.90), while it was significantly lower in the corneal incision group at 3 (p.0.03) and 6 months (p.0.01).

Conclusions Postoperative astigmatism after paediatric cataract surgery by clear corneal incision was lower compared with scleral incision. However, the difference was small and clinically insignificant.

Safety profile of primary intraocular lens implantation in children below 2 years of age

Amit Gupta, Ramesh Kekunnaya, Muralidhar Ramappa, Pravin K Vaddavalli Br J Ophthalmol. 2011 Apr;95(4):477-80 (s12)

Aim To study the safety profile of primary intraocular lens (IOL) implantation in children below 2 years of age

Methods Retrospective, non-comparative, consecutive and interventional clinical case series of all patients who underwent surgery between January 2006 and December 2007.

Results The data were collected for 120 eyes of 80 children with congenital/developmental cataract with a mean follow-up of 8.8567.73 months (median 6, range 3e40). The age ranged from 1 to 23 months (mean 11.2165.90 months, median 10 months). 31 eyes were operated on before the age of 6 months, and 89 were operated on after 6 months of age. The axial length of children ranged from 16.27 mm to 25.65 mm (mean 19.8461.71, median 19.65). The IOL power implanted in these children ranged from 11 D to 30 D (mean 24.5164.06 D, median 25.00). 30 eyes were implanted with rigid polymethylmethacrylate lenses, and the remaining 90 received acrylic hydrophobic foldable lenses. 8 eyes (6.7%) developed opacification of the visual axis, decentration of IOL was noticed in 2 (1.7%), increased anterior chamber inflammation was observed in five eyes (4.2%) in the early postoperative

period, pigment dispersion on IOL was seen in four eyes (3.3%), and posterior synechiae were noticed in five eyes (4.2%). None of the children developed glaucoma; nor were there any endophthalmitis and retinal detachment at the last follow-up. There was no difference in terms of complications in children younger than 6 months and older than 6 months.

Conclusion The results suggest that implantation of IOL in children below 2 years of age is safe and can be considered as a viable option for their visual rehabilitation

Clinical Characteristics and Early Postoperative Outcomes of Pediatric Cataract Surgery with IOL implantation from Lahan, Nepal

M. Edward Wilson, Albrecht Hennig, Rupal H. Trivedi, et al Journal of Pediatric Ophthalmology and Strabismus September 2011; 48: 286-291 (s12)

The Sagarmatha Choudhary Eye Hospital (SCEH) is in a little town of Southeast Nepal. It is a tertiary care center to provide pediatric-oriented services. The outcome of a consecutive series of pediatric cataract surgeries with intraocular lens (IOL) implantation at SCEH is reported including 2,633 eyes that were operated on with primary IOL implantation. Delayed presentation and poor follow up was the main obstacle in the management of pediatric cataract. Educating families as well as primary care physicians, pediatricians, neonatologists, and general physicians to the importance of early intervention to prevent adverse visual outcome.

Vision-Related Quality of Life Assessment Using the NEI-VFQ-25 in Adolescents and Young Adults With a History of Congenital Cataract

Caitriona Kirwan, Bernadette Lanigan, Michael O'Keefe, Journal of Pediatric Ophthalmology and Strabismus January 2012; 49: 26-31 (s12)

Visual function and self perceived visual impairment are important aspects of health-related quality of life. A reliable and valid measure of vision-specific health related quality of life is the National Eye Institute 25-item visual function questionnaire (NEI-VFQ-25). This study uses the NEI-VFQ-25 to assess adolescent and young adults quality of Life who underwent cataract surgery – wither unilateral or bilateral – prior to 2 years of age. The study separated the patients into those with unilateral disease and those with bilateral disease. The two groups were comparable in terms of general vision; however, the unilateral group scored better than the bilateral in most other subscales such as performing near and distance activities and certain specific tasks . Overall, the study is promising. The study was a retrospective study and the cataract surgeries were done many years prior, as surgical techniques improve and management of refractive error and amblyopia improve the NEI-VFQ-25 may also improve.

Complications, Adverse Events and Additional Intraocular Surgery 1 Year After Cataract Surgery in the Infant Aphakia Treatment Study (IATS)

David A. Plager, MD, Michael J. Lynn, MS, Edward G. Buckley, MD, M. Edward Wilson, MD, Scott R. Lambert, MD *for the Infant Aphakia Treatment Study Group Ophthalmology*: December 2011; 118: 2330-2334- (s12)

The purpose of this randomized multicenter clinical trial was to compare rates and severity of complications between infants undergoing cataract surgery with and without intraocular lens (IOL) implantation.

The rates of the intraocular complications, adverse events and additional intraocular surgeries 1 year after surgery were numerically higher in the IOL group than the non-IOL group. However their functional impact does not clearly favor either treatment group.

XIII. REFRACTIVE SURGERY

Laser In Situ Keratomileusis for the Treatment of Accommodative Esotropia

Ofelia M Brugnoli de Pagano, Gabriela L Pagano, *Ophthalmology* 2012 January; 119: 159-163 (s12)

Forty –six eyes of 23 patients with hyperopia and fully or partially refractive accommodative esotropia were treated with excimer laser or LASIK techniques between 2000 and 2010 in a prospective, noncomparative, interventional cases series.

The purpose of the study was to demonstrate the effectiveness of refractive surgery with an excimer laser to correct hyperopia and convergent strabismus caused by compensatory accommodation of refractive error.

The main outcome criteria were pre and post-operative spherical equivalent and ocular alignment.

The authors reported an average reduction of esotropia from 21D to 3D in their series and stated that the excimer laser is a promising treatment for refractive accommodative esotropia.

The study was performed at the National University of Cuyo, Mendoza, Argentina.

COMMENT: It would be interesting to see what the FDA would have to say about this treatment modality. Much more than meets the eye in this study.

XIV GENETICS

A dominant mutation in RPE65 identified by whole-exome sequencing causes retinitis pigmentosa with choroidal involvement.

Bowne SJ, Humphries MM, Sullivan LS, Kenna PF, Tam LC, Kiang AS, Campbell M, Weinstock GM, Koboldt DC, Ding L, Fulton RS, Sodergren EJ, Allman D, Millington-Ward S, Palfi A, McKee A, Blanton SH, Slifer S, Konidari I, Farrar GJ, Daiger SP, Humphries P. *Eur J Hum Genet.* 2011 Jun 8. (f11)

Linkage testing using Affymetrix 6.0 SNP Arrays mapped the disease locus in TCD-G, an Irish family with autosomal dominant retinitis pigmentosa (adRP), to an 8.8Mb region on 1p31. Of 50 known genes in the region, 11 candidates, including RPE65 and PDE4B, were sequenced using di-deoxy capillary electrophoresis. Simultaneously, a subset of family members was analyzed using Agilent SureSelect All Exome capture, followed by sequencing on an Illumina GAllx platform. Candidate gene and exome sequencing resulted in the identification of an Asp477Gly mutation in exon 13 of the RPE65 gene tracking with the disease in TCD-G. All coding exons of genes not sequenced to sufficient depth by next generation sequencing were sequenced by di-deoxy sequencing. No other potential disease-causing variants were found to segregate with disease in TCD-G. The Asp477Gly mutation was not present in Irish controls, but was found in a second Irish family provisionally diagnosed with choroideremia, bringing the combined maximum two-point LOD score to 5.3. Mutations in RPE65 are a known cause of recessive Leber congenital amaurosis (LCA) and recessive RP, but no dominant mutations have been reported. Protein modeling suggests that the Asp477Gly mutation may destabilize protein folding, and mutant RPE65 protein migrates marginally faster on SDS-PAGE, compared with wild type. Gene therapy for LCA patients with RPE65 mutations has shown great promise, raising the possibility of related therapies for dominant-acting mutations in this gene. *European Journal of Human Genetics* advance online publication, 8 June 2011; doi:10.1038/ejhg.2011.8

Comment: This paper shows how next generation sequencing can be used to find unsuspected associations between diseases and genes. They found that RPE65 gene mutations can cause an **autosomal dominant** form of RP, in addition to autosomal recessive LCA.

Anesthetic agents are commonly used for a variety of medical procedures in infants and children, but little is known about their effects on the developing brain. A growing body of data from studies in animals suggests that under certain circumstances, such as prolonged anesthesia, these drugs could adversely affect neurologic, cognitive, and social development of neonates and young children. We believe that these findings should be of concern to the scientific and medical communities.

Over the past decade, studies in rodents have found that exposure to anesthetic agents during sensitive periods of brain development (i.e., the brain growth spurt) results in widespread neuronal apoptosis and functional deficits later in development. So far, agents that either antagonize *N*-methyl-D-aspartate (NMDA) receptors or potentiate the neurotransmission of γ -aminobutyric acid (GABAergic agents) have been implicated, and no safe doses of these agents or safe durations of administration have been defined.

More recent investigations in nonhuman primates have extended these findings. Studies conducted by the National Center for Toxicology Research (NCTR) of the Food and Drug Administration (FDA) have demonstrated that exposure to ketamine — the prototypical NMDA-receptor antagonist — resulted in increased neuronal cell death in nonhuman primates. Specifically, a dose of ketamine sufficient to produce a light surgical plane of anesthesia for either 9 or 24 hours resulted in neuroapoptosis in 5-day-old rhesus monkeys. No similar effect was seen when ketamine was administered for only 3 hours. Neuroapoptosis in the brain of the fetus was also evident when pregnant rhesus monkeys were exposed to ketamine for 24 hours on day 122 of gestation (equivalent to the third trimester of human pregnancy), but no neuroapoptosis was noted following administration of ketamine on postnatal day 35.¹ Neuroapoptosis has also been demonstrated in primates who were given isoflurane (predominantly a GABAergic agent) on postnatal day 6.²

Although the functional consequences of these histopathologic changes can only be inferred at this time, the FDA and others are currently conducting studies in animals to address the neurocognitive and neurobehavioral effects of anesthetic-induced apoptosis. At the NCTR, the FDA is using a so-called operant test battery to evaluate the cognitive function of rhesus monkeys exposed to a dose of ketamine sufficient to produce a light surgical plane of anesthesia for 24 hours on postnatal day 5 or 6. This battery consists of a number of tasks that evaluate short-term memory and attention, learning, time perception, motivation, and color and position discrimination. The results to date indicate that, as compared with controls, ketamine-treated animals have lower training scores — and continue to score lower than controls for at least 10 months after the administration of ketamine.³ Similar studies of isoflurane in primates are ongoing.

Nonhuman primates are believed to offer the most appropriate model for assessing neurodevelopmental risk to humans; however, such cognitive testing in primates is expensive and requires many years to complete. Therefore, limited data exist to date. More rapid progress can be made using rodent models. Additional data from animal studies may help to define the window of vulnerability and the extent of anesthesia-induced neuronal alterations and provide insights both into the functional end points that should be assessed in clinical studies and into ways of blocking or ameliorating potential adverse effects. It is not known how the data from rodents or primates translate to humans, but such findings raise questions that require further scientific investigation.

Studies in children have attempted to assess the effects of anesthetics on the developing human brain. For instance, a retrospective cohort analysis followed a birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life and compared them with 5050 children in a control sample who had undergone no hernia repair before the age of 3.⁴ The children who underwent hernia repair were twice as likely as those who did not to be given a diagnosis of a developmental or behavioral disorder (adjusted hazard ratio, 2.3; 95% confidence interval [CI], 1.3 to 4.1). A population-based, retrospective, birth-cohort study examined the educational and medical records of children who were exposed to a single anesthetic (n=449), two anesthetics (n=100), or more (n=44). In contrast to the hernia-repair study, this study reported no increased risk of learning disabilities with a single anesthetic (hazard ratio, 1.0; 95% CI, 0.79 to 1.27). However, an increasing risk of learning disabilities was associated with two or more anesthetics (hazard ratio, 1.59; 95% CI, 1.06 to 2.37; and hazard ratio, 2.60; 95% CI, 1.60 to 4.24, respectively). The risk of learning

disabilities also increased with greater cumulative exposure to anesthesia.⁵

No conclusions about causality can be drawn on the basis of these nonrandomized studies in humans because of the substantial potential for confounding. Indeed, there are conflicting findings between the two cited studies regarding a single exposure to anesthetics. It is not possible to discern from the published study reports whether or how differences in surgical procedures, anesthetic drugs, patient monitoring, or anesthesia techniques affected the outcomes. It is possible that the children undergoing surgery also differed from the nonexposed children in ways that were not discernible. At present, there is not enough information to draw any firm conclusions regarding an association between anesthetic exposure and subsequent learning disabilities, and additional studies such as those that are ongoing (see box) are warranted.

Ongoing Clinical Trials Assessing the Effects of Anesthetics on Neurocognitive Development. Generating definitive data about the effects of anesthetics on the developing brain will most likely take numerous animal and human studies spanning many years. Planning, conducting, and interpreting these studies will pose enormous challenges to the medical and scientific community. It seems unlikely that any single individual or organization will be able to muster the resources to take on this project.

The FDA is continuing efforts to address the pediatric safety of anesthetics. On March 29, 2007, the FDA's Anesthetic and Life Support Drugs Advisory Committee met to discuss the data from animal studies suggesting that exposure to anesthetic agents during the period of rapid brain growth produces widespread neuronal apoptosis with possible long-term functional consequences. The committee members agreed that additional research was essential to understanding the implications of the animal data for children who must be exposed to anesthetic and sedative drugs for necessary medical procedures. They also concluded that there was insufficient information to warrant changing the practice of pediatric anesthesia, other than to forgo elective procedures in children less than 3 years of age. Since that time, numerous nonclinical and clinical studies have been undertaken (and published) in an attempt to further understand this challenging issue; therefore, a second advisory committee meeting on this issue is scheduled for March 10, 2011. The committee will evaluate the weight of existing scientific evidence and discuss the research agenda and potential risk-communication issues.

As part of its Critical Path Initiative, the FDA has entered into a public-private partnership with the International Anesthesia Research Society (IARS) called SmartTots (Strategies for Mitigating Anesthesia-Related Neuro-Toxicity in Tots). This partnership will seek to mobilize the scientific community, stimulate dialogue among thought leaders in the anesthesia community, and work to raise funding for the necessary research.

But these activities are just the first step. We need to definitively answer the questions of whether anesthetic use in children poses a risk to their development and, if so, under what circumstances. Although withholding anesthesia from children who need surgery is unreasonable, obtaining more information about safe use is imperative. If anesthetic agents are found, in certain cases, to affect the developing brain, strategies for mitigating and managing such risks can be implemented. The FDA is committed to pursuing these answers

with the medical and scientific communities and will take the steps necessary to ensure that the benefits of anesthetic use in children continue to outweigh any potential risks

Clinical and Oculomotor Characteristics of Albinism Compared to FRMD7 Associated Infantile Nystagmus

Kumar A, Gottlob I, McLean RJ, Thomas S, Thomas MG, Proudlock FA.

Invest Ophthalmol Vis Sci. 2011 Apr 8;52(5):2306-13. (f11)

Purpose. Previous studies have found no difference between nystagmus characteristics associated with idiopathic infantile nystagmus (IIN) and that associated with albinism. The present aim is to compare the oculomotor characteristics and other associated clinical features of albinism and a genetically homogenous group of IIN volunteers where the nystagmus is associated with FRMD7 mutations. **Methods.** Oculomotor characteristics and related clinical features between albinism (n = 52) and idiopathic nystagmus associated with FRMD7 mutations (FRMD7-IIN, n = 83) were compared. The nystagmus characteristics compared included amplitude, frequency, intensity of nystagmus, foveation characteristics, and waveform type. Other clinical features compared were strabismus, stereopsis and anomalous head posture. **Results.** The FRMD7-IIN group contained a higher proportion of pendular waveform types compared with the albinism group ($P < 0.0001$). Nystagmus frequency was significantly lower in albinos (mean = 3.3 Hz, SD = 0.13 Hz) compared with the FRMD7-IIN group (mean = 4.3 Hz, SD = 0.18 Hz) ($F = 14.5$, $P < 0.0001$). Strabismus and anomalous head posture was seen in higher proportions in the albinism group, and stereopsis was worse compared with the FRMD7-IIN group ($P \ll 0.0001$). **Conclusions.** Differences in nystagmus characteristics associated with albinism and those associated with FRMD7 mutations leading to IIN are described for the first-time. These findings may provide useful information in the future elucidation of mechanisms underlying the nystagmus associated with albinism and idiopathic infantile nystagmus.

Comment: This is an excellent study because they compared 83 patients with idiopathic (motor) nystagmus of one genetic subtype, that caused by mutations of the FRMD7 gene, with another specific type, that of albinism. They did find some differences in the appearance of the nystagmus, namely the FRMD7 patients were more likely to have pendular nystagmus of higher frequency than the patients with albinism, however both type appeared in both groups, so it was not diagnostic. The major difference, as one would expect, is that the albinism patients had worse vision and more vision related issues such as strabismus and lack of stereopsis.

Cone photoreceptors are the main targets for gene therapy of NPHP5 (IQCB1) or NPHP6 (CEP290) blindness: generation of an all-cone Nphp6 hypomorph mouse that mimics the human retinal ciliopathy.

Cideciyan AV, Rachel RA, Aleman TS, Swider M, Schwartz SB, Sumaroka A, Roman AJ, Stone EM, Jacobson SG, Swaroop A.

Hum Mol Genet. 2011 Apr 1;20(7):1411-23. (f11)

Leber congenital amaurosis (LCA), a severe autosomal recessive childhood blindness, is caused by mutations in at least 15 genes. The most common molecular form is a ciliopathy due to NPHP6 (CEP290) mutations and subjects have profound loss of vision. A similarly severe phenotype occurs in the related ciliopathy NPHP5 (IQCB1)-LCA. Recent success of retinal gene therapy in one form of LCA prompted the question whether we know enough about human NPHP5 and NPHP6 disease to plan such treatment. We determined that there was early-onset rapid degeneration of rod photoreceptors in young subjects with these ciliopathies. Rod outer segment (OS) lamination, when detectable, was disorganized. Retinal pigment epithelium lipofuscin accumulation indicated that rods had existed in the past in most subjects. In contrast to early rod losses, the all-cone human fovea in NPHP5- and NPHP6-LCA of all ages retained cone nuclei, albeit with abnormal inner segments and OS. The rd16 mouse, carrying a hypomorphic *Nphp6* allele, was a good model of the rod-dominant human extra-foveal retina. Rd16 mice showed normal genesis of photoreceptors, including the formation of cilia, followed by abnormal elaboration of OS and rapid degeneration. To produce a model of the all-cone human fovea in NPHP6-LCA, we generated rd16;*Nrl*^{-/-} double-mutant mice. They showed substantially retained cone photoreceptors with disproportionate cone function loss, such as in the human disease. NPHP5- and NPHP6-LCA across a wide age spectrum are thus excellent candidates for cone-directed gene augmentation therapy, and the rd16;*Nrl*^{-/-} mouse is an appropriate model for pre-clinical proof-of-concept studies.

Comment: this is a useful new model for gene therapy for types of LCA other than RPE65 related, which is now in clinical trials.

Copy-Number Variations in *EYS*. A significant event in the appearance of arRP

Juan I Pieras, Isabel Barragán, Salud Borrego, Isabelle Audo, María González-del Pozo, Sara Bernal, Montserrat Baiget, Christina Zeitz, Shomi S. Bhattacharya, Guillermo Antiñolo
Invest. Ophthalmol. Vis. Sci. April 25, 2011 iovs.11-729 (f11)

PURPOSE. Autosomal recessive Retinitis Pigmentosa (arRP) has recently been associated with mutations in a novel gene, *EYS*, which is a major gene for this disease. All published mutations so far are based upon conventional PCR and are not adequate to identify mid-sized DNA rearrangements. This study was conducted to establish the prevalence of Copy-Number Variations (CNVs) in the *EYS* gene in a cohort of arRP patients, including individuals in whom only one pathogenic change was detected by PCR-based sequencing.

METHODS. We used Multiple Ligation-dependent Probe Amplification (MLPA) for the molecular genetic analyses of CNVs by a novel *EYS* specific kit. PCR-based direct sequencing was employed in families where a pathogenic deletion/duplication was identified in one allele. Bioinformatics analyses was undertaken to study the effect of the mutations on protein structure and function.

RESULTS. Six novel pathogenic CNVs were identified. Also, we confirmed the presence of 4 mid-sized deletions in patients previously identified. Mid-sized genomic rearrangements in EYS are disease-causing in ~4% of the families with no reported mutations and constitute the second pathogenic variation in ~15% of cases where a mutation has been detected by direct sequencing.

CONCLUSIONS. This is the first report of a systematic CNV screening of EYS gene in a cohort of arRP patients. Our results suggest that mid-sized genomic rearrangements in EYS gene would be a common event in the appearance of RP phenotype. We have demonstrated an efficient and cost-effective strategy validating a novel MLPA Kit as a complementary diagnostic method for EYS pathogenic evaluation

Comment: Gene sequencing is the most common method of looking for disease causing mutations for genetic eye diseases. Using variations of this method, many genes causing retinitis pigmentosa have been found. But in a large number of ARRP patients, only one mutation can be found, even though we know they have two. This paper shows that that a large number of these patients have a second mutation which cannot be detected by sequencing—a copy number variation. That is they have a deletion or insertion of a gene. This should help us identify both mutations in more patients and gives us a better understanding of causation. It might also be the reason for “missing mutations” in other recessive disorders.

First Mutation in the β A2-crystallin Encoding Gene is Associated with Small Lenses and Age-Related Cataracts

Oliver Puk, Nafees Ahmad, Sibylle Wagner, Martin Hrabé de Angelis, Jochen Graw

Ophthalmol. Vis. Sci. April 6, 2011 vol. 52 no. 5 2219- (f11)

Purpose. A new mouse mutant with small lenses was identified within a mutagenesis screen. The aim of the study was to determine its molecular and morphologic characterization.

Methods. The offspring of paternally N-ethyl-N-nitrosourea (ENU)-treated C57BL/6J mice were analyzed for eye-size parameters by noninvasive in vivo laser interference biometry.

Results. A new mutant characterized by a clear, but significantly smaller lens without any changes for cornea thickness, anterior chamber depth, or aqueous humor size, was identified. The smaller size of the lens was more pronounced in the homozygous mutants, which were fully fertile and viable. The mutation was mapped to chromosome 1 between the markers D1Mit251 and D1Mit253. Using a positional candidate approach, the β A2-crystallin encoding gene *Cryba2* was sequenced; a T→C exchange at cDNA position 139 led to a p.S47P amino-acid alteration. The eyes of newborn homozygous mutants showed no gross changes. At the age of three weeks, some clefts appeared at the cornea, but the lens and retina appeared without major changes. At the age of 25 weeks, the lenses of the heterozygous mutants develop a subcapsular cortical cataract, but the lenses of homozygous mutants were completely opaque.

Conclusions. These findings demonstrate the first mutation in the *Cryba2* gene. In contrast to

the closely linked Cryg gene cluster, no congenital cataract mutation could be attributed to the Cryba2 gene. Therefore, the human CRYBA2 gene should be considered as a strong candidate gene for age-related cataracts, and the slightly smaller size of the lens might be recognized as an early biomarker for age-related cataracts.

Comments: The crystallin genes are important causes of congenital cataracts when mutated. The novel gene reported here has not been reported to cause congenital cataracts, but appears to play a role in small lenses and adult cataracts.

Longitudinal Study of Cone Photoreceptors during Retinal Degeneration and in Response to Ciliary Neurotrophic Factor Treatment

Katherine E. Talcott, Kavitha Ratnam, Sanna M. Sundquist, Anna S. Lucero, Brandon J. Lujan, Weng Tao, Travis C. Porco, Austin Roorda, Jacque L. Duncan Invest Ophthalmol Vis Sci. 2011 Apr 6;52(5):2219-26 (f11)

Purpose. To study cone photoreceptor structure and function in patients with inherited retinal degenerations treated with sustained-release ciliary neurotrophic factor (CNTF).

Methods. Two patients with retinitis pigmentosa and one with Usher syndrome type 2 who participated in a phase 2 clinical trial received CNTF delivered by an encapsulated cell technology implant in one eye and sham surgery in the contralateral eye. Patients were followed longitudinally over 30 to 35 months. Adaptive optics scanning laser ophthalmoscopy (AOSLO) provided high-resolution images at baseline and at 3, 6, 12, 18, and 24 months. AOSLO measures of cone spacing and density and optical coherence tomography measures of retinal thickness were correlated with visual function, including visual acuity (VA), visual field sensitivity, and full-field electroretinography (ERG).

Results. No significant changes in VA, visual field sensitivity, or ERG responses were observed in either eye of the three patients over 24 months. Outer retinal layers were significantly thicker in CNTF-treated eyes than in sham-treated eyes ($P < 0.005$). Cone spacing increased by 2.9% more per year in sham-treated eyes than in CNTF-treated eyes ($P < 0.001$, linear mixed model), and cone density decreased by 9.1%, or 223 cones/degree² more per year in sham-treated than in CNTF-treated eyes ($P = 0.002$, linear mixed model).

Conclusions. AOSLO images provided a sensitive measure of disease progression and treatment response in patients with inherited retinal degenerations. Larger studies of cone structure using high-resolution imaging techniques are urgently needed to evaluate the effect of CNTF treatment in patients with inherited retinal degenerations.

Comment: In the CNTF trial, RP patients receive an implant that gives a continuous supply of this neurotrophic factor. While vision is not significantly different between treated and untreated groups, Advanced Optics Scanning Laser Ophthalmoscopy does show a difference, with treated eyes have thicker outer retinas and less space between cones. The utility of CNTF in treating RP is still being investigated.

Effect of brimonidine on retinal and choroidal neovascularization in a mouse model of retinopathy of prematurity and laser-treated rats.

Kusari J, Padillo E, Zhou SX, Bai Y, Wang J, Song Z, Zhu M, Le YZ, Gil DW. Invest Ophthalmol Vis Sci. 2011 Jul 20;52(8):5424-31 (f11)

Purpose. To determine whether chronic treatment with brimonidine (BRI) attenuates retinal vascular leakage and neovascularization in neonatal mice after exposure to high oxygen in a mouse model of retinopathy of prematurity (ROP), and choroidal neovascularization (CNV) in rats after laser treatment. **Methods.** Experimental CNV was induced by laser treatment in Brown Norway (BN) rats. BRI or vehicle (VEH) was administered by osmotic minipumps, and CNV formation was measured 11 days after laser treatment. Oxygen-induced retinopathy was generated in neonatal mice by exposure to 75% oxygen from postnatal day (P)7 to P12. BRI or VEH was administered by gavage, and vitreoretinal vascular endothelial growth factor (VEGF) concentrations and retinal vascular leakage, neovascularization, and vaso-obliteration were measured on P17. Experimental CNV was induced in rabbits by subretinal lipopolysaccharide/fibroblast growth factor-2 injection.

Results. Systemic BRI treatment significantly attenuated laser-induced CNV formation in BN rats when initiated 3 days before or within 1 hour after laser treatment. BRI treatment initiated during exposure to high oxygen significantly attenuated vitreoretinal VEGF concentrations, retinal vascular leakage, and retinal neovascularization in P17 mice subjected to oxygen-induced retinopathy. Intravitreal treatment with BRI had no effect on CNV formation in a rabbit model of nonischemic angiogenesis.

Conclusions. BRI treatment significantly attenuated vitreoretinal VEGF concentrations, retinal vascular leakage, and retinal and choroidal neovascularization in animal models of ROP and CNV. BRI may inhibit underlying event(s) of ischemia responsible for upregulation of vitreoretinal VEGF and thus reduce vascular leakage and retinal-choroidal neovascularization

Comments: A rat model of rop responded favorably to brimonidine, which decreased VEGF. This could potentially be a medical treatment for human rop in the future.

Systemic administration of PRO051 in Duchenne's muscular dystrophy.

Goemans NM, Tulinius M, van den Akker JT, Burm BE, Ekhardt PF, Heuvelmans N, Holling T, Janson AA, Platenburg GJ, Sipkens JA, Sitsen JM, Aartsma-Rus A, van Ommen GJ, Buyse G, Darin N, Verschuuren JJ, Campion GV, de Kimpe SJ, van Deutekom JC. N Engl J Med. 2011 Apr 21;364(16):1513-22 (f11)

BACKGROUND: Local intramuscular administration of the antisense oligonucleotide PRO051 in patients with Duchenne's muscular dystrophy with relevant mutations was previously reported to induce the skipping of exon 51 during pre-messenger RNA splicing of the dystrophin gene and to facilitate new dystrophin expression in muscle-fiber membranes.

The present phase 1-2a study aimed to assess the safety, pharmacokinetics, and molecular and clinical effects of systemically administered PRO051.

METHODS:We administered weekly abdominal subcutaneous injections of PRO051 for 5 weeks in 12 patients, with each of four possible doses (0.5, 2.0, 4.0, and 6.0 mg per kilogram of body weight) given to 3 patients. Changes in RNA splicing and protein levels in the tibialis anterior muscle were assessed at two time points. All patients subsequently entered a 12-week open-label extension phase, during which they all received PRO051 at a dose of 6.0 mg per kilogram per week. Safety, pharmacokinetics, serum creatine kinase levels, and muscle strength and function were assessed.

RESULTS:The most common adverse events were irritation at the administration site and, during the extension phase, mild and variable proteinuria and increased urinary $\alpha(1)$ -microglobulin levels; there were no serious adverse events. The mean terminal half-life of PRO051 in the circulation was 29 days. PRO051 induced detectable, specific exon-51 skipping at doses of 2.0 mg or more per kilogram. New dystrophin expression was observed between approximately 60% and 100% of muscle fibers in 10 of the 12 patients, as measured on post-treatment biopsy, which increased in a dose-dependent manner to up to 15.6% of the expression in healthy muscle. After the 12-week extension phase, there was a mean (\pm SD) improvement of 35.2 ± 28.7 m (from the baseline of 384 ± 121 m) on the 6-minute walk test.

CONCLUSIONS:Systemically administered PRO051 showed dose-dependent molecular efficacy in patients with Duchenne's muscular dystrophy, with a modest improvement in the 6-minute walk test after 12 weeks of extended treatment.

Comment: We are in a very hopeful era when many previously untreatable genetic diseases are beginning to have useful therapies developed using novel techniques. This paper talks about a clinical trial using intramuscular injection of an antisense oligonucleotide in patients with Duchenne's muscular dystrophy. This causes the skipping of exon 51 during pre-messenger RNA splicing of the dystrophin gene and increases normal dystrophin expression in muscle-fiber membranes. They were able to detect new dystrophin expression in 60% and 100% of muscle fibers in 10 of 12 patients, as measured on post-treatment biopsy. Patients also did better on the 6 minute walk test.

Tauroursodeoxycholic Acid (TUDCA) Prevents Retinal Degeneration in Transgenic P23H Rats.

Fernández-Sánchez L, Lax P, Pinilla I, Martín-Nieto J, Cuenca N.

Invest Ophthalmol Vis Sci. 2011 Apr 20. (f11)

Purpose. To evaluate the preventive effect of tauroursodeoxycholic acid (TUDCA) on photoreceptor degeneration, synaptic connectivity and functional activity of the retina in the transgenic P23H rat, an animal model of autosomal dominant retinitis pigmentosa (RP). **Methods.** P23H line-3 rats were injected with TUDCA once a week from P21 to P120, in parallel to vehicle-administered controls. At P120 functional activity of the retina was evaluated by electroretinographic (ERG) recording. The effects of TUDCA on the number, morphology, integrity and synaptic connectivity of retinal cells were characterized by immunofluorescent confocal microscopy. **Results.** The amplitude of ERG a- and b-waves was significantly higher in TUDCA-treated animals under both scotopic and photopic conditions, as compared to obtained in control animals. In the central area of the retina, TUDCA-treated

P23H rats showed three-fold more photoreceptors than control animals. The number of TUNEL-positive cells was significantly smaller in TUDCA-treated rats, in which photoreceptors morphology was preserved. Presynaptic and postsynaptic elements, as well as the synaptic contacts between photoreceptors and bipolar or horizontal cells, were preserved in TUDCA-treated P23H rats. Furthermore, in TUDCA-treated rat retinas the number of both rod bipolar and horizontal cell bodies, as well as the density of their synaptic terminals in the outer plexiform layer, was greater than in control rats. Conclusions. TUDCA treatment was capable of preserving cone and rod structure and function, together with their contacts with their postsynaptic neurons. The neuroprotective effects of TUDCA make this compound potentially useful to delay retinal degeneration in RP

Comment: TUDCA is a neuroprotective agent that has great promise as a treatment for RP.

The human visual cortex responds to gene therapy-mediated recovery of retinal function.

Ashtari M, Cyckowski LL, Monroe JF, Marshall KA, Chung DC, Auricchio A, Simonelli F, Leroy BP, Maguire AM, Shindler KS, Bennett J.
J Clin Invest. 2011 Jun 1;121(6):2160-8. (f11)

Leber congenital amaurosis (LCA) is a rare degenerative eye disease, linked to mutations in at least 14 genes. A recent gene therapy trial in patients with LCA2, who have mutations in RPE65, demonstrated that subretinal injection of an adeno-associated virus (AAV) carrying the normal cDNA of that gene (AAV2-hRPE65v2) could markedly improve vision. However, it remains unclear how the visual cortex responds to recovery of retinal function after prolonged sensory deprivation. Here, 3 of the gene therapy trial subjects, treated at ages 8, 9, and 35 years, underwent functional MRI within 2 years of unilateral injection of AAV2-hRPE65v2. All subjects showed increased cortical activation in response to high- and medium-contrast stimuli after exposure to the treated compared with the untreated eye. Furthermore, we observed a correlation between the visual field maps and the distribution of cortical activations for the treated eyes. These data suggest that despite severe and long-term visual impairment, treated LCA2 patients have intact and responsive visual pathways. In addition, these data suggest that gene therapy resulted in not only sustained and improved visual ability, but also enhanced contrast sensitivity.

Comment: Many people wonder whether gene therapy will work in patients with LCA who have dense amblyopia due to abnormal retinas since birth. Using functional MRI on RPE65 gene therapy patients, this study suggests that the visual cortex can develop responsive cortical visual pathways.

Genomics and the Eye

Val C. Sheffield, M.D., Ph.D., and Edwin M. Stone, M.D., Ph.D.
N Engl J Med May 2011; 364:1932-1942 (f11)

The eye has had a pivotal role in the evolution of human genomics. At least 90% of the genes in the human genome are expressed in one or more of the eye's many tissues and cell types at some point during a person's life. Consistent with this impressive genomic footprint is the

observation that about a third of entries in the Online Mendelian Inheritance in Man database for which a clinical synopsis is provided include a term that refers to the structure or function of the eye.¹ Moreover, the phenotypic effects of even small genetic variations are made readily apparent by the many layers of amplification in the human visual system. For example, a single-nucleotide change in *PAX6* can cause an anatomic abnormality of the macula less than a millimeter in diameter that results in noticeably reduced visual acuity and nystagmus.

The heritable inability to correctly perceive the color green, known as Daltonism (after the English chemist John Dalton, who himself was affected), was the first human trait mapped to the X chromosome.³

The Coppock cataract was the first human trait mapped to an autosome,⁴ and Leber's hereditary optic neuropathy was the first human disease shown to be caused by a mutation in mitochondrial DNA.⁵ More recently, age-related macular degeneration (AMD) and glaucoma^{6,7} — two common causes of human blindness — have been shown to be largely genetic, as has Fuchs' endothelial dystrophy,⁸ the most common cause of corneal transplantation in developed countries. Here, we review discoveries in mendelian and complex ophthalmic disorders and their implications for genetic testing and therapeutic intervention...

Comment: this excellent review article summarizes the history of ocular genetics and describes in clear terms our current understanding as well as future directions. And the interactive graphics are phenomenal!

Long-Term Preservation of Cones and Improvement in Visual Function Following Gene Therapy in a Mouse Model of Leber Congenital Amaurosis Caused by Guanylate Cyclase-1 Deficiency.

Mihelec M, Pearson RA, Robbie SJ, Buch PK, Azam SA, Bainbridge JW, Smith AJ, Ali RR.

Hum Gene Ther. 2011 Oct;22(10):1179-90 (f11)

Abstract Leber congenital amaurosis (LCA) is a severe retinal dystrophy manifesting from early infancy as poor vision or blindness. Loss-of-function mutations in *GUCY2D* cause LCA1 and are one of the most common causes of LCA, accounting for 20% of all cases. Human *GUCY2D* and mouse *Gucy2e* genes encode guanylate cyclase-1 (GC1), which is responsible for restoring the dark state in photoreceptors after light exposure. The *Gucy2e(-/-)* mouse shows partially diminished rod function, but an absence of cone function before degeneration. Although the cones appear morphologically normal, they exhibit mislocalization of proteins involved in phototransduction. In this study we tested the efficacy of an rAAV2/8 vector containing the human rhodopsin kinase promoter and the human *GUCY2D* gene. Following subretinal delivery of the vector in *Gucy2e(-/-)* mice, GC1 protein was detected in the rod and cone outer segments, and in transduced areas of retina cone transducin was appropriately localized to cone outer segments. Moreover, we observed a dose-dependent restoration of rod and cone function and an improvement in visual behavior of the treated mice. Most importantly, cone preservation was observed in transduced areas up to 6 months post injection. To date, this is the most effective rescue of the *Gucy2e(-/-)* mouse model of LCA and we propose that a vector, similar to the one used in this study, could be suitable for use

in a clinical trial of gene therapy for LCA1.

Comment: The original ocular gene therapy trial for RPE65 used an AAV5 vector. Other vectors are being developed, and attempts are being made to treat many other types of retinal degeneration using gene therapy. This study successfully treats a model of GUCY2D LCA in mice with an AAV2/8 vector.

Identification of ADAMTS18 as a gene mutated in Knobloch syndrome.

Aldahmesh MA, Khan AO, Mohamed JY, Alkuraya H, Ahmed H, Bobis S, Al-Mesfer S, Alkuraya FS.

J Med Genet. 2011 Sep;48(9):597-601. (f11)

Background: Knobloch syndrome (KS) is a developmental disorder characterised by occipital skull defect, high myopia, and vitreo-retinal degeneration. Although genetic heterogeneity has been suspected, COL18A1 is the only known KS disease gene to date. **Objective** To identify a novel genetic cause of KS in a cohort of Saudi KS patients enrolled in this study.

Methods: When COL18A1 mutation was excluded, autozygosity mapping was combined with exome sequencing.

Results: In one patient with first cousin parents, COL18A1 was excluded by both linkage and direct sequencing. By filtering variants generated on exome sequencing using runs of autozygosity in this simplex case, the study identified ADAMTS18 as the only gene carrying a homozygous protein altering mutation. It was also shown that Adamts18 is expressed in the lens and retina in the developing murine eye.

Conclusion: The power of combining exome and autozygome analysis in the study of genetics of autosomal recessive disorders, even in simplex cases, has been demonstrated.

Comments: A new gene causing Knobloch syndrome (occipital skull defect, high myopia, vitreoretinal degeneration) has been identified.

The genetics of anophthalmia and microphthalmia.

Bardakjian TM, Schneider A.

Curr Opin Ophthalmol. 2011 Sep;22(5):309-13.(s12)

PURPOSE OF REVIEW:

To summarize recent breakthroughs regarding the genes known to play a role in normal ocular development in humans and to elucidate the role mutations in these genes play in anophthalmia and microphthalmia.

RECENT FINDINGS:

The main themes discussed within this article are the various documented genetic advances in identifying the various causes of anophthalmia and microphthalmia. In addition, the complex interplay of these genes during critical embryonic development will be addressed.

SUMMARY:

The recent identification of many eye development genes has changed the ability to identify a cause of anophthalmia and microphthalmia in many individuals. Syndrome identification and the availability of genetic testing underscores the desirability of evaluation by a geneticist for all individuals with anophthalmia and microphthalmia in order to provide appropriate management, long-term guidance, and genetic counseling.

Comment: Many genes are now known to cause anophthalmia and microphthalmia. In order for families to have correct genetic counseling, these patients should be offered clinical genetic testing.

DNA-based eye colour prediction across Europe with the IrisPlex system.

Walsh S, Wollstein A, Liu F, Chakravarthy U, Rahu M, Seland JH, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR, Vioque J, Fletcher AE, Ballantyne KN, Kayser M. *Forensic Sci Int Genet.* 2011 Aug 1. (s12)

The ability to predict Externally Visible Characteristics (EVCs) from DNA, also referred to as Forensic DNA Phenotyping (FDP), is an exciting new chapter in forensic genetics holding great promise for tracing unknown individuals who are unidentifiable via standard forensic short tandem repeat (STR) profiling. For the purpose of DNA-based eye colour prediction, we previously developed the IrisPlex system consisting of a multiplex genotyping assay and a prediction model based on genotype and phenotype data from 3804 Dutch Europeans. Recently, we performed a forensic developmental validation study of the highly sensitive IrisPlex assay, which currently represents the only validated tool available for DNA-based prediction of eye colour in forensic applications. In the present study, we validate the IrisPlex prediction model by extending our initially described model towards genotype and phenotype data from multiple European populations. We performed IrisPlex analysis on 3840 individuals from seven sites across Europe as part of the European Eye (EUREYE) study for which DNA and high-resolution eye images were available. The accuracy rate of correctly predicting an individual's eye colour as being blue or brown, above the empirically established probability threshold of 0.7, was on average 94% across all seven European populations, ranging from 91% to 98%, despite the large variation in eye colour frequencies between the populations. The overall prediction accuracies expressed by the area under the receiver characteristic operating curves (AUC) were 0.96 for blue and 0.96 for brown eyes, which is considerably higher than those established before. The IrisPlex prediction model parameters generated from this multi-population European dataset, and thus its prediction capabilities, were highly comparable to those previously established. Therefore, the increased information regarding eye colour phenotype and genotype distributions across Europe, and the system's ability to provide eye colour predictions across Europe accurately, both highlight additional evidence for the utility of the IrisPlex system in forensic casework.

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Comment: DNA samples at crime scenes can now be used to determine the eye color of

suspects with accuracy up to 98%. Criminals beware!

Two novel mutations of the PAX6 gene causing different phenotype in a cohort of Chinese patients.

Zhang X, Tong Y, Xu W, Dong B, et al *Eye (Lond)*. December 2011;25(12):1581-9. (s12)

This is a phenotype genotype correlation study from China of six unrelated families and 10 sporadic patients having clinical phenotypes of aniridia, iris/choroid coloboma, or anterior segment dysgenesis (including Peters anomaly). All patients had all exons of the PAX6 gene sequenced. The authors discovered nonsense mutations in the PAX6 gene causing premature stop codons, and a large deletion, among the aniridic patients. One of the nonsense mutations was a novel splicing mutation. They found no PAX6 mutations in the iris/choroid coloboma patients. They found a missense mutations in the highly conserved homeodomain region of the PAX6 gene in a family with nystagmus, sclerocornea and posterior staphyloma. The authors confirmed that different kind of PAX6 gene mutations can cause different ocular phenotypes: nonsense mutations and large deletions lead to aniridia, whereas missense mutations lead to anterior segment dysgenesis..

Ophthalmic features of Friedreich ataxia.

Noval S, Contreras I, Sanz-Gallego I, Manrique RK, Arpa J.*Eye (Lond)*. February 2012; 26(2):315-20. (s12)

Friedreich ataxia (FRDA) is the most frequent form of hereditary ataxia among Caucasians, affecting about 1 in 30 000 individuals in Western Europe. It is a neurodegenerative disease, which affects the central and peripheral nervous systems and has an autosomal recessive pattern of inheritance. The disease is characterized by progressive limb and gait ataxia, leg weakness, dysarthria, hypertrophic cardiomyopathy, hypoacusia, and an increased incidence of diabetes mellitus. It typically begins in the second decade. It is caused by a trinucleotide repeat within a gene responsible for mitochondrial function. Affected individuals' mitochondria are prone to oxidative stress, including the mitochondria within the retinal ganglion cells.

The authors prospectively studied the ophthalmic features of Friedrich's ataxia in patients ages 9 to 34 years. Although most patients retained good visual acuity of 0.8 or better, most also had decreased contrast sensitivity and mild subclinical optic neuropathy. The subclinical optic neuropathy was detectable by OCT and was correlated with disease duration. The authors recommend that OCT and contrast sensitivity tests be performed to evaluate progression and response to treatment in Friedrich's ataxia patients.

Stickler syndrome, ocular-only variants and a key diagnostic role for the ophthalmologist.

Snead MP, McNinch AM, Poulson AV, Bearcroft P, et al *Eye (Lond)*. November 2011; 25(11):1389-400. (s12)

This is a clinical and molecular genetics review of the Stickler Syndromes, which are hereditary connective tissue disorders of collagen associated with (1) ocular findings (vitreopathy, cataract, high risk of retinal detachment), (2) hearing loss, (3) cleft palate and (4) musculoskeletal problems (spinal abnormalities, joint hypermobility, premature osteoarthritis). The most common Stickler syndrome is type 1, which is due to a genetic defect in type 2 collagen, a constituent of vitreous. However, other subtypes of Stickler syndrome can be due to defects in type 9 and type 11 collagen, which are also found in the vitreous.

The authors make the following key points re: the clinical assessment:

Clinical assessment

- (1) Approximately 20% of patients are not myopic.
- (2) Oral clefting may be asymptomatic and examination of palate is important
- (3) An audiogram may reveal subclinical hearing loss and differentiate conductive from sensorineural components.
- (4) Radiographs of hips, lumbar spine, and knees may demonstrate features characteristic of Stickler syndrome not evident clinically, but interpretation of these may require the assistance of a radiologist with specialist expertise in skeletal dysplasias.
- (5) Examination of parents and siblings may assist in the clinical assessment of a neonate or very young patient in whom vitreous assessment is difficult.
- (6) The ophthalmologist has a key role to have in identifying and diagnosing the 'ocular-only' variants.
- (7) Type 1 Stickler syndrome has a high risk of retinal detachment and blindness from giant retinal tear, and prophylaxis should be considered and discussed with patients and parents to reduce this risk.

The ophthalmologist should maintain a high index of clinical suspicion for Stickler syndrome, particularly in the following scenarios:

- (i) Neonates with Pierre-Robin/cleft and myopia.
- (ii) Infants with spondyloepiphyseal dysplasia associated with myopia or deafness.
- (iii) Patients with a family history of retinal detachment.
- (iv) Sporadic cases of retinal detachment associated with joint hypermobility, midline clefting or deafness.

Zebrafish Model of Axenfeld-Rieger Syndrome Reveals That *pitx2* Regulation by Retinoic Acid Is Essential for Ocular and Craniofacial Development

Brenda L. Bohnsack, Daniel S. Kasprick, Phillip E. Kish, Daniel Goldman, and Alon Kahana. Invest Ophthalmol Vis Sci. January 2012;53:7–22) DOI:10.1167/iovs.11-8494 (s12)

PURPOSE. The homeobox transcription factor *PITX2* is a known regulator of mammalian ocular development, and human *PITX2* mutations are associated with Axenfeld-Rieger syndrome (ARS). However, the treatment of patients with ARS remains mostly supportive and palliative. **METHODS.** The authors used molecular genetic, pharmacologic, and embryologic techniques to study the biology of ARS in a zebrafish model that uses transgenes to mark neural crest and muscle cells in the head. **RESULTS.** The authors demonstrated *in vivo* that *pitx2* is a key downstream target of retinoic acid (RA) in craniofacial development, and this pathway is required for coordinating neural crest, mesoderm, and ocular development. *pitx2a* knockdown using morpholino oligonucleotides disrupts jaw and pharyngeal arch formation and recapitulates ocular characteristics of ARS, including corneal and iris stroma maldevelopment. These phenotypes could be rescued with human *PITX2A* mRNA, demonstrating the specificity of the knockdown and evolutionary conservation of *pitx2a* function. Expression of the ARS dominant negative human *PITX2A* K50E allele also caused ARS-like phenotypes. Similarly, inhibition of RA synthesis in the developing eye (genetic or pharmacologic) disrupted craniofacial and ocular development, and human *PITX2A* mRNA partially rescued these defects. **CONCLUSIONS.** RA regulation of *pitx2* is essential for coordinating interactions among neural crest, mesoderm, and developing eye. The marked evolutionary conservation of *Pitx2* function in eye and craniofacial development makes zebrafish a potentially powerful model of ARS, amenable to *in vivo* experimentation and development of potential therapies.

The roles of RA and *PITX2* in ocular and craniofacial development reveal remarkable functional conservation between vertebrate classes. Such conservation can be used to probe the regulation of morphogenesis using a variety of approaches, including *in vivo* models, and to screen through phenotypic modifiers to identify potential therapies for ARS and other genetic disorders.

Abnormal Achromatic and Chromatic Contrast Sensitivity in Neurofibromatosis Type 1

Maria Jose´ Ribeiro, Ineˆs Ribeiro Violante, Ineˆs Bernardino, Fabiana Ramos, Jorge Saraiva, Pablo Reviriego, Meena Upadhyaya, Eduardo Duarte Silva, and Miguel Castelo-Branco. (Invest Ophthalmol Vis Sci. January 2012;53:287–293) DOI:10.1167/iovs.11-8225. (s12)

PURPOSE. Neurofibromatosis type 1 (NF1) is a monogenic disorder with the majority of patients presenting subtle to moderate cognitive impairments. Visuospatial deficits are considered to be one of the hallmark characteristics of their cognitive profile. However, low-level visual processing has not been previously investigated. Our aim was to study contrast perception

in these patients to assess the function of early visual areas. **METHODS.** Contrast sensitivity was tested in 19 children and adolescents with NF1 and 33 control children and adolescents and 12 adults with NF1 and 24 control adults. The tasks used probed two achromatic spatiotemporal frequency channels and chromatic red–green and blue–yellow pathways.

RESULTS. Individuals with NF1 showed significant contrast sensitivity deficits for the achromatic higher spatial frequency channel [$F_{(1,83)} = 36.1$, $P < 0.001$] and for the achromatic low spatial high temporal (magnocellular) frequency channel [$F_{(1,72)} = 8.0$, $P < 0.01$]. Furthermore, individuals with NF1 presented a significant deficit in chromatic red–green (parvocellular) contrast sensitivity ($P < 0.01$) but not in blue–yellow (koniocellular) sensitivity. The decrease in achromatic sensitivity for higher spatial frequency was observed throughout the visual field, in both central and peripheral locations. In contrast, central contrast sensitivity for the magnocellular-biased condition was relatively preserved and only peripheral sensitivity was affected. Interestingly, the same pattern of deficits was found in both age groups tested.

CONCLUSIONS. These findings showed that contrast sensitivity is impaired in patients with NF1, associating for the first time abnormal low-level vision to the cognitive profile of this disorder. The authors tested contrast sensitivity in children and adolescents with NF1 and adults with NF1 using low-level visual stimulation that preferentially activate the red–green (parvocellular), blue–yellow (koniocellular), or low spatial high temporal frequency (strongly magnocellular biased) channels. In addition, they also tested a parvocellular-biased achromatic channel (stimuli with higher spatial and lower temporal frequency). Furthermore, they studied if the dependence of contrast sensitivity on eccentricity was altered. Parvo- and magnocellular pathways differ in the way their responses depend on the eccentricity of the visual stimuli, with the magnocellular pathway dominating at more peripheral locations. Thus, impairments of these pathways in central or peripheral locations could have different behavioral consequences.

Long-term Preservation of Cone Photoreceptors and Restoration of Cone Function by Gene Therapy in the Guanylate Cyclase-1 Knockout (GC1KO) Mouse

Sanford L. Boye, Thomas Conlon, Kirsten Erger, Renee Ryals, Andy Neeley, Travis Cossette, Jijing Pang, et al, *Invest Ophthalmol Vis Sci.* 2011;52:7098–7108) (s12)

PURPOSE. The authors previously showed that subretinal delivery of AAV5 vectors containing murine guanylate cyclase-1 (GC1) cDNA driven by either photoreceptor-specific (hGRK1) or ubiquitous (smCBA) promoters was capable of restoring cone-mediated function and visual behavior and preserving cone photoreceptors in the GC1 knockout (GC1KO) mouse for 3 months. Here, the authors compared therapy conferred by the aforementioned vectors to that achieved with the highly efficient capsid tyrosine mutant AAV8(Y733F) and asked whether long-term therapy is achievable in this model.

METHODS. AAV5-hGRK1-mGC1, AAV5-smCBA-mGC1, or AAV8(Y733F)-hGRK1-mGC1 was delivered subretinally to GC1KO mice between postnatal day (P)14 and P25. Retinal

function was assayed by electroretinography. Localization of AAV-mediated GC1 expression and cone survival were assayed with immunohistochemistry, and the spread of vector genomes beyond the retina was quantified by PCR of optic nerve and brain tissue.

RESULTS. Cone function was restored with all vectors tested, with AAV8(Y733F) being the most efficient. Electroretinographic responses were clearly measurable out to 1 year after treatment. AAV-mediated expression of GC1 was found exclusively in photoreceptors out to 15 months after injection. Cones were preserved for at least 11 months after treatment. AAV5- and AAV8(733)-delivered vector genomes were recovered primarily from optic nerve of the treated eye and, in only once instance, from brain (1 of 20 samples).

CONCLUSIONS. The authors demonstrate for the first time that long-term therapy (1 year) is achievable in a mammalian model of GC1 deficiency. These data provide additional justification for the development of an AAV based gene therapy vector for the clinical treatment of Leber congenital amaurosis-1.

Comment: RPE65 LCA was the first human photoreceptor degeneration to show benefit from subretinal gene replacement therapy. This study shows proof of concept in another mouse model of LCA, that caused by mutations in the guanylate cyclase gene. The authors point out that an AAV vector with a modified capsid was the most efficient vector to restore cone function, and that improvement in function lasted a long time, up to a year. They did note, however, that they could recover the vector genome in the optic nerve of the treated eye in some cases, and in one animal, even in the brain. This study shows that there is promise for gene therapy in this type of LCA in humans, and that modified viral vectors may offer better delivery of genes to specific retinal cells. Safety studies must be done with each change in protocol so the risks are understood.

The Health-Related Quality of Life of Children with Hereditary Retinal Disorders and the Psychosocial Impact on Their Families

Esther Louise Hamblion, Anthony Thomas Moore and Jugnoo Sangeeta Rahi, Invest. Ophthalmol. Vis. Sci. October 8, 2011 vol. 52 no. 11 7981-7986 (s12)

Purpose. Childhood-onset hereditary retinal disorders comprise a group of visually disabling conditions with variable onset and progression of visual impairment. Their impact on the health-related quality of life (HRQoL) of affected individuals, as well as the broader impact on their families has not been investigated previously.

Methods. In a cross-sectional study, a generic age-appropriate instrument, the PedsQL, was used to assess self-reported HRQoL in a subsample of a representative group of children with hereditary retinal disorders and their siblings as well as parental (proxy) assessment of HRQoL of their affected children. In addition, parents reported the broader impact and effect on functioning of the family using the PedsQL Family Impact Module.

Results. Affected children (n = 44) reported worse HRQoL than their unaffected siblings (n = 34) and notably, also worse scores than those reported by children with various serious

chronic systemic disorders. On average, parents assessed their child's HRQoL to be worse than that self-reported by the child. There was an overall adverse impact on the family and its functioning, although siblings did not report impaired HRQoL themselves.

Conclusions. This study demonstrates the significant impact, on both affected children and their families, of living with an untreatable, often progressive, and sometimes blinding ophthalmic disorder. It highlights the importance of support for affected individuals and their families, which may be targeted through use of generic or vision-related quality-of-life instruments for children as the latter become more widely available. Assessment of HRQoL would also be an important outcome measure in clinical trials of novel therapies for hereditary retinal disorders.

Comment: Health related quality of life (HRQoL) can be measured with several instruments. In this study the authors used one such instrument to show that children with progressive retinal degenerations have a worse HRQoL than unaffected kids, and worse than children with other chronic diseases. Families of affected children also have adverse affects, but healthy sibs do not report worse HRQoL. The impact vision loss has on children and families should be kept in mind, and can be measured as part of treatment trials.

X-linked Retinoschisis: *RS1* mutation severity and age affect the ERG phenotype in a cohort of 68 affected male subjects

Kristen Bowles, O.D, Catherine Cukras, Amy Turriff, Yuri Sergeev, Susan Vitale, Ronald A. Bush, and Paul A. Sieving, Invest. Ophthalmol. Vis. Sci. October 28, 2011 iovs.11-811 (s12)

Purpose: Assess the effect of age and *RS1* mutation on phenotype of X-linked retinoschisis (XLRS) subjects using the clinical electroretinogram (ERG) in a cross-sectional analysis.

Methods: Sixty-eight XLRS males age 4.5 - 55 year old were genotyped, and the retinoschisis (*RS1*) mutations were classified as less severe (27 subjects) or more severe (41 subjects) based on putative impact on the protein. ERG parameters of retinal function were analyzed by putative mutation severity and also for age as a continuous variable.

Results: A-wave amplitude remained greater than the lower normal limit (mean -2SD) for 72% of XLRS males and correlated neither with age nor mutation class. However, b-wave and b/a-ratio amplitudes were significantly lower in the more versus less severe mutation groups and also in older versus younger subjects. Subjects up to 10 years of age with more severe *RS1* mutations had significantly greater b-wave amplitudes and faster a-wave trough implicit time compared to older subjects in this group.

Conclusions: *RS1* mutation putative severity and age both had significant effect on retinal function in XLRS only in the severe mutation group as judged by ERG analysis of b-wave amplitude and b/a-ratio, whereas a-wave amplitude remained normal in majority. A new observation is that increasing age (limited to <55 y/o) causes a significant delay in XLRS b-wave onset (i.e., a-wave implicit time), even for those who retained considerable b-wave

amplitudes. The delayed b-wave onset suggests that dysfunction of the photoreceptor synapse or of bipolar cells increases with age of XLR subjects.

Comment: This study shows that mutations in the RS1 gene, which cause juvenile X-linked retinoschisis, can be assigned a severity score based on the predicted change in the protein. More severe mutations cause worsening of ERG with increased age (studied to age 55 years). This data may help with prognosis in JXLR patients.

Population differences in genetic risk for AMD and implications for genetic testing. Spencer KL, Glenn K, Brown-Gentry K, Haines JL, Crawford DC. Arch Ophthalmol 2012; 130(1); 116-17. (s12)

Purpose: The personal genetics revolution has promised patients an account of their individual risks of common, complex diseases based on their DNA sequence. Although under increased scrutiny from the US FDA, several direct to consumer genetic testing companies offer such services, and conflicting results for the same disease in the same individual are commonly reported....Furthermore, most genetic association studies have been conducted in European American individuals, and because the frequency of genetic polymorphisms varies across race-ethnicities, the predictive value of any genetic algorithm developed in one population may not translate to another. We have seen an extreme example of this for the ARMS2 AMD susceptibility locus....

Methods: As part of the Population Architecture Using Genomics and Epidemiology Study, we characterized ARMS2 A69S in the National Health and Nutrition Examination Survey, a cross-sectional survey of non-Hispanic white individuals....

Results. The T allele of the ARMS2 variant, which changes the amino acid residue from alanine to serine, was in Hardy-Weinberg equilibrium in all 3 race-ethnicities and of similar frequency across groups (0.22-0.25). As expected, the T allele was associated with AMD in all groups...However the direction of the effect was reversed in non-Hispanic black individuals compared with non-hispanic white individuals and Mexican American individuals. In contrast to non-Hispanic white and Mexican American individuals, the T-allele frequency was approximately 13% lower in non-Hispanic black patients compared with non-Hispanic black control subjects.

Conclusion: There are several possible explanations for our findings....Regardless of the reason, if this inverse association in non-Hispanic black individuals is confirmed, genetic tests that naively incorporate ARMS2 A69S without considering ancestry will consistently give incorrect results to non-Hispanic black individuals....

Comment: This important Research Letter describes and discusses one of the serious challenges in direct-to-consumer test interpretation, and individual genome sequencing as a whole. The challenge is in interpretation of the data. In this case, a variant, A69S, in the ARMS2 gene has been definitively linked to development of Age Related Macular Dystrophy in large studies. However, the authors point out that these studies were done on predominantly white European patients. When the authors looked at non-Hispanic black patients and controls, they discovered that for this group the A69S allele is actually correlated

with a LOWER risk of developing AMD. We are in the infancy of learning how to interpret the huge amounts of genetic data now being generated on individuals and groups. Results reported by direct-to-consumer testing, and research studies, must be very carefully interpreted.

Exome sequencing and analysis of induced pluripotent stem cells identify the cilia-related gene male germ cell-associated kinase (MAK) as a cause of retinitis pigmentosa. Tucker BA, Scheetz TE, Mullins RF, et al. Proc Natl Acad Sci USA 2011; 108(34):E569-76. (s12)

Abstract: Retinitis pigmentosa (RP) is a genetically heterogeneous heritable disease characterized by apoptotic death of photoreceptor cells. We used exome sequencing to identify a homozygous Alu insertion in exon 9 of male germ cell-associated kinase (MAK) as the cause of disease in an isolated individual with RP. Screening of 1,798 unrelated RP patients identified 20 additional probands homozygous for this insertion (1.2%). All 21 affected probands are of Jewish ancestry. MAK encodes a kinase involved in the regulation of photoreceptor connecting cilium length. Immunohistochemistry of human donor tissue revealed that MAK is expressed in the inner segments, cell bodies, and axons of rod and cone photoreceptors. Several isoforms of MAK that result from alternative splicing were identified. Induced pluripotent stem cells were derived from the skin of the proband and a patient with non-MAK-associated RP (RP control). In the RP control individual, we found that a transcript lacking exon 9 was predominant in undifferentiated cells, whereas a transcript bearing exon 9 and a previously unrecognized exon 12 predominated in cells that were differentiated into retinal precursors. However, in the proband with the Alu insertion, the developmental switch to the MAK transcript bearing exons 9 and 12 did not occur. In addition to showing the use of induced pluripotent stem cells to efficiently evaluate the pathogenicity of specific mutations in relatively inaccessible tissues like retina, this study reveals algorithmic and molecular obstacles to the discovery of pathogenic insertions and suggests specific changes in strategy that can be implemented to more fully harness the power of sequencing technologies.

Comment: This study uses a novel combination of exome sequencing and analysis of induced pluripotent stem cells from the skin of an affected patient to discover a previously unknown disease causing gene for RP. In addition, it identifies exons within the gene that are differentially expressed in different tissues and different disease states, and discusses the difficulties in finding insertion mutations as the cause of disease using current techniques.

Autosomal recessive retinitis pigmentosa caused by mutations in the MAK gene. Stone EM, Luo X, Heon E, et al. Invest Ophthalmol Vis Sci 2011;52(13):9665-73. (s12)

Purpose: To determine the disease expression in autosomal recessive (ar) retinitis pigmentosa (RP) caused by mutations in the MAK (male germ cell-associated kinase) gene.

Methods: Patients with RP and MAK gene mutations (n=24; age, 32-77 years at first visit) were studied by ocular examination, perimetry and optical coherence tomography (OCT).

Results: All but one MAK patient were homozygous for an identical truncating mutation in exon 9 and had Ashkenazi Jewish heritage. The carrier frequency of this mutation among 1207 unrelated Ashkenazi control subjects was 1/55, making it the most common cause of heritable retinal disease in this population and MAK-associated RP the sixth most common Mendelian disease overall in this group. Visual acuities could be normal into the eighth decade of life. Kinetic fields showed early loss in the superior-temporal quadrant. With more advanced disease, superior and midperipheral function was lost, but the nasal field remained. Only a central island was present at late stages. Pigmentary retinopathy was less prominent in the superior nasal quadrant. Rod-mediated vision was abnormal but detectable in the residual field; all patients had rod>cone dysfunction. Photoreceptor layer thickness was normal centrally but decreased with eccentricity. At the stages studied, there was no evidence of photoreceptor ciliary elongation.

Conclusions: The patterns of disease expression in the MAK form of arRP showed some resemblance to patterns described in autosomal dominant RP, especially the form caused by RP1 mutations. The similarity in phenotypes is of interest, considering that there is experimental evidence of interaction between Mak and RP1 in the photoreceptor cilium.

Comment: A new genetic cause of autosomal recessive RP has been discovered: mutations of the MAK gene. The salient features of this type of RP include that this is the most common cause of RP in patients of Ashkenazi Jewish descent; 1 in 55 people with this heritage is a carrier. It is the 6th most common genetic disorder overall in this group. Also, good central vision may be present until late in life, but peripheral vision is very poor. Mutations in the MAK gene should be considered in patients of Ashkenazi Jewish descent who have autosomal recessive RP.

Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. Do CB, Tung JY, Dorfman E, et al. PLoS Genet 2011;7(6):e1002141. (s12)

Abstract: Although the causes of Parkinson's disease (PD) are thought to be primarily environmental, recent studies suggest that a number of genes influence susceptibility. Using targeted case recruitment and online survey instruments, we conducted the largest case-control genome-wide association study (GWAS) of PD based on a single collection of individuals to date (3,426 cases and 29,624 controls). We discovered two novel, genome-wide significant associations with PD-rs6812193 near SCARB2 ($p = 7.6 \times 10^{-10}$, OR = 0.84) and rs11868035 near SREBF1/RAI1 ($p = 5.6 \times 10^{-8}$, OR = 0.85)-both replicated in an independent cohort. We also replicated 20 previously discovered genetic associations (including LRRK2, GBA, SNCA, MAPT, GAK, and the HLA region), providing support for our novel study design. Relying on a recently proposed method based on genome-wide sharing estimates between distantly related individuals, we estimated the heritability of PD to be at least 0.27....

Comment: This article is very interesting because it represents a collaboration of sorts between 23andMe, the direct to consumer genetic testing company, and some of its customers. This company accepts sputum samples from consumers, does exome sequencing, then reports disease susceptibility back to the consumer based on SNPs, which

are pieces of DNA reported in the literature to be associated with certain disease states or traits. Customers are invited to enter their own data about a myriad of physical traits and illnesses into the company's database as their DNA is being analysed. 23andMe is now using this customer supplied data to do genome-wide association studies (GWAS) with considerable statistical power. This study confirms and expands the genetic loci for Parkinson disease. Another publication reports the locus for the photic sneeze (Eriksson, et al. 23andMe. PLoS Genet. 2010;6(6):e1000993), a condition well known to ophthalmologists! While this is a novel use of direct-to-consumer testing, the utility of self-reported association studies remains to be seen. The utility of direct-to-consumer genetic testing in ophthalmology is not high at present (see the article on ARMS2 above), and is not recommended for patients as outlined in a recent position paper by the American Academy of Ophthalmology.

GPR179 Is Required for Depolarizing Bipolar Cell Function and Is Mutated in Autosomal-Recessive Complete Congenital Stationary Night Blindness.

Peachey NS, Ray TA, Florijn R, et al. Am J Hum Genet. 2012 Feb 10;90(2):331-9. (s12)

Complete congenital stationary night blindness (cCSNB) is a clinically and genetically heterogeneous group of retinal disorders characterized by nonprogressive impairment of night vision, absence of the electroretinogram (ERG) b-wave, and variable degrees of involvement of other visual functions. We report here that mutations in GPR179, encoding an orphan G protein receptor, underlie a form of autosomal-recessive cCSNB. The Gpr179(nob5/nob5) mouse model was initially discovered by the absence of the ERG b-wave, a component that reflects depolarizing bipolar cell (DBC) function. We performed genetic mapping, followed by next-generation sequencing of the critical region and detected a large transposon-like DNA insertion in Gpr179. The involvement of GPR179 in DBC function was confirmed in zebrafish and humans. Functional knockdown of gpr179 in zebrafish led to a marked reduction in the amplitude of the ERG b-wave. Candidate gene analysis of GPR179 in DNA extracted from patients with cCSNB identified GPR179-inactivating mutations in two patients. We developed an antibody against mouse GPR179, which robustly labeled DBC dendritic terminals in wild-type mice. This labeling colocalized with the expression of GRM6 and was absent in Gpr179(nob5/nob5) mutant mice. Our results demonstrate that GPR179 plays a critical role in DBC signal transduction and expands our understanding of the mechanisms that mediate normal rod vision.

Comment: This study reports a new gene associated with complete congenital stationary night blindness, GPR179. An animal model exists for this genetic defect.

Genome-wide meta-analysis of five Asian cohorts identifies PDGFRA as a susceptibility locus for corneal astigmatism.

Fan Q, Zhou X, Khor CC, Cheng CY, Goh LK, Sim X, Tay WT, Li YJ, Ong RT, Suo C, Cornes B, Ikram MK, Chia KS, Genet. 2011 Dec;7(12):e1002402. (s12)

Corneal astigmatism refers to refractive abnormalities and irregularities in the curvature of the cornea, and this interferes with light being accurately focused at a single point in the eye. This ametropic condition is highly prevalent, influences visual acuity, and is a highly heritable trait. There is currently a paucity of research in the genetic etiology of corneal astigmatism. Here we report the results from five genome-wide association studies of corneal astigmatism across three Asian populations, with an initial discovery set of 4,254 Chinese and Malay individuals consisting of 2,249 cases and 2,005 controls. Replication was obtained from three surveys comprising 2,139 Indians, an additional 929 Chinese children, and an independent 397 Chinese family trios. Variants in PDGFRA on chromosome 4q12 (lead SNP: rs7677751, allelic odds ratio = 1.26 (95% CI: 1.16-1.36), $P(\text{meta}) = 7.87 \times 10^{-9}$) were identified to be significantly associated with corneal astigmatism, exhibiting consistent effect sizes across all five cohorts. This highlights the potential role of variants in PDGFRA in the genetic etiology of corneal astigmatism across diverse Asian populations.

Comments: Refractive errors are usually considered polygenic and multifactorial. This study had a large enough study population, with a large enough population of ethnically matched controls, to do a powerful statistical analysis and found that the PDGFRA gene may be involved in inheritance of astigmatism.

X-Linked Megalocornea Caused by Mutations in CHRDL1 Identifies an Essential Role for Ventroptin in Anterior Segment Development.

Webb TR , Matarin M , Gardner JC et al. Am J Hum Genet. 2012 Feb 10;90(2):247-59. (s12)

X-linked megalocornea (MGC1) is an ocular anterior segment disorder characterized by an increased cornea diameter and deep anterior chamber evident at birth and later onset of mosaic corneal degeneration (shagreen), arcus juvenilis, and presenile cataracts. We identified copy-number variation, frameshift, missense, splice-site and nonsense mutations in the Chordin-like 1 gene (CHRDL1) on Xq23 as the cause of the condition in seven MGC1 families. CHRDL1 encodes ventroptin, a bone morphogenic protein antagonist with a proposed role in specification of topographic retinotectal projections. Electrophysiological evaluation revealed mild generalized cone system dysfunction and, in one patient, an interhemispheric asymmetry in visual evoked potentials. We show that CHRDL1 is expressed in the developing human cornea and anterior segment in addition to the retina. We explored the impact of loss of ventroptin function on brain function and morphology in vivo.

CHRDL1 is differentially expressed in the human fetal brain, and there is high expression in cerebellum and neocortex. We show that MGC1 patients have a superior cognitive ability despite a striking focal loss of myelination of white matter. Our findings reveal an unexpected requirement for ventroptin during anterior segment development and the consequences of a lack of function in the retina and brain.

Comment: The authors report discovery of a novel gene which causes X-linked megalocornea when mutated. Of interest, many different types of disruption of the gene can cause the disease. Also of interest is the fact that the gene is expressed in brain and anterior segment, and the authors report that some patients have cone dysfunction and asymmetric

VEP in addition to megalocornea. In addition, there is loss of myelination in the brain, but high cognitive ability.

ADAMTSL4, a Secreted Glycoprotein Widely Distributed in the Eye, Binds Fibrillin-1 Microfibrils and Accelerates Microfibril Biogenesis.

Gabriel LA, Wang LW, Bader H, Ho JC, Majors AK, Hollyfield JG, Traboulsi EI, Apte SS. Invest Ophthalmol Vis Sci. 2012 Jan 31;53(1):461-9.(s12)

Purpose. ADAMTSL4 mutations cause autosomal recessive isolated ectopia lentis (IEL) and ectopia lentis et pupillae. Dominant FBN1 mutations cause IEL or syndromic ectopia lentis (Marfan syndrome and Weill-Marchesani syndrome). The authors sought to characterize recombinant ADAMTSL4 and the ocular distribution of ADAMTSL4 and to investigate whether ADAMTSL4 influences the biogenesis of fibrillin-1 microfibrils, which compose the zonule.

Methods. ADAMTSL4 was expressed by the transfection of HEK293F cells. Protein extracts and paraffin sections from human eyes were analyzed by Western blot analysis and by immunoperoxidase staining, respectively. Immunofluorescence was used to evaluate fibrillin-1 deposition in the ECM of fetal bovine nuchal ligament cells after culture in ADAMTSL4-conditioned medium or control medium. Confocal microscopy was performed to investigate ADAMTSL4 and fibrillin-1 colocalization in these cultures.

Results. Western blot analysis identified ADAMTSL4 as a glycoprotein in HEK293F cells and as a major band of 150 kDa in ocular tissues including ciliary body, sclera, cornea, and retina. Immunoperoxidase staining showed a broad ocular distribution of ADAMTSL4, associated with both cells and fibrillar ECM. When cultured in ADAMTSL4-containing medium, fetal bovine nuchal ligament cells showed accelerated fibrillin-1 deposition in ECM. ADAMTSL4 colocalized with fibrillin-1 microfibrils in the ECM of these cells.

Conclusions. ADAMTSL4 is a secreted glycoprotein that is widely distributed in the human eye. Enhanced fibrillin-1 deposition in the presence of ADAMTSL4 and colocalization of ADAMTSL4 with fibrillin-1 in the ECM of cultured fibroblasts suggest a potential role for ADAMTSL4 in the formation or maintenance of the zonule.

Comment: There is an intimate association between the functions of ADAMTSL4 and Fibrillin. ADAMTSL4 is now a known cause of isolated ectopia lentis and ectopia lentis et pupillae, while Fibrillin is classically associated with Marfan syndrome, which includes ectopia lentis, but also many other physical findings of connective tissue disorder. This study shows that ADAMTSL4 interacts with fibrillin-1 and this is likely how it affects the zonules. Autosomal recessive Weill Marchesani syndrome can be caused by mutations of a different gene in the ADAMTS family, ADAMTSL10. Weill Marchesani patients usually have short stature and short fingers with ectopia lentis; they may have aortic abnormalities. Their phenotype is in many ways opposite of Marfan syndrome. Ectopia lentis et pupillae patients appear to have only the ectopia lentis. This study further expands our knowledge of how these genes and their products interact to create this spectrum of connective tissue disorders.

AAV2 Gene Therapy Readministration in Three Adults with Congenital Blindness. Bennett J, Ashtari M, Wellman J et al. Sci Transl Med 2012; 4, 120ra15 (s12)

Subjects included in this study all suffered from LCA due to RPE65 mutations and had been previously enrolled in a Phase 1 Study [AAV2-hRPE65v2-102] to test safety and efficacy of subretinal delivery of AAV2-hRPE65v2 (www.clinicaltrials.gov identifier NCT01208389).

Seropositivity for AAV2 was not an exclusion for enrollment. Surgical delivery of AAV2-hRPE65v2 was carried out as previously described.

Comment: Three adults from the original clinical trial had their previously uninjected eye treated. Extensive studies were done to evaluate inflammatory response and vision in both eyes. There was no significant inflammatory response; the second eye injection was well tolerated. The viral vector was found in blood and tears in some patients out to day 3 but not thereafter. Patients reported improved vision in the second injected eye, and none reported diplopia. This study provides further hope that patients with RPE65 LCA may obtain benefit from subretinal gene therapy treatment in both eyes, even in adulthood.

XV. RETINOBLASTOMA

Occurrence of sectoral choroidal occlusive vasculopathy and retinal arteriolar embolization after superselective ophthalmic artery chemotherapy for advanced intraocular retinoblastoma.

Munier FL, Beck-Popovic M, Balmer A, Gaillard MC, Bovey E, Binaghi S. Retina. 2011 Mar;31(3):566-73.(f11)

BACKGROUND: Superselective ophthalmic artery chemotherapy (SOAC) has recently been proposed as an alternative to intravenous chemoreduction for advanced intraocular retinoblastoma. In this study, we report on the vascular adverse effects observed in our initial cohort of 13 patients.

METHODS: The charts of 13 consecutive patients with retinoblastoma who received a total of 30 injections (up to 3 injections of a single agent per patient at 3-week interval) of melphalan (0.35 mg/kg) in the ophthalmic artery between November 2008 and June 2010 were retrospectively reviewed. RetCam fundus photography and fluorescein angiography were performed at presentation and before each injection. Vision was assessed at the latest visit.

RESULTS: Enucleation and external beam radiotherapy could be avoided in all cases but one, with a mean follow-up of 7 months. Sectoral choroidal occlusive vasculopathy leading to chorioretinal atrophy was observed temporally in 2 eyes (15%) 3 weeks to 6 weeks after the beginning of SOAC and retinal arteriolar emboli in 1 eye 2 weeks after injection. There was no stroke or other clinically significant systemic side effects except a perioperative transient spasm of the internal carotid artery in one patient. Vision ranged between 20/1600 and 20/32 depending on the status of the macula.

CONCLUSION: : Superselective ophthalmic artery chemotherapy was effective in all patients with no stroke or other systemic vascular complications. Unlike intravenous chemoreduction, SOAC is associated with potentially sight-threatening adverse effect. Further analysis of the risks and benefits of SOAC will define its role within the therapeutic arsenal. Meanwhile, we suggest that SOAC should be given in one eye only and restricted to advanced cases of retinoblastoma, as an alternative to enucleation and/or external beam radiotherapy.

Comment: Fortunately no patient had a sustained systemic complication but there was one case of carotid spasm. Three patients had sight-threatening complications, however 12/13 avoided enucleation and/or radiation with this treatment.

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Pre-enucleation chemotherapy for eyes severely affected by retinoblastoma masks risk of tumor extension and increases death from metastasis.

Zhao J, Dimaras H, Massey C, Xu X, Huang D, Li B, Chan HS, Gallie BL. *J Clin Oncol*. 2011 Mar 1;29(7):845-51. (f11)

PURPOSE Initial response of intraocular retinoblastoma to chemotherapy has encouraged primary chemotherapy instead of primary enucleation for eyes with clinical features suggesting high risk of extraocular extension or metastasis. Upfront enucleation of such high-risk eyes allows pathologic evaluation of extraocular extension, key to management with appropriate surveillance and adjuvant therapy. Does chemotherapy before enucleation mask histologic features of extraocular extension, potentially endangering the child's life by subsequent undertreatment?

METHODS We performed retrospective analysis of 100 eyes with advanced retinoblastoma enucleated with, or without, primary chemotherapy, in Beijing Tongren Hospital, retrospectively, from October 31, 2008. The extent of retinoblastoma invasion into optic nerve, uvea, and anterior chamber on histopathology was staged by pTNM classification. The treatment groups were compared for pathologic stage and disease-specific mortality. **Results:** Children who received chemotherapy before enucleation had lower pTNM stage than primarily enucleated children ($P = .01$). Five patients who received pre-enucleation chemotherapy died as a result of extension into brain or metastasis. No patients who had primary enucleation died. For children with group E eyes, disease-specific survival (DSS) was lower with pre-enucleation chemotherapy ($n = 45$) than with primary enucleation ($n = 37$; $P = .01$). Enucleation longer than 3 months after diagnosis was also associated with lower DSS ($P < .001$).

CONCLUSION Chemotherapy before enucleation of group E eyes with advanced retinoblastoma downstaged pathologic evidence of extraocular extension, and increased the risk of metastatic death from reduced surveillance and inappropriate management of high-risk disease, if enucleation was performed longer than 3 months after diagnosis.

Comment: In this important paper the data suggest that children with advanced retinoblastoma have a greater chance of metastasis and death if they receive chemotherapy before enucleation. Parents of children with advanced Rb should know the risks. Rapid enucleation of group E eyes may give the greatest chance of disease-free survival. More data would be helpful in this decision-making.

Rabbit model of retinoblastoma.

Kang SJ, Grossniklaus HE.

J Biomed Biotechnol. December 2011;2011:394730. (s12)

We created a rabbit model of retinoblastoma and confirmed the tumor clinically and histopathologically. Seventeen New Zealand rabbits were immunosuppressed with cyclosporin A at doses of 10-15 mg/kg. At day 3, the animals received a 30 μ l subretinal injection of 1×10^6 cultured WERI retinoblastoma cells. Digital fundus images were captured before euthanasia, and the eyes were submitted for histopathology. Retinoblastoma cells

grew in all the inoculated eyes and established a tumor under the retina and/or in the vitreous. New blood vessels in the tumor were observed starting at week 5. Cuffs of viable tumor cells surrounded the blood vessels with regions of necrosis present at 70-80 μ m from nutrient vessels. Occasional tumor seeds in the vitreous histologically exhibited central necrosis. This rabbit model demonstrated similar fundus appearance and pathologic features to human retinoblastoma and may be used as a model to test various routes of drug delivery for retinoblastoma.

Comment: This is a very useful new model to study treatments for Rb.

Pre-enucleation chemotherapy for eyes severely affected by retinoblastoma masks risk of tumor extension and increases death from metastasis.

Zhao J, Dimaras H, Massey C, Xu X, Huang D, Li B, Chan HS, Gallie BL. J Clin Oncol. 2011 Mar 1;29(7):845-51. (f11)

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Periocular Topotecan for Intraocular Retinoblastoma.

Ashwin C. Mallipatna, MB, BS; Helen Dimaras, PhD; Helen S. L. Chan, MB, BS, FRCPC; Elise Héon, MD, FRCSC; Brenda L. Gallie, MD, FRCSC. Arch Ophthalmol. June 2011;129(6):738-745. (f11)

The purpose of this paper was to review the effectiveness and toxicity of periocular topotecan hydrochloride in fibrin sealant (Tisseel) for the control of intraocular retinoblastoma. This was a retrospective medical record review of visually threatening or recurrent intraocular retinoblastoma treated with periocular topotecan. In this study, eight children (10 eyes) received 1 to 4 injections of periocular topotecan in fibrin sealant, without or with concomitant laser and/or single freeze-thaw prechemotherapy cryotherapy. Median dose was 0.18 mg/kg (3.72 mg/m²). The 6 children who responded to treatment had small discrete tumors (8 International Intraocular Retinoblastoma Classification group A or B eyes). Of these, prior primary treatment for 3 children (3 eyes) was laser; for 1 child (2 eyes), systemic chemotherapy with focal laser; and for 2 children (3 eyes), periocular topotecan. In 4 children (4 eyes), tumor regression was sufficient for effective focal therapy, but in 2 children (4 eyes), long-term control required systemic chemotherapy. The 2 children who did not respond each had an International Intraocular Retinoblastoma Classification group D eye treated primarily with systemic chemotherapy, focal laser, and cryotherapy and recurrent disease that was not controlled by periocular topotecan; both eyes were eventually enucleated. No ocular and minimal hematological toxic effects were observed. At 11 months' median follow-up after topotecan treatment (18 months since diagnosis), all 8 group A and B eyes were retained with ongoing focal therapy required in only 1 group B eye; the 2 group D eyes were enucleated. The authors concluded that periocular topotecan in fibrin sealant can achieve volume reduction of small and recurrent retinoblastoma sufficient to allow successful focal therapy.

Intra-arterial Chemotherapy for the Management of Retinoblastoma: Four-Year Experience.

Y. Pierre Gobin, MD; Ira J. Dunkel, MD; Brian P. Marr, MD; Scott E. Brodie, MD, PhD; David H. Abramson, MD. Arch Ophthalmol. June. 2011;129(6):732-737. (f11)

The purpose is to determine whether intra-arterial chemotherapy is safe and effective in advanced intraocular retinoblastoma. Retinoblastoma often presents with advanced intraocular disease and, despite conventional treatment with intravenous chemotherapy and external beam radiation therapy, may still require enucleation. This was a single-arm, prospective registry from May 30, 2006, to May 30, 2010, at an ophthalmic oncology referral center with ambulatory care. A total of 95 eyes of 78 patients with unilateral or bilateral retinoblastoma were treated. The intervention was selective catheterization of the ophthalmic artery and injection of chemotherapy, usually melphalan with or without topotecan. Drug dosage was determined by age and angioanatomy. The main outcome measures were procedural success, event-free (enucleation or radiotherapy) ocular survival, and ocular and extraocular complications. Catheterization succeeded in 98.5% of procedures. There were 289 chemotherapy injections (median, 3 per eye). The Kaplan-Meier estimates of ocular event-free survival rates at 2 years were 70.0% (95% confidence interval, 57.9%-82.2%) for all eyes, 81.7% (95% confidence interval, 66.8%-96.6%) for eyes that received intra-arterial chemotherapy as primary treatment, and 58.4% (95% confidence interval, 39.5%-77.2%) for

eyes that had previous treatment failure with intravenous chemotherapy and/or external beam radiation therapy. There were no permanent extraocular complications. The authors feel that their experience suggests that intra-arterial chemotherapy is safe and effective in the treatment of advanced intraocular retinoblastoma.

Ultrasound biomicroscopy in the management of retinoblastoma

LM Vasquez,, GP Giuliani,, W Halliday, CJ Pavlin, BL Gallie and E He'ón, *Eye* February (2011) 25, 141–147 (f11)

Purpose To determine the role of ultrasound biomicroscopy (UBM) in the management of children affected with retinoblastoma.

Methods A review of clinical records of children with the diagnosis of retinoblastoma at the Hospital for Sick Children from January 1995 to December 2007, for whom UBM was used to determine the extent of intraocular

tumor. Clinical characteristics were compared with UBM. Pathological correlation was performed for enucleated eyes.

Results In total, 101 eyes of 75 patients were included in the final analysis. Only 11 eyes were diagnosed on UBM to have extension of the tumor anterior to the ora serrata, and were enucleated. Histopathological examination confirmed the anterior extension in all the 11 eyes.

In total, 50 eyes were enucleated because

of various reasons, such as poor visual prognosis (12 eyes), unilateral group D or E (23 eyes), recurrences

(8 eyes), and treatment failure (7 eyes). None of those patients were found to have anterior extension of the disease on histopathological examination. UBM did not yield any false negative (0/50) or any false positives (0/11).

Conclusions The UBM provided a sensitive and reproducible visualization of the anterior retina, ciliary region, and anterior segment allowing a better staging of the advanced disease process. Primary assessment of the true extent of retinoblastoma is critical for the selection of an optimal management approach.

A clinicopathological correlation of 67 eyes primarily enucleated for advanced intraocular retinoblastoma.

Wilson MW, Quaddoumi I, Billups C et al. *Br J Ophthalmol.* 2011 Apr;95(4):553-8 (f11)

Aims To correlate the clinical and histopathological findings of eyes primarily enucleated for advanced intraocular retinoblastoma.

Methods In a retrospective study, the authors identified patients primarily enucleated for advanced intraocular retinoblastoma. The authors retrieved patient demographics, clinical findings, subsequent treatments and outcomes, and reviewed the histopathology of each eye for invasion of the anterior chamber, iris, ciliary body, choroid, sclera and optic nerve, and extraocular extension. The authors used the Fisher exact, exact Jonkheere-Terpstra, exact Wilcoxon rank sum and Kruskal-Wallis statistical tests ($p < 0.05$) to study associations between clinical and histopathological findings.

Results The authors identified 67 eyes of 67 patients (33 males) primarily enucleated for retinoblastoma between March 1997 and January 2008. Corneal diameter, intraocular pressure and Reese-Ellsworth Classification had no significant association with invasive

disease. The International Classification, however, was associated with optic nerve ($p=0.026$), choroid ($p<0.001$), ciliary body ($p=0.002$), iris ($p=0.002$), anterior chamber ($p=0.025$) and scleral ($p<0.001$) invasion. Eyes classified as International Classification Group E were more likely to have invasion of these sites and have more severe optic-nerve invasion.

Conclusions Corneal diameter, intraocular pressure and Reese-Ellsworth Classification do not correlate with histopathological evidence of invasive retinoblastoma. Eyes classified as International Classification Group E are more likely to have elevated intraocular pressure, invasion of the anterior chamber, uveal tract, optic nerve and sclera. The findings warrant primary enucleation with meticulous histopathological examination of such eyes prior to any adjuvant therapy.

Familial retinoblastoma: fundus screening schedule impact and guideline proposal. A retrospective study.

Rothschild PR, Lévy D, Savignoni A, Lumbroso-Le Rouic L, Aerts I, Gauthier-Villars M, Esteve M, Bours D, Desjardins L, Doz F, Lévy-Gabriel C. *Eye (Lond)*. December 2011;25(12):1555-61. (s12)

This was a retrospective study from one clinical center assessing if systematic fundus screening according to an 'intensive' schedule alters ocular outcome for children related to a retinoblastoma patient.

The institution performs fundus exams shortly after birth under general anesthesia and then at regular intervals according to schedules based on the risk of retinoblastoma (see table 1). Familial retinoblastoma cases seen from January 1995 to December 2004 were retrospectively classified as 'screened' or 'non-screened' (NS) and, among the 'screened' patients, as 'intensively screened' (IS) if screening matched their recommendations or 'non-intensively screened' (S).

59 retinoblastoma patients were familial cases. In all, 20 were in the NS group, 23 in the S group, and 16 in the IS group. The number of children enucleated was, respectively, 13, 2, and 0 ($P<0.0001$); external beam radiation (EBRT) was required for, respectively, 6, 0, and 2 children ($P<0.009$).

The authors conclude that an 'intensive' fundus screening schedule decreased the need for enucleation and EBRT.

Ultrasound biomicroscopy evaluation of anterior extension in retinoblastoma: a clinicopathological study

Alexandre P Moulin, Marie-Claire Gaillard, Aubin Balmer, Francis L Munier
Br J Ophthalmol March 2012;96:337-340. (s12)

Background Extension of retinoblastoma cells into the posterior chamber is a criterion for group E according to the international classification of intraocular retinoblastoma. Currently, the anterior extension of retinoblastoma is based on the presence of tumour cells in the

anterior chamber assessed by biomicroscopy.

Aim To determine the value of ultrasound biomicroscopy (UBM) in the assessment of posterior chamber involvement in advanced retinoblastoma.

Methods Retrospective review of all retinoblastoma cases enucleated at the Jules Gonin Eye Hospital from January 1996 to December 2009 for which UBM (35 MHz) evaluation was available. The patients' records were reviewed for patient and tumour features and histopathological findings. UBM findings were compared with histopathological features.

Results UBM documentation was available in 31 cases. Retinoblastoma was detected by UBM in the posterior chamber in 18 cases and was absent in 13 cases while histopathological analysis demonstrated its presence in the posterior chamber in 22 cases and its absence in 9 cases. Among the 18 UBM-positive cases, 7 had biomicroscopic detectable involvement of the anterior chamber. There was a significant correlation between echodensities consistent with retinoblastoma on UBM in the posterior chamber and histopathological tumorous involvement of the posterior chamber (p.0.0001). The sensitivity of UBM in the assessment of posterior chamber invasion by retinoblastoma was 81% and the specificity was 100%.

Conclusion In selected cases of advanced retinoblastoma, UBM appears to represent a valuable tool in the precise evaluation of anterior extension of disease, with good sensitivity and specificity for the assessment of posterior chamber involvement. UBM may provide useful criteria governing the indication for enucleation

Outcomes of Integrating Genetics in Management of Patients With Retinoblastoma

Shweta U. Dhar, MD, MS; Murali Chintagumpala, MD; Claire Noll, MS; Patricia Chévez-Barrios, MD; Evelyn A. Paysse, MD; Sharon E. Plon, MD, PhD

Arch Ophthalmol. November 2011;129(11):1428-1434 (s12)

The goal of this paper was to present the outcome of a comprehensive team approach to provide genetic evaluation and testing for a large cohort of children diagnosed with retinoblastoma. The multidisciplinary team included pediatric oncologists, an ophthalmologist, an ophthalmic pathologist, a geneticist, and genetic counselors. Retrospective data from 8 years included 90 initial evaluations, of which 81 probands were diagnosed with retinoblastoma (34 bilateral and 47 unilateral) and 9 were evaluated because of a positive family history. Genetic testing was accomplished equivalently in bilateral and unilateral cases in 51 of 81 patients (63%). In 5 of 30 patients (17%), with unilateral disease an *RB1* mutation was identified in peripheral blood samples. In another 7 of 30 patients (23%), mutation analysis confirmed the occurrence of sporadic retinoblastoma. Overall, genetic testing of 48 at-risk family members from 21 families revealed 6 individuals positive and 42 negative for the familial mutation. This study emphasizes that genetics can be incorporated into the management plan of all retinoblastoma patients using a team approach to ensure timely evaluations and appropriate counseling. Genetic evaluations improved risk prediction for patients and family members as well as prevented overutilization of clinical screening tests, which had potential morbidity for relatives documented to not carry an *RB1* mutation.

Postenucleation Adjuvant Chemotherapy With Vincristine, Etoposide, and Carboplatin for the Treatment of High-Risk Retinoblastoma

Swathi Kaliki, MD; Carol L. Shields, MD; Sanket U. Shah, MD; Ralph C. Eagle Jr, MD; Jerry A. Shields, MD; Ann Leahey, MD

Arch Ophthalmol. November 2011;129(11):1422-1427. (s12)

An analysis of 52 eyes with high-risk retinoblastoma managed with postenucleation adjuvant chemotherapy using vincristine sulfate, etoposide phosphate, and carboplatin showed no evidence of systemic metastasis in any case during a mean (range) follow-up of 66 (12-202) months. The goal of this paper was to determine the efficacy of postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin in the prevention of metastasis for patients with high-risk retinoblastoma. This was a retrospective, nonrandomized, interventional case series of 52 eyes in 51 patients with high-risk retinoblastoma consisting of tumor invasion into the anterior segment, posterior uvea 3 mm or greater, postlaminar optic nerve, or any combination of posterior uvea and optic nerve involvement. Of 51 consecutive patients with high-risk retinoblastoma, there were 30 males (59%) and 21 females (41%), with a median age of 28 months at diagnosis. All 52 eyes were classified as group E. The main histopathologic risk factors included anterior segment invasion (7 [13%]), isolated massive posterior uveal invasion of 3 mm or greater (6 [12%]), isolated postlaminar optic nerve invasion (15 [29%]), or any posterior uveal invasion with any optic nerve involvement (24 [46%]). There was additional invasion into the sclera (3 [6%]) and extrascleral structures, including the orbit (1 [2%]). A single histopathologic high-risk factor was present in 32 eyes (62%), whereas 20 eyes (38%) manifested 2 or more high-risk characteristics. Based on previously published series, untreated high-risk retinoblastoma carries at least a 24% risk for metastatic disease. In the present series, using vincristine, etoposide, and carboplatin in all cases, there was no metastasis during a mean follow-up of 66 months (median [range], 55 [12-202] months). In summary, retinoblastoma with invasion into the postlaminar optic nerve and/or posterior uvea is at high risk for metastasis and death. In this study, postenucleation chemotherapy using vincristine, etoposide, and carboplatin was effective in preventing metastasis in every case (100%).

Histopathologic Observations After Intra-arterial Chemotherapy for Retinoblastoma

Ralph C. Eagle Jr, MD; Carol L. Shields, MD; Carlos Bianciotto, MD; Pascal Jabbour, MD; Jerry A. Shields, MD

Arch Ophthalmol. November 2011;129(11):1416-1421. (12)

The purpose of this paper was to describe histopathologic observations in eyes enucleated after intra-arterial chemotherapy (IAC) for retinoblastoma (Rb). This was a retrospective histopathologic analysis of 8 eyes. The eyes were enucleated for tumor viability (n = 4), neovascular glaucoma (n = 2), anaphylactic reaction from IAC (n = 1), and persistent retinal detachment with poor visualization of the tumor (n = 1). Of the 2 eyes judged clinically with complete tumor regression and the 5 with viable tumor, the findings were confirmed on histopathology. The Rb response ranged from minimal (n = 1) to moderate (n = 1) to extensive (n = 4) to complete regression (n = 2). Viable vitreous seeds (n = 4 eyes), invasion into the optic nerve (n = 3), reaching the lamina cribrosa in 2 cases, and invasion into the choroid (n = 1) were observed. Histopathologic evidence of ischemic atrophy involving the

outer retina and choroid was found in 4 eyes. One eye treated at another center with IAC and enucleated by our team for recurrence was observed to have extensive choroidal and outer retinal atrophy. This case showed orbital vascular occlusion and subendothelial smooth muscle hyperplasia. Intravascular birefringent foreign material was observed in 5 cases within occluded vessels, stimulating a granulomatous inflammatory response. The foreign material comprised cellulose fibers (n = 3), synthetic fabric fibers (n = 1), or unknown composition (n = 2). Thrombosed blood vessels were identified in 5 eyes and involved ciliary arteries in the retrobulbar orbit (n = 5), scleral emissarial canals (n = 1), small choroidal vessels (n = 1), and central retinal artery (n = 1). Retinoblastoma can be controlled with IAC, but histopathology of enucleated eyes reveals that ocular complications including thromboembolic events can occur.

Intra-arterial Chemotherapy for Retinoblastoma

Report No. 2, Treatment Complications

Carol L. Shields, MD; Carlos G. Bianciotto, MD; Pascal Jabbour, MD; Gregory C. Griffin, MD; Aparna Ramasubramanian, MD; Robert Rosenwasser, MD; Jerry A. Shields, MD

Arch Ophthalmol. November 2011;129(11):1407-1415. (12)

The purpose was to describe treatment complications following intra-arterial chemotherapy (IAC) for retinoblastoma. This was a retrospective interventional series of ophthalmic artery cannulation for IAC injection (3 planned sessions at 1-month intervals) was undertaken. Thirty-eight catheterizations of 17 eyes of 17 patients were performed from September 2008 to September 2010. Fluoroscopy of the ophthalmic artery was performed before and immediately after treatment. Heparin was given during the procedure and aspirin (40 mg) was given orally for 1 week. The treatment complications were determined. Only 17 of 190 children were selected for treatment with IAC during this period. Following successful ophthalmic artery cannulation in 16 cases, there was no evidence of metastasis, stroke, brain injury, or persistent systemic toxic effects. Fluoroscopy demonstrated patent ophthalmic artery immediately before and after IAC injection in each case. Following therapy, orbital and adnexal findings at 1 month included eyelid edema (n = 13), blepharoptosis (n = 10), cilia loss (n = 1), and orbital congestion with temporary dysmotility (n = 12). These findings resolved within 6 months in all cases. Following therapy, vascular findings included ophthalmic artery stenosis (permanent in 3 cases, temporary in 1 case), confirmed on fluoroscopy in 3 cases. Concomitant central or branch retinal artery occlusion was noted (permanent in 2 cases, temporary in 1 case). Subtle retinal pigment epithelial mottling in 9 cases that slowly evolved to later-onset underlying choroidal atrophy in 5 cases was noted. Treatment with IAC for retinoblastoma can lead to mild and severe short-term ocular complications, including eyelid edema as well as potentially blinding vascular obstruction. This procedure should be used with caution.

Intra-arterial Chemotherapy for Retinoblastoma

Report No. 1, Control of Retinal Tumors, Subretinal Seeds, and Vitreous Seeds

Carol L. Shields, MD; Carlos G. Bianciotto, MD; Pascal Jabbour, MD; Aparna Ramasubramanian, MD; Sara E. Lally, MD; Gregory C. Griffin, MD; Robert Rosenwasser, MD; Jerry A. Shields, MD

Arch Ophthalmol. November 2011;129(11):1399-1406 (s12)

The purpose of this paper was to describe tumor control following intra-arterial chemotherapy (IAC) for retinoblastoma. This was a retrospective interventional series in which 17 patients were treated with ophthalmic artery injection of melphalan, 5 mg, was undertaken to determine retinoblastoma control. Of 190 children with retinoblastoma, 17 (9%) were treated with IAC. Catheterization was successful in 37 of 38 attempts. The treatment was primary in 13 cases (1 failed catheterization) and secondary in 4. The median retinoblastoma base was 20 mm and the median retinoblastoma thickness was 9.0 mm. Iris neovascularization was present in 5 cases. Following IAC, complete response of the main tumor was found in 14 cases (88%) and partial response was found in 2 (12%). Eyes with complete response and followed up for a minimum of 1 year ($n = 10$) showed no solid tumor recurrence. Of 11 eyes with subretinal seeds, 9 (82%) had complete response, 1 (9%) had partial response, and 1 (9%) had recurrence. Of 9 eyes with vitreous seeds, 6 (67%) had complete response, 2 (22%) had partial response, and 1 (11%) had recurrence. Globe salvage was achieved in 8 of 12 eyes (67%) treated with primary IAC, including 2 of 2 group C eyes, 4 of 4 group D eyes, and 2 of 6 group E eyes according to the International Classification of Retinoblastoma. Globe salvage was achieved in 2 of 4 eyes (50%) treated secondarily after failure of other methods. Of 12 eyes managed with IAC as primary treatment, globe salvage was achieved in 67%. Eyes classified as group C or D showed 100% globe salvage, whereas group E had 33% salvage. Of 4 eyes managed with IAC as secondary treatment, globe salvage was achieved in 50%

Success of Intra-arterial Chemotherapy (Chemosurgery) for Retinoblastoma: Effect of Orbitovascular Anatomy

Brian P. Marr, MD; Crystal Hung, MD; Yves P. Gobin, MD; Ira J. Dunkel, MD; Scott E. Brodie, MD; David H. Abramson, MD

Arch Ophthalmol. February 2012;130(2):180-185 (s12)

The purpose of this paper was to review results of orbital angiography performed during intra-arterial chemotherapy (chemosurgery) for treatment of retinoblastoma to assess the association of angiographic variability in orbitovascular anatomy with tumor response and outcomes. The medical records and 64 orbital angiograms were reviewed for 56 pediatric patients with retinoblastoma undergoing chemosurgery using a combination of melphalan hydrochloride, topotecan hydrochloride, or carboplatin. The major orbital arteries and capillary blush patterns were graded, and tumor response and recurrence were compared using the log-rank and Fisher exact tests. Statistically significant variables for tumor response were lacrimal artery prominence ($P = .001$), previous treatment ($P = .003$), and lacrimal blush

($P = .004$). The only statistically significant variable for vitreous seed response was ciliary body blush ($P = .03$). Statistically significant variables influencing time to recurrence and time to enucleation were choroidal blush absence ($P = .01$) and lacrimal artery presence ($P = .03$), respectively. In conclusion, the success of intra-arterial chemotherapy is dependent on delivery of drug to the target tumor within the eye via the ophthalmic artery. Because of the small volume of drug used (0.50-1.25 mL per treatment) and the selectivity of catheterization, variables affecting orbital blood flow greatly influence drug delivery and the success of chemosurgery.

Selective Ophthalmic Arterial Injection Therapy for Intraocular Retinoblastoma: The Long Term Prognosis

Shigenobu Suzuki, Takashi Yamane, Makoto Mohri, Akihro Kaneko,

Ophthalmology: 2011; 118: 2081-2087 (October) (s12)

This study represents a retrospective, noncomparative case series of 408 eyes in 343 patients who underwent a selective ophthalmic arterial injection (SOAI) of melphelan for treatment of intraocular retinoblastoma between 1988 and 2007. The study reports ocular and systemic adverse events, secondary neoplasms, eye survival and visual acuity.

The authors report a 98% success rate for successful injection of melphelan using a balloon catheter. They also report "few adverse events including secondary neoplasms, loss of the eye/enucleation and good maintenance of acuity in eyes that did not have macular tumors.

The authors feel that selective ophthalmic arterial injection (SOAI) is "an established treatment method" for intraocular retinoblastoma.

The study was completed at the National Cancer Center Hospital, Tokyo Japan.

COMMENT: This article shows that Japanese ocular oncologists have been using this method of treatment at approximately twenty years before Abramson and his group reported this treatment in *Ophthalmology* (2008).

Guidelines for imaging retinoblastoma: imaging principles and MRI standardization

Pim de Graaf, Sophia Göricke, Firazia Rodjan, Paolo Galluzzi, Philippe Maeder, Jonas A. Castelijns, Hervé J. Brisse and on behalf of the European Retinoblastoma Imaging Collaboration (ERIC)

Pediatric Radiology. January 2012;42(1):2-14. (s12)

Retinoblastoma is the most common intraocular tumor in children. The diagnosis is usually established by the ophthalmologist on the basis of fundoscopy and ultrasound (US). Together with US, high-resolution MRI has emerged as an important imaging modality for pretreatment assessment to provide diagnostic confirmation, detection of local tumor extent, detection of

associated developmental malformation of the brain and detection of associated intracranial primitive neuroectodermal tumor (trilateral retinoblastoma). Minimum requirements for pretreatment diagnostic evaluation of retinoblastoma or mimicking lesions are presented, based on consensus among members of the European Retinoblastoma Imaging Collaboration (ERIC). Together with US, high-resolution MR imaging has emerged as the most important imaging modality in the assessment of retinoblastoma. CT is no longer recommended in children with leukocoria due to ionizing radiation and lack of diagnostic value. US combined with MRI using the suggested standardized retinoblastoma MRI protocol provides state-of-the-art pretreatment diagnostic evaluation in children with retinoblastoma. The most appropriate techniques for imaging in a child with leukocoria are reviewed. Implementation of a standardized MRI protocol for retinoblastoma in clinical practice may benefit children worldwide since a decreased use of CT reduces the exposure to ionizing radiation.

Profiling safety of intravitreal injections for retinoblastoma using an anti-reflux procedure and sterilisation of the needle track.

Munier FL , Soliman S , Moulin AP , Gaillard MC , Balmer A , Beck-Popovic M ., Br J Ophthalmol. 2012 Feb 24. [Epub ahead of print] (s12)

The preservation of globe integrity has always been a major concern during the treatment of retinoblastoma for fear of extraocular or metastatic spread. Intravitreal chemotherapy has been attempted as a desperate salvage therapy only for eyes with refractory retinoblastoma. Published data on the safety and efficacy of this route are, however, limited. A modified technique of intravitreal injection in eyes with retinoblastoma is described. All children with retinoblastoma who received one or more intravitreal injections using this technique were retrospectively reviewed concerning ocular complications of the injection procedure as well as clinical or histopathological evidence of tumour spread. 30 eyes of 30 children with retinoblastoma received a total of 135 intravitreal injections, with a median follow-up duration of 13.5 months. No extraocular spread was seen on clinical follow-up in any patients and there was no tumour contamination of the retrieved entry sites histopathologically analysed among the five enucleated eyes. No significant ocular side effects were observed except transient localised vitreous haemorrhage (3/135). This technique is potentially safe and effective at a low cost and may play a promising role, especially in the treatment of recurrent and/or resistant vitreous disease in retinoblastoma, as an alternative to enucleation and/or external beam radiotherapy. However, this treatment should not replace the primary standard of care of retinoblastoma and should not be considered in group E eyes. Its application should be approved by an ophthalmological oncological team and it should be performed by an experienced eye surgeon in a tertiary referral centre after careful selection of a tumour-free injection site.

Comment: The authors provide data on their experience of using intravitreal injection of chemotherapy for retinoblastoma with vitreous seeds in 30 eyes of 30 children. 5 of the eyes went to enucleation despite treatment. In these enucleated eyes, no seeding was noted at the site of injection. Except for transient vitreous hemorrhage, there were no complications.

This is a very useful article because the authors report on a fairly large number of patients, it was safe, and it was apparently successful in saving the eyes of 25/30 patients. However the authors are careful to note that this should not be used in group E eyes; it seems clear that the risk of spread would be much higher in these eyes and the chance of salvage much lower.

Carboplatin-Associated Ototoxicity in Children With Retinoblastoma.

Qaddoumi I, Bass JK, Wu J, Billups CA, Wozniak AW, Merchant TE, Haik BG, Wilson MW, J Clin Oncol. 2012 Feb 27. [Epub ahead of print] (s12)

PURPOSE: Carboplatin-induced ototoxicity remains poorly defined but is of potential great consequence in children with retinoblastoma. We retrospectively assessed the incidence of ototoxicity and its risk factors in children with retinoblastoma who were treated with carboplatin.

PATIENTS AND METHODS: We reviewed the audiologic test results of 60 patients with retinoblastoma who received front-line treatment with systemic carboplatin and vincristine according to the St Jude RET-3 protocol (n = 23) or best clinical management (n = 37). Ototoxicity was evaluated by three different grading systems.

Results: Twelve patients (20%) developed ototoxicity at some time after treatment initiation; however, ototoxicity resolved in two patients, and thus, 10 patients (17%) had sustained hearing loss as documented at their most recent audiologic evaluation. Nine of these 10 patients had grade 3 or 4 ototoxicity, and nine patients were less than 6 months of age at the start of chemotherapy. Age at the start of chemotherapy was the only risk factor identified as a significant predictor of sustained hearing loss. Younger age was associated with an increased incidence of hearing loss. The different ototoxicity grading systems showed good overall agreement in the identification of patients with ototoxicity. Agreement was greatest between the Brock and Children's Cancer Group systems.

CONCLUSION: We found that young patients with retinoblastoma who were treated with systemic carboplatin had a higher incidence of ototoxicity than previously reported. Younger patients (< 6 months of age at the start of treatment) were more likely to have ototoxicity than were older patients. Children treated with carboplatin should routinely undergo thorough, long-term audiologic monitoring.

Comment: This study shows that ototoxicity from carboplatin, a chemotherapeutic agent very commonly used in children with retinoblastoma, is more common than thought—17% of patients had sustained hearing loss. 9/10 patients with significant hearing loss were less than 6 months old at the time of treatment. Children treated with carboplatin should have ongoing hearing screens, and young age at treatment may carry a poor prognosis for hearing.

Combined intravitreal and subconjunctival carboplatin for retinoblastoma with vitreous seeds.

Smith SJ, Pulido JS, Salomão DR, Smith BD, Mohny B. Br J Ophthalmol. 2012 Feb 24. [Epub ahead of print] (s12)

Purpose: To describe the technique of intravitreal chemotherapy preceded by subconjunctival chemotherapy for the treatment of vitreous seeds in advanced stage retinoblastoma.

Methods: This non-comparative interventional case series retrospectively reviewed the medical records and postenucleation histopathological findings of two patients who presented within weeks of each other with bilateral retinoblastoma, Reese-Ellsworth (R-E) stage Vb in the worse eye. Both patients had failed systemic chemotherapy prior to receiving a single treatment of 0.5 ml (5 mg per 0.5 ml) of subconjunctival carboplatin, through which 0.05 ml (3 mcg per 0.05 ml) of carboplatin was injected into the vitreous (Case 2 received 0.1 ml of intravitreal carboplatin). The subconjunctival chemotherapy was given to reduce the risk of orbital tumour seeding following intravitreal injection. Following enucleation, ocular toxicity and the presence or absence of viable tumour cells at the intravitreal injection site were recorded.

Results: Histopathological examination did not reveal patency of the pars plana intravitreal penetration site in either case at 6 weeks post-treatment nor was malignant seeding detected in the area of injection. Examination of the two enucleated eyes did not demonstrate structural toxicity to the cornea, anterior segment, iris or retina. Additionally, both cases were followed for over 37 months post-treatment, without the occurrence of orbital malignancy.

Conclusions: Injecting a bleb of subconjunctival chemotherapy prior to intravitreal drug delivery appeared to mitigate the risk of orbital tumour seeding in two patients with advanced stage retinoblastoma. Incorporating this technique may allow further investigation of intravitreal chemotherapy for the treatment of vitreous seeds in retinoblastoma.

Comment: The authors describe pre-treating with sub-conjunctival carboplatin before intravitreal injection to treat intravitreal seeds in retinoblastoma in 2 patients. It appeared safe and there was no ocular or orbital extension on enucleation specimens later. See the previous article on intravitreal chemotherapy in Rb—it may be safe with or without pre-treatment, but given the risks, this pre-treatment may be a good idea if it is safe.

XVI TRAUMA

Ocular Consequences of Bottle Rocket Injuries in Children and Adolescents.

Mehnaz Khan, MS; David Reichstein, MD; Franco M. Recchia, MD. Arch Ophthalmol. June. 2011;129(5):639-642. (f11)

This paper's goal is to describe the spectrum of ocular injuries and associated visual morbidity in the pediatric and adolescent population caused by bottle rockets. This was a retrospective review of consecutive medical records of patients 18 years or younger seen during a recent 4-year period. Outcome measures were ocular injuries at time of visit, interventions required, visual acuity at most recent follow-up, and most recent anatomic findings. Eleven eyes from 10 patients (8 boys and 2 girls aged 5-17 years) were identified. Significant ocular injuries included corneal epithelial defect (7 eyes), hyphema (6 eyes), traumatic iritis (2 eyes), iridodialysis (4 eyes), cataract (4 eyes), retinal dialysis (1 eye), and vitreous hemorrhage (2 eyes). Eight eyes required primary intervention (lensectomy in 4 eyes, corneal debridement in 2 eyes, globe exploration in 1 eye, and retinal laser photocoagulation in 1 eye). Three patients required additional procedures. These secondary interventions included pars plana vitrectomy (1 eye), muscle surgery for sensory strabismus (1 eye), corneal debridement (1 eye), and intraocular lens placement (1 eye). Most recent visual acuity (10 eyes with follow-up) was 20/30 or better in 4 eyes and 20/200 or worse in 6 eyes (for 1 eye, the patient was unavailable for follow-up). Permanent visual impairment was typically due to traumatic maculopathy. The authors conclude that bottle rockets can cause significant ocular injury in children, often with permanent loss of vision.

An inter-observer and intra-observer study of a classification of RetCam images of retinal haemorrhages in children

Alan O Mulvihill, Patricia Jones, Anamika Tandon, et al *Br J Ophthalmol* January 2011 95: 99-104 (f11)

Background There is currently no universally accepted classification of childhood retinal haemorrhages.

Aim To measure the inter- and intra-observer agreement of clinical classifications of retinal haemorrhages in children.

Methods Four examiners (two consultant ophthalmologists and two other clinicians) were shown 142 retinal haemorrhages on 31 RetCam photographs. The retinal haemorrhages were from children with

accidental or abusive head injury, or other encephalopathies, and included retinal haemorrhages of different ages. Specified haemorrhages were initially classified by each examiner according to their clinical understanding. Altogether, 26 haemorrhages were represented to test intra-observer consistency. Examiners then agreed a common description for each haemorrhage type and five categories were described (vitreous, pre-retinal, nerve fibre layer, intra-retinal/subretinal or indeterminate) and the study repeated.

Results There was 'fair agreement' initially (Fleiss' unweighted $k=0.219$) and, with the agreed classification, slight improvement (0.356). Intra-observer agreement marginally improved on re-test. The two consultant ophthalmologists showed 'fair' agreement on both occasions (paired k statistic). The other rater pair improved from 'fair' to 'substantial' agreement with the new classification.

Conclusions The classification of retinal haemorrhage in children by appearance alone shows only fair agreement between examiners. Clinicians who are not consultant ophthalmologists appear to benefit from the new succinct classification.

Epidemiological characteristics and visual outcomes after open globe injuries in children

Tok O, Tok L, Ozkaya D, et al J AAPOS. 2011 Dec;15(6):556-61 (s12)

Demographic, etiologic, and clinical characteristics of patients operated on for open globe injuries in two different centers were evaluated. This was a retrospective review of patients 16 years and younger over an eleven year period. Of 82 included children, 54 were boys (66%). The open globe injuries were penetration (67/82), rupture (10/82), intraocular foreign bodies (3/82) and perforation (2/82). The most common cause of injury was pointed objects poked by the child into his/her own eye, or from projectiles. Complications included endophthalmitis, retinal detachment, lens damage, afferent papillary defect, hyphema, uveal tissue prolapse, vitreous prolapse and lid laceration. The final visual acuity was NLP in 11% of patients and 20/40 or better in 39% of patients. The risk of a final acuity worse than 20/200 was increased 25-fold in patients with a presenting acuity of hand motion or worse. Presenting visual acuity was felt to be the best predictor of final outcome. Posterior wound location is also a predictor of poor final visual outcome.

Pediatric Ocular Injuries From Airsoft Toy Guns

Tarek A Shazly, A.K. Al-Hussaini, Journal of Pediatric Ophthalmology and Strabismus, January 2012; 49: 54-57 9 (s12)

Airsoft guns are nonpowder firearms in which a plastic pellet is propelled by compressed gas. The article draws attention to the severity of the injury that can be caused by this seemingly harmless toy gun. A retrospective chart review of 32 cases was reviewed looking at place of trauma, presenting signs and symptoms, surgery done (if any), and visual acuity at presentation and after treatment. Injuries included traumatic cataract, corneal abrasions, hyphemas (most common injury reported). A small number of patients sustained permanent visual disability secondary to traumatic cataract. Recommendations for use of these weapons are highlighted. Education for all physicians taking care of these injuries as well as parents is important to prevent severe visual disability due to a delay in seeking medical care which was found in several cases

Scleral Fixation of Intraocular Lens in Eyes With History of Open Globe Injury

Touka Banaee, Setareh Sagheb, Journal of Pediatric Ophthalmology and Strabismus September 2011; 48: 292-297 (s12)

Aphakia in children needs to be managed aggressively to prevent severe amblyopia. There are various methods to manage aphakia, one being implantation of an intraocular lens (IOL) in the capsular bag. This, however, requires adequate capsular support which is not always possible in cases of traumatic cataract. This study reports results and complications of sclera fixation of intraocular lens in traumatized eyes. Without adequate capsule and iris tissue (if there is no iris tissue, an anterior chamber IOL or an iris supported IOL cannot be implanted). Intraocular complications were mild including mild hemorrhage from pars plicata ciliaris that stopped spontaneously. The study found that overall sclera fixated IOL is a viable

option for eyes where there is minimal or no capsular support and no iris support so that an ACIOL or iris supported IOL cannot be used. However, it is important to consider nonsurgical option in these difficult cases first.

XVII Anterior Segment

The Outcome of Corneal Transplantation in Infants, Children, and Adolescents

Marie T Lowe, BSc, Miriam C Keane, BPsych (Hons), Douglas J Coster, FRANZCO, Keryn A Williams, PhD Ophthalmology Volume 118, Number 3, March 2011 (f11)

Type of Study

Large prospective, cohort study included 640 patients younger than 20 years of age at the time of penetrating keratoplasty. The records of these surgeries were submitted to the Australian Corneal Graft Registry by 381 ophthalmic surgeons and 253 follow-up practitioners from May 1985 to June 2009. The Kaplan-Meier survival plots and Cox proportional hazards regression analysis were used for statistical evaluation. This study was performed by members of the Department of Ophthalmology, Flinders University, Adelaide, Australia, all data sourced from the Australian Corneal Graft Registry.

Key Study Conclusions

Infants less than 5 years exhibited poor graft survival in children ages 5 to 12 years, adolescents 13 to 19 years exhibited better corneal graft survival than other age groups, 86% of grafts in adolescents were for keratoconus, factors significantly affecting corneal graft survival in pediatric patients included a) indication of a graft, b) graft inflammation, c) history of intraocular surgery, d) vascularization, e) rejection episodes, f) post graft operative procedures and g) refractive surgery. 14% of pediatric grafts failed of which 65% failed within 2 years. 44% of failures were due to unknown causes or irreversible rejection.

Importance for Pediatric Ophthalmologists

Corneal grafts for keratoconus adolescence show excellent survival. Infants exhibit poor graft survival and visual outcome especially those undergoing transplantation for Peters' anomaly. Corneal graft survival and visual outcomes vary more by indication for the graft than the recipient age. The major reason for graft failure is irreversible rejection. Corneal transplantation improves overall bilateral vision in pediatric patients. Despite technical, immunologic and clinical advances of penetrating keratoplasty for infants and children, PKP in this age group, remains labor intensive and challenging for parents and ophthalmologists alike. The visual results for keratoconus are significantly greater than for Peters' anomaly and all other corneal conditions. With recent advances in deep anterior stromal lamellar keratoplasty (DALK) and Descemet stripping, automated endothelial keratoplasty (DSAEK) there may be a definite trend toward replacing conventional penetrating keratoplasty (where there is an increased risk for rejection with these newer procedures).

Anterior Segment Optical Coherence Tomography (AS-OCT) of Conjunctival Nevus

Carol L Shields, MD, Irina Belinsky, MD, Massi Romanelli-Gobbi, BM, et. al. Ophthalmology Volume 118, Number 5, May 2011 (f11)

Type of Study

Retrospective interventional case series involving 22 eyes in 21 patients with conjunctival nevus imaged with anterior segment optical coherence tomography (AS-OCT) for evaluation

and detection of cysts within conjunctival nevi. This study was performed by the Ocular Oncology Service of the Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania.

Study Objectives and Design

Evaluation of intralesional cyst by use of ocular coherence tomography.

Key Study Conclusions

Anterior segment OCT provides high resolution imaging of the conjunctival nevi with the ability to demonstrate all margins and to provide information on the presence of intralesional cysts which are important in the diagnosis. The main drawback is optical shadowing of deeper structures from pigment within the nevi.

The visibility of the intrinsic cyst with histopathology showed a high correlation with clinical examination by experienced clinicians. The preliminary report shows evidence that AS-OCT may provide important data regarding the configuration of the conjunctival lesions, tumor boundaries and internal structures. This information contributes to establishing a clinical diagnosis of a benign conjunctival nevus and assist in defining the extent of the tumor.

THE AUTHORS STRESS THAT FURTHER RESEARCH INTO IMAGING OF CONJUNCTIVAL LESIONS WITH AS-OCT MAY ALLOW CHARACTERIZATION OF CLASSIC FEATURES TO BETTER AID IN ESTABLISHING A CLINICAL DIAGNOSIS AND DETECTING EARLY MALIGNANT TRANSFORMATION.

Importance for Pediatric Ophthalmologists

Conjunctival nevi are very common in childhood. Typical clinical features of conjunctival nevus include onset in childhood, pigmentation in 84% of lesions, location within 1mm of the limbus and the nasal or temporal bulbar region in 90% of the lesions and the presence of intralesional or intrinsic cysts in 65% of lesions.

Pearls/Comments

It is unclear from this article if information provided by AS-OCT will increase or decrease the need for formal incisional biopsy with a definitive pathological diagnosis.

Immunization and nutritional profile of cases with atraumatic microbial keratitis in preschool age group

Jhanji V, Naithani P, Lamoureux E, Agarwal T, Sharma N, Vajpayee RB.
Am J Ophthalmol. 2011 Jun;151(6):1035-1040. (f11)

Purpose

To evaluate the role of protein energy malnutrition and immunization profile in cases of atraumatic microbial keratitis in preschool children.

Design

Retrospective case analysis.

Methods

Case records of all children 5 years of age and younger with atraumatic microbial keratitis treated at the Dr Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, India, between January and December 2006 were reviewed retrospectively. Main parameters evaluated were age, degree of protein-energy malnutrition, immunization profile, microbiologic profile, and final outcome.

Results

Fifty-four consecutive children were enrolled during the study period. The mean age was 33.69 ± 21.91 months (range, 3 to 60 months). Mean weight on presentation was 10.57 ± 3.87 kg (range, 4 to 17 kg), with an average protein-energy malnutrition grade of 1.77 ± 0.74 . The immunization for age was complete in 43 (80%) children. Severe protein-energy malnutrition was associated with the occurrence of bilateral keratitis ($P < .001$) and incomplete immunization ($P < .001$). Positive bacterial culture results were obtained in 44 (82%) cases, with *Staphylococcus* species being the most prevalent isolate (33/44; 75%). Cases requiring emergency corneal transplantation (24%) were associated with severe protein-energy malnutrition ($P < .00$) and bilaterality ($P < .00$). In multivariate analyses, cases without severe protein-energy malnutrition were 36% less likely to undergo any kind of surgical intervention (odds ratio, 0.64; 95% confidence interval, 0.04 to 0.91).

Conclusions

Our study highlights the association of protein-energy malnutrition and immunization profile with the occurrence of atraumatic microbial keratitis in preschool children. Most of these cases required corneal transplantation surgery to preserve the ocular integrity and to restore vision.

Reviewer Comment

Malnutrition increased the severity and the likelihood of bilaterality in microbial keratitis in children.

Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis

J C Goebel, M Roesel, C Heinz, et al. Br J Ophthalmol. 2011 Feb;95(2):209-13 (f11)

Aim To investigate the therapeutic value of azathioprine as monotherapy or combined with other immunosuppressive drugs for uveitis in patients with juvenile idiopathic arthritis (JIA). **Methods** A retrospective multicentre study including 41 children with JIA (28 (68.2%) female) with unilateral or bilateral (n1/428) chronic anterior uveitis. Azathioprine was used to treat uveitis that was active in patients receiving topical or systemic corticosteroids, methotrexate or other immunosuppressive drugs. The primary end point was assessment of uveitis inactivity. Secondary end points comprised dose sparing of topical steroids and systemic corticosteroids, and immunosuppression.

Results At 1 year, uveitis inactivity was achieved in 13/ 17 (76.5%) patients by using azathioprine as systemic monotherapy and in 5/9 (56.6%) as combination therapy. During the entire azathioprine treatment period (mean 26 months), inactivity was obtained in 16/26 patients (61.5%) with monotherapy and in 10/15 (66.7%) when combined with other immunosuppressives (p1/41.0). With azathioprine, dosages of systemic immunosuppression and steroids could be reduced by 50% (n1/412) or topical steroids reduced to #2

drops/eye/day in six patients. In three patients (7.3%), azathioprine was discontinued because of nausea and stomach pain.

Conclusions Azathioprine may be reconsidered in the step-ladder approach for the treatment of JIA-associated uveitis. The addition of azathioprine may also be beneficial for patients not responding properly to methotrexate

Ocular and systemic findings in a survey of aniridia subjects

Netland PA, Scott ML, Boyle JW, and Lauderdale JD J AAPOS. 2011 Dec;15(6):562-6 (s12)

Prevalence of ocular and systemic abnormalities associated with aniridia in members of the Aniridia Foundation International was studied. Results were based on a survey. 83 subjects with a mean age of 25.4 +/- 18.4 years completed the survey. 2/3 of the patients had sporadic aniridia and 1/3 were familial cases (this is the exact opposite of reported rates). The reported rate of nystagmus was 83% and 41% reported foveal hypoplasia. 71% reported cataracts, 46% reported glaucoma, 45% reported keratopathy and 31% reported strabismus. These patients also had dental and musculoskeletal abnormalities as well as developmental delays. Asthma, depression, infertility and obesity were other relatively common diagnoses. This study was limited by the survey method. Some disorders may have been underreported because of patient lack of knowledge of less common conditions. There is also an inherent bias because patients were culled from members of the AFI.

Anterior segment imaging in pediatric ophthalmology.

Mireskandari K, Tehrani NN, Vandenhoven C, Ali A. *J Cataract Refract Surg.* December 2011; 37(12):2201-10. (s12)

In this review, the authors demonstrate how external and slit lamp photography, Scheimpflug imaging, handheld digital fundus camera (Retcam), ultrasound biomicroscopy, and anterior segment optical coherence tomography can be valuable in the documentation, diagnosis, and management of pediatric anterior segment disease. The authors provide practical tips on how to achieve high-quality images using various instruments, and they provide clinical examples of patients imaged with the aforementioned techniques.

Don't it make my blue eyes brown: heterochromia and other abnormalities of the iris

IG Rennie *Eye (Lond).* January 2012; 26(1):29-50. (s12)

Eye color is one of the most important characteristics in determining facial appearance. In this review containing over 300 references, the author discusses the anatomy and genetics of normal eye color. Iris color is determined primarily by the composition of the anterior iris stroma, not the posterior pigment epithelium. The iris stroma of blue-eyed individuals scatters light of short wavelengths. The more pigment contained in the iris stroma (within stromal melanocytes), the darker the iris color. The iris adopts its true color at roughly four months of age due to continued migration or differentiation of stromal melanocytes during the first few months of life.

In addition to answering simple questions about iris color that families of our patient may be interested in, the author covers a wide and diverse range of conditions that may produce and alteration in normal iris pigmentation or form. Many of these conditions are particularly applicable to the pediatric ophthalmologist (**in bold**).

The following topics are covered:

- iris heterochromia (including **congenital Horner's syndrome, Waardenburg syndrome**),
- iris freckles,
- **Lisch nodules**,
- ocular/oculodermal melanocytosis,
- iris cysts (including **primary iris stromal cysts**, posterior iridociliary cysts, and **central pigment epithelial cysts arising after miotic therapy**)
- vascular tumors and malformations of the iris
- iris tumors (adenomas and adenocarcinomas of the iris pigment epithelium, metastases)
- melanocytic tumors of the iris stroma (including nevi, melanocytomas, melanomas)

Axenfeld-Rieger syndrome: new perspectives

Ta C Chang,1 C Gail Summers, Lisa A Schimmenti, Alana L Grajewski
Br J Ophthalmol March 2012;96:318e322 (s12)

Axenfeld-Rieger syndrome is a genetic disease affecting multiple organ systems. In the eye, this condition manifests with varying degrees of anterior segment dysgenesis and carries a high risk of glaucoma. Other associated systemic issues include cardiovascular outflow tract malformations, craniofacial abnormalities and pituitary abnormalities, which can result in severe endocrinological sequelae. Recent advances in molecular genetics have identified two major genes, PITX2 and FOXC1, demonstrating a wide spectrum of mutations, which aids in the molecular diagnosis of the disease, although evidence exists to implicate other loci in this condition. The management of individuals affected by Axenfeld-Rieger syndrome requires a multidisciplinary approach and would include dedicated surveillance and management of glaucoma, sensorineural hearing loss, and cardiac, endocrinological, craniofacial and orthopaedic abnormalities. This is good review article on AR syndrome.

Poststreptococcal syndrome uveitis in South African children

Christopher Tinley, Lourens Van Zyl, Rhian Gro'tte
Br J Ophthalmol January 2012;96:87-89 (s12)

Objective To describe the demographics, clinical features and management of the largest case series to date on poststreptococcal syndrome uveitis (PSU), a newly recognised immune-mediated response to group A **b**-haemolytic streptococcus infection.

Methods Case notes of all patients presenting to the Red Cross War Memorial Children's Hospital, Cape Town, with serologically confirmed PSU between 2004 and 2010, were retrospectively reviewed.

Results A total of 22 cases were identified. Ages ranged from 4 to 12 years. 64% were black children and 64% were boys. Presenting visual acuities ranged from 6/6 to hand movements (median 6/24). 68% had bilateral disease. All had anterior uveitis (27% with posterior synechiae and 27% with hypopyon). 36% had vitritis and 23% had panuveitis. None had systemic illness or features of other poststreptococcal syndromes such as rheumatic fever, glomerulonephritis or polyarthritis. Anti-streptococcal titres (anti-streptolysin O and/or anti-deoxyribonuclease B) were significantly raised in all cases. Treatment comprised topical steroids and cycloplegic agents. Those with severe posterior segment involvement (41%) were treated with systemic corticosteroids. 55% received a course of oral penicillin. 82% had a single episode of uveitis. Four children had recurrences. Final visual acuities ranged from 6/6 to 6/36 (median 6/6).

Conclusion This case series significantly increases the evidence for PSU currently available in the world literature. The condition can manifest with the full spectrum of ocular inflammation, and most cases respond well to standard uveitis regimens. The role of antibiotic therapy remains unclear and requires further investigation.

Anophthalmos, Microphthalmos and Coloboma in the United Kingdom: Clinical Features, Results of Investigations and Early Management

Ophthalmology, 2012 February; 119: 362-368 (s12)

Shaheen P Shah, Amy E Taylor, Jane Sowden, Nicky Ragge , Clare E. Gilbert, et al. *for the Surveillance of Eye Anomalies Special Interest Group*

1. Descriptive, observational, cross-sectional study of the United Kingdom involving 135 children with Anophthalmos, Microphthalmos and Coloboma (AMC) diagnosed over a period of 18 months beginning in October 2006.
2. Main outcome measures were: 1. Ocular and systemic phenotype description 2. Clinical investigations 3. Therapeutic interventions.
3. Colobomatous defects were the most common phenotype within this spectrum of anomalies. The high frequency of posterior segment colobomatous involvement means that a dilated fundus examination should be performed in all cases.

4. The significant visual and systemic morbidity in affected children underlines the importance of a multidisciplinary management approach.

Study performed at The International Center for Eye Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

Viral anterior uveitis Jap, Aliza; Chee, Soon-Phaik. *Current Opinion in Ophthalmology*. November 2011;22(6):483-488 (s12)

With improvements in molecular diagnostics tests, viruses are increasingly being found to be associated with what was previously described as idiopathic anterior uveitis. This review presents the clinical features of viral anterior uveitis.

Herpes simplex virus/varicella zoster virus (HSV/VZV) are important causes of anterior uveitis, but other viruses including cytomegalovirus (CMV) and rubella are also found in a significant number of cases. The various viral anterior uveitides have similar features and should be suspected in eyes with diffuse, fine, stellate keratic precipitates, iris atrophy or ocular hypertension. Acyclovir remains the mainstay of therapy in HSV/VZV infections. CMV responds to ganciclovir, but the relapse rate is high and prolonged therapy may be required. Cataract and glaucoma are the main complications of viral anterior uveitis requiring appropriate management.

Not all centers have access to diagnostic tests for viral uveitis, which require aqueous analysis. Hence, the International Uveitis Study Group (IUSG) is organizing a multicenter prospective study to determine whether there are features that may differentiate between the different viral anterior uveitides and distinguish them from noninfectious uveitis, without performing aqueous analysis. Until these data are available, a virus cause should be suspected in cases of hypertensive anterior uveitis with iris atrophy. In such cases, corticosteroids should be withheld if aqueous analysis is not available.

Seasonal hyperacute panuveitis: an update Manandhar, Anu. *Current Opinion in Ophthalmology*. November 2011;22(6):496-501 (s12)

Seasonal hyperacute panuveitis (SHAPU) is a very strange disease reported to occur only in Nepal, in the form of outbreaks of unilateral severe panuveitis or endophthalmitis. It targets children in particular. The course of this disease is so hyperacute that it takes a toll on children's vision within hours or days leaving them disfigured with one phthisical eye. SHAPU has increased the burden of childhood blindness ever since it was described in 1975. Although moths are the suspected cause, this is not proven. There is no uniform management of this disease. This article reviews recent developments in the understanding of SHAPU pathogenesis, clinical features, cause, and preventive measures as well as treatment. Smaller summer outbreaks occur every even year together with larger autumn outbreaks every odd year. Vitreous fluid from some cases have grown bacteria on culture. Viruses were isolated in one case. Tiny hair follicles thought to be from the moth proboscis have been identified in ocular structures. Several cases had decreased corneal sensation

and few cases had iris atrophy. Early vitrectomy is beneficial. Intravitreal vancomycin, amikacin, and dexamethasone injection have given good results. Contrary to previous reports, the use of repeated subconjunctival dexamethasone injection has been shown to reverse disease. However, treatment helped save vision only in cases that presented early (within 7 days of onset). Recent findings have shown a correlation between SHAPU and moths (probably *Gazalina*). However, it is still inconclusive whether SHAPU is just an ophthalmia nodosa. New findings also suggest microbial involvement. Further studies are needed to determine whether the toxic venom of the moth, or the microbes (bacteria or virus) carried by moth hair follicles or scales, cause SHAPU.

XVIII Retina

Differentiation of Optic Nerve Head Drusen and Optic Disc Edema with Spectral-Domain Optical Coherence Tomography (SD-OCT)

Kyoung Min Lee, MD, Se Joon Woo, MD, Jeong-Min Hwang, MD
Ophthalmology Volume 118, Number 5, May 2011 (f11)

Type of Study

Comparative case series of 45 patients with optic nerve head drusen and 15 patients with optic disc edema and 32 normal controls. Spectral-Domain Optical Coherence Tomography (SD-OCT) was performed with scans on the optic nerve head and measurements of retinal nerve fiber layer thickness. The main outcome measures were qualitative findings of optic nerve head scans and retinal nerve fiber layer thickness profiles on Spectral-Domain Optical Coherence Tomography (SD-OCT).

This study was performed at the Department of Ophthalmology, Seoul National University College of Medicine in Seoul, Korea.

Study Objectives and Design

Optic nerve head drusen was visualized as focal hyperreflective subretinal mass with discrete margin on the Spectral-Domain OCT. Optic disc edema, peripapillary retinal nerve fiber layer changes were significantly thicker in all sections than in sections with optic nerve head drusen. Retinal nerve fiber thickness in the nasal section provides a good differential marker for optic disc edema versus optic nerve head drusen.

Key Study Conclusions

With the use of Spectral-Domain OCT, noninvasive and accurate differentiation of optic nerve head drusen and optic disc edema is possible.

Importance for Pediatric Ophthalmologists

The Spectral-Domain OCT may be a superior instrument in determining optic nerve head drusen versus optic disc edema when compared to ophthalmic ultrasound or CT. Review of the photographs in figure 1, page 973, are fairly conclusive of the optic nerve head changes in the 2 conditions. We strongly recommend review of the photographs with this article.

Pearls

Spectral-Domain OCT may be the modality of choice to look at pseudopapilledema in patients with suspected optic nerve head drusen and associated papilledema versus pseudopapilledema.

High-Resolution in Vivo Imaging in Achromatopsia

Mervyn G Thomas, BSc, Anil Kumar, MRCS, MRCOphth, Susanne Kohl, MSc, PhD, et. al. Ophthalmology Volume 118, Number 5, May 2011(f11)

Type of Study

Comparative case series utilizing an ultrahigh-resolution optical coherence tomography (UHR-OCT) (Copernicus; OPTOPOL Technology S.A., Zawiercie, Poland) to obtain scans from 26 eyes with achromatopsia and from 40 controlled eyes. This study was performed by ophthalmology groups at the School of Medicine University of Leicester, United Kingdom and the Molecular Genetics Laboiture for Ophthalmic Research, Department of Ophthalmology University of Tuebingen, Germany.

Study Objectives and Design

The purpose of the study is to characterize the retinal changes in patients with achromatopsia utilizing an

ultrahigh-resolution spectral-domain optical coherence tomography (UHR-OCT) to examine how human achromatopsia corresponds to its animal model.

The main outcome measures included gross morphologic changes in OCT as characterized by the UHR-OCT instrument. Specifically, inner segment and outer segment junction (IS/OS) and cone outer segment tip (COST) disruption was evaluated and noted. Using the reflectance profiles, foveal depth, thickness of the outer nuclear layer (ONL), and retinal thickness (RT) were measured. Inner segment and outer segment junctions were also measured (IS-OS).

Patients with achromatopsia also demonstrate a hyporeflective zone (HRZ), which is most prominently noted in high-resolution OCT. This high-resolution zone was noted in 7 out of 13 patients. The high reflective zone was age dependent. The area of the high reflective zone was asymmetric with the nasal area being significantly greater than the temporal area.

In all patients there is disruption of the inner segment/outer segment junction at the foveal or parafoveal regions. Five out of 13 patients had a disrupted cone outer segment tip (COST). Patients with achromatopsia also had a significant reduced foveal depth.

Key Study Conclusions

A range of signs associated with achromatopsia are described in this study. This includes the inner segment/outer segment junction changes, disruption in cone outer segment tip (COST) reflectivity in the presence of a hyporeflective zone (HRZ) near the fovea. The presence of a hyporeflective zone and thickness of the outer nuclear layer are age dependent and suggest that achromatopsia is a progressive disorder. In addition foveal

maldevelopment is described in the paper. The foveal maldevelopment represents a fetal development defect linked to cone photoreceptor degeneration.

Importance for Pediatric Ophthalmologists

The ultrahigh-resolution OCT scan provides new information about the morphology of achromatopsia. It does not provide information about the etiology of the morphologic changes nor does it provide any new information on its diagnosis or treatment.

Pearls/Comments

The high resolution ocular coherence tomography is another example of how a study can present more questions than it answers or another example of how high resolution tomography makes what we don't know bigger.

Effects of green diode laser in the treatment of pediatric Coats disease

Shapiro MJ, Chow CC, Karth PA, Kiernan DF, Blair MP.
Am J Ophthalmol. 2011 Apr;151(4):725-731. (f11)

Purpose

To review the effect of green diode laser ablation therapy on retinal structure and functional outcome in patients with advanced Coats disease.

Design

Retrospective, interventional case series.

Methods

Fourteen eyes of 13 patients with Coats disease were included in this study. Medical records, Retcam photographs (Clarity Medical Systems, Pleasanton, CA), and fluorescein angiograms were reviewed. All patients initially were treated with green diode laser (532 nm) ablation therapy to areas of the retinal telangiectasis associated with exudation. Main outcome measures included visual acuity, treatment outcome defined as complete resolution of telangiectatic lesions or exudative detachment, and macular status at the end of follow-up.

Results

Before treatment, 1 eye was at stage 2 (telangiectasis and exudation), 12 eyes were at stage 3 (exudative retinal detachment), and 1 eye was at stage 4 (total retinal detachment with glaucoma). Five eyes had highly detached retina of more than 4 mm. Median age at diagnosis was 51 months (range, 0.5 to 153 months). Median follow-up was 39.5 months (range, 15 to 70 months). Median number of green diode laser photocoagulation treatments was 2 (range, 1 to 5). After laser photocoagulation, 13 (93%) of 14 eyes had no active exudation. Functionally, 4 (29%) of 14 eyes had 20/50 or better visual acuity, 3 (21%) of 14 eyes had 20/60 to 20/200 visual acuity, 5 (36%) of 14 eyes had 20/400 to light perception visual acuity, and 2 (14%) of 14 eyes had no light perception visual acuity. No eye was phthisical or enucleated.

Conclusions

Green diode laser therapy can be an effective treatment for advanced Coats disease, even in the presence of a moderate to severely elevated retinal detachment.

Reviewer Comment

These data are useful for providing prognostic information for patients receiving treatment for advanced Coats disease.

Preferences of pediatric ophthalmologists and vitreoretinal surgeons of the treatment of scleral perforations during strabismus surgery.

Hwang C, Phoenix V, Hutchinson A. JPOS 2011;48:232-237. (July-August) (f11)

Purpose: to evaluate the preferences of pediatric ophthalmologists and vitreoretinal surgeons with regard to the initial management of scleral perforation during strabismus surgery.

Methods: 665 pediatric ophthalmologists and 494 vitreoretinal surgeons were invited by email to respond to an anonymous, web-based survey with responses subsequently compared.

Results: 169 ophthalmologists responded (133 pediatric ophthalmologists and 36 vitreoretinal surgeons). Significantly more pediatric ophthalmologists recommended initially managing scleral perforation with observation alone. Laser photocoagulation was perceived to result in the best outcome among vitreoretinal surgeons; method of treatment was not felt to affect outcome among pediatric ophthalmologists. The recalled rate of endophthalmitis was not significantly different between the 417 cases of ophthalmologists who routinely treat with antibiotics and the 116 cases of those who do not use antibiotics.

Conclusion: The management and perceived outcome of scleral perforation during strabismus surgery differs significantly between pediatric ophthalmologists and vitreoretinal surgeons.

Comment: An interesting study and review of the literature regarding an uncommon complication of strabismus surgery. The response rate was low for both groups (7% of vitreoretinal surgeons and 20% of pediatric ophthalmologists) limiting definitive conclusions. The initial decision to observe may reflect the fact that pediatric ophthalmologists are generally performing the strabismus surgery, often in children with formed vitreous. In addition, the higher rate of retinal detachment noted by vitreoretinal surgeons may represent referral bias of more severe perforations. There was no perceived difference in outcome between cryotherapy and laser treatment. Initial observation of scleral perforation during strabismus surgery may be a safe option, but the indications for treatment and the benefits of antibiotic use warrant further study.

Autofluorescence of treated retinoblastoma.

Ramasubramanian A, Shields CL, Mellen PL, et al. Apr. J AAPOS 2011;15:167-172 (f11)

Fundus autofluorescence (AF) is a noninvasive tool used to image retinal disease. This study evaluated AF of treated retinoblastomas. HyperAF strongly correlated with the presence of calcium within the regressed tumor. RPE hyperplasia appeared to show moderate to marked hypoAF. RPE atrophy showed varying AF features.

Pediatric sickle cell retinopathy: Correlation with clinical factors.

Rosenberg JB, and Hutcheson KA. J AAPOS. 2011 Feb;15(1):49-53. (f11)

This study evaluated whether sickle cell retinopathy is correlated with a greater incidence of other sickle cell disease manifestations. A retrospective chart review was performed. Of 258 patients who had received an eye examination, 65 had some degree of retinopathy. Patients with hemoglobin SC had higher rates of retinopathy than patients with hemoglobin SS (32.7% vs 17.2%), and higher rates of proliferative retinopathy (16.4% vs 0.54%). Of 14 factors reviewed, pain crisis, male sex, and splenic sequestration were all found to be significantly associated with sickle retinopathy. Selection bias may have been present in this study because over half of the patients treated for sickle cell at this institution had not had an eye examination, and the patient draw for this large urban center may bias towards a more severe disease state.

Feasibility and quality of nonmydriatic fundus photography in children

Toffoli D, Bruce BB, Lamirel C, et al J AAPOS. 2011 Dec;15(6):567-72 (s12)

What is the feasibility of obtaining adequate quality nonmydriatic ocular fundus photos in children? Photos were obtained by an Ophthalmologist or medical student, who had less than thirty minutes of camera-use training time. 878 ocular fundus photographs were obtained in 212 children. At least one ocular fundus photograph was obtained in 190 children (89.6%). There was a linear relationship between the child's age and an increasing proportion of shorter photography sessions. Photographs of some clinical value were obtained 33% of the time in children <3 years of age and 95% of the time in children \geq 3 years of age. Interobserver agreement was very good. There was a trend suggesting the older the person, the higher proportion of photography sessions lasting under 2 minutes. Photos of the optic disc region were of higher quality than the foveal region. This camera has limitations: subjects must position themselves correctly, quality photos for peripheral retinal abnormalities are difficult, and difficulty exists with obtaining photos in children <3 years of age.

Unilateral sporadic retinal dysplasia: Results of histopathologic, immunohistochemical, chromosomal, genetic, and VEG-F analyses

Jakobiec FA, Zakka FR, D'Amato R, et al J AAPOS. 2011 Dec;15(6):579-86 (s12)

Noninherited sporadic unilateral retinal dysplasia is rare and must be distinguished from retinoblastoma and Norrie disease. The enucleated globe of a 16-day-old girl was studied histopathologically, and with correlative immunohistochemistry and genetic investigations. Also an assay was used to determine the levels of vascular endothelial growth factor-A (VEGF-A) in the aqueous humor. Clinically there was no evidence of Norrie disease. Histopathologic examination of the globe revealed retinal dysplasia with pseudorosette formation, abnormal or absent retinal nuclear lamination, retinal infoldings and a paucity of disorganized retinal microvasculature, advanced gliosis, persistent hyperplastic vitreous, and vitreal and iris neovascularization. Karyotyping was normal. DNA sequencing revealed no known mutation in the region of Norrie gene in the sputum or retinal DNA. Immunohistochemistry disclosed GFAP-positive and GLUT-1 positive gliosis and C34-positive and GLUT-1 negative retinal and persistent hyperplastic vitreous microvessels. Aqueous

obtained immediately after the enucleation showed an exceptionally high concentration of VEGF-A.

Subfoveal Fluid in Healthy Full-term Newborns Observed by Handheld Spectral-Domain Optical Coherence Tomography Cabrera MT, Maldonado RS, Toth CA, et al Am J Ophthalmol January 2012; 153(1): 167-75. (s12)

This prospective observational study enrolled 39 full-term newborn infants who underwent dilated fundus examinations and retinal imaging by handheld spectral-domain optical coherence tomograph (SD-OCT) performed without sedation. The purpose of the paper was to report retinal findings for healthy newborn infants imaged with handheld spectral-domain optical coherence tomography (SD OCT). Of the 39 infants imaged, 44% (17/39) were male. Race and ethnicity composition was 56% white, 38% black, 3% Asian, and 3% Hispanic. Median gestational age was 39 weeks (range, 36 to 41 weeks). Six (15%) of the 39 infants had bilateral subfoveal fluid on SD OCT not seen by indirect ophthalmoscopy. Eight infants (21%) had retinal hemorrhages noted on dilated retinal examination, 1 of which had subretinal fluid on SD OCT. Subretinal fluid was noted on follow-up examination to have resolved on SD OCT 1 to 4 months later. Infants with bilateral subretinal fluid had an older gestational age compared with infants without subretinal fluid (median, 40.4 vs 39.1 weeks, respectively; $P = .03$) and were more likely to have had mothers with diabetes (2/6 vs 0/33, respectively; $P = .02$). Vaginal versus Caesarian section delivery was not significantly different between the 2 groups. The authors concluded that some healthy full-term infants have bilateral subfoveal fluid not obvious on dilated retinal examination. This fluid resolves within several months. The visual significance of this finding is unknown, but clinicians should be aware that it is common when evaluating newborn infants for retinal pathologic features using SD OCT.

This paper is one of the first to describe normal characteristics of the newborn retina using SD-OCT. Interestingly, the authors detected subfoveal fluid not detectable using indirect ophthalmoscopy – a finding not previously described. Although the authors were not able to explain the underlying pathophysiology, the knowledge that subfoveal fluid may be present in the normal newborn retina (and resolves over time) will be invaluable to clinicians as the use of handheld SD-OCT increases.

Cone dystrophy with supranormal rod response in children

Arif O Khan, May Alrashed, Fowzan S Alkuraya

Br J Ophthalmol March 2012;96:422- 426 (s12)

Aim To describe the initial clinical presentation of children with 'cone dystrophy with supranormal rod response,' a distinct retinal disorder from recessive KCNV2 mutations.

Methods Retrospective case series.

Results Nine children (seven families) initially examined from 2 to 8 years of age were identified. Three had a similar initial presentation of abnormal head position with head shaking and nystagmus, while the other six presented with either infantile nystagmus (without abnormal head position or head shaking), suspected congenital glaucoma (with associated nystagmus), intermittent exotropia, V-pattern esotropia, comitant esotropia or difficulty with near vision only (reading). Only two children had clinically

evident retinal changes (macular discoloration), and only two had a myopic cycloplegic refraction (the child with infantile nystagmus and the glaucoma suspect who actually had megalocornea). In addition to cone dystrophy, ERGs showed delayed scotopic responses with supranormal (six), high normal (two) or normal (one) scotopic b-wave responses to bright flash. Only one ERG (with a supranormal response) did not show a broad a-wave trough response to scotopic flash. For all patients,

KCNV2 sequencing revealed one of three homozygous recessive mutations (one previously reported (p.E143X), two novel (p.Y53X, p.E80D)). The three children who presented with an abnormal head position, head shaking and nystagmus and the child who presented with infantile nystagmus had several years' follow-up, during which these findings resolved (two) or decreased (two).

Conclusions Initial clinical presentation varied, the most common presentation being abnormal head position, head shaking and nystagmus that improved with time. ERG findings are characteristic and specific for KCNV2 mutations but do not necessarily include a scotopic b-wave flash response that is supranormal under standard ERG conditions.

Epidemiology, risk factors and management of paediatric diabetic retinopathy

Marla B Sultan, Carla Starita, Kui Huang
Br J Ophthalmol March 2012;96:312-317 (s12)

Diabetic retinopathy (DR), a common complication of both type 1 and type 2 diabetes, is rarely expressed at a level greater than background retinopathy during childhood and adolescence. Epidemiological studies in paediatric diabetic patients together with data from the Diabetes Control and Complications Trial have demonstrated the importance of glycaemic control in delaying or preventing the development of DR; thus, the incidence of DR has declined somewhat over the past two decades. Both prepubertal and postpubertal years with diabetes contribute to the overall probability of DR development. In addition to duration of disease and degree of glycaemic control, other risk factors for DR development include elevated blood pressure, lipid profiles, serum levels of advanced glycation endproducts, evidence for early stage atherosclerosis, increased calibre of retinal blood vessels and several genetic factors, such as enzymes involved in glucose and lipid metabolism. Annual screening is recommended, with mydriatic stereoscopic fundus photography being the most sensitive detection method. Both pathophysiology and treatment in paediatric populations are essentially the same as described for adult populations, with treatment usually not required until adulthood is reached.

This is a good review article.

Clinical Presentation of Familial Exudative Vitreoretinopathy

Tushar M. Ranshod, Lawrence Y Ho, Kimberly A. Drenser, Antonio Capone , Michael T. Trese, *Ophthalmology* 118:2070-2075 (October) (s12)

The authors report a retrospective review of a case series involving 273 eyes of 145 patients. The purpose of the study was to describe the clinical characteristics, staging and

presentation of patients with familial exudative vitreoretinopathy (FEVR) over a period of twenty five years.

The main outcome measures were demographics on presentation and clinical staging.

The average age of diagnosis was 6 years; males were 57% of the population; mean birth weight was 2.8 kilograms and mean gestational age was 37.8 weeks. A positive family history was present in 18% of patients.

The FEVR population includes a wide range of age at presentation, gestational age, and birth weight. A negative family history was present in the majority of patients. The majority of retinal folds extended radially in the temporal quadrants but can be seen in all quadrants. Fellow eyes demonstrated a wide variation in symmetry.

The presentation of FEVR may mimic the presentation of other pediatric and adult vitreoretinal disorders. Careful examination, including fluorescein angiography is often required in making the diagnosis of FEVR.

The study was performed by Associated Retinal Consultants, Royal Oak, Michigan

COMMENT; Comprehensive report on the clinical staging and demographics of FEVR; excellent staging pictures are found on pp 2072.

CLINICAL CHARACTERISTICS AND SURGICAL MANAGEMENT OF FAMILIAL EXUDATIVE VITREORETINOPATHY–ASSOCIATED RHEGMATOGENOUS RETINAL DETACHMENT

Chen, San-Ni ; Hwang, Jiunn-Feng ; Lin, Chun-Ju,Retina. February 2011; 32(2):220-225 (s12)

Familial exudative vitreoretinopathy (FEVR) is a congenital retinal vascular anomaly characterized by incomplete vascularization of the temporal retina, extensive anastomosis and branching of the temporal retinal vessels, macular heterotopia, falciform fold, temporal vascular exudation and retinal detachment. This is a retrospective review of FEVR associated with rhegmatogenous retinal detachment (RRD) and discusses the clinical characteristics, surgical management and outcome. Twenty four eyes in 22 patients were divided into three groups with absent (14 eyes), moderate (5 eyes), or severe (5 eyes) foveal dragging. Scleral buckling and/or vitrectomy were performed to reattach the retina. The male to female ratio was 18:4. The average age was 16.42 ± 5.48 years. The vast majority of patients were myopic with the severity of myopia increasing in the groups with macular dragging. In the subgroups with absent or moderate foveal dragging fewer operations were needed and surgical success was comparable to RRD without FEVR. In the subgroup with severe foveal dragging surgical success was worse than RRD without FEVR. Overall, final visual acuity improved in 23 out of 24 eyes and final retinal attachment was obtained in 95.8% of eyes.

EARLY NEURAL AND VASCULAR CHANGES IN THE ADOLESCENT TYPE 1 AND TYPE 2 DIABETIC RETINA

Bronson-Castain, Kevin W ; Bearnse, Marcus A Jr ; Neuville, Jessica ; Jonasdottir, Soffia ; King-Hooper, Barbara ; Barez, Shirin ; Schneck, Marilyn E ; Adams, Anthony J, Retina. January 2011; 32(1):92-102 (s12)

Current clinical techniques for diagnosing and monitoring diabetic eye disease focus largely on the presence of visible vascular-related lesions or changes in visual acuity. Recent diagnostic advances have shown that morphologic and physiologic changes in retinal structures can occur before visible lesions and loss of visual acuity. Multifocal electroretinogram (mfERG) response delays occur before visible vascular lesions. These local delays have been shown to be indicative of future vascular lesions in the corresponding region. Other studies have shown that retinal thickness can be affected in the absence of retinal vascular lesions. Digital imaging and analysis of the retinal vasculature around the optic disk has been used to assess vascular changes and found to be associated with diabetes related complications throughout the body.

In this study 32 adolescents with Type 1 diabetes (mean duration 5.7 ± 3.6 years), 15 with Type 2 diabetes (mean duration 2.1 ± 1.3 years) and 26 age-matched controls were examined. MfERG responses were recorded. OCT was used to measure retinal thickness. Vascular diameter around the optic nerve was also assessed. 28% of Type 1 diabetics and 40% of Type 2 diabetics had significant MfERG implicit time delays compared with 8% of controls. Retinal thicknesses in both patient groups were significantly thinner than controls. The Type 2 group also showed significant retinal venular dilation. The present study illustrates that subtle but significant functional and structural changes occur very early in Type 1 diabetes. Adolescents with Type 2 diabetes appear to be more affected than those with Type 1 diabetes. Further longitudinal examination of the etiology and progression of these abnormalities is warranted.

PROPHYLACTIC ANTIBIOTIC USE AFTER INTRAVITREAL INJECTION: Effect on Endophthalmitis Rate

Bhatt, Shabari S ; Stepien, Kimberly E ; Joshi, Komal , Retina. November 2011; 32(10):2032-2036 (s12)

Endophthalmitis after intravitreal injection is a serious complication. There are limited data to support the use of postinjection antibiotics to prevent endophthalmitis. Current endophthalmitis rates after intravitreal injection in the literature are based on studies where patients routinely received postinjection antibiotics. This study is a retrospective chart review comparing a 12-month period where patients received postinjection topical antibiotics after intravitreal injection with anti-vascular endothelial growth factor (VEGF) and the next 12-month period where no postinjection topical antibiotics were used. Cases of suspected endophthalmitis after intravitreal injection during this period were identified and reviewed. The rate of clinically suspected endophthalmitis in patients receiving postinjection antibiotics (0.22%) was comparable to that in the group that did not receive postinjection antibiotics (0.20%). One culture-positive case was found overall. The rate of endophthalmitis after

intravitreal injections of anti-VEGF in a clinical practice setting with aseptic technique is similar with or without the use of postinjection antibiotics.

COMMOTIO RETINAE WITH SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Oh, Jaeryung ; Jung, Jae-Hoon ; Moon, Sang Woong ; Song, Su Jeong ; Yu, Hyeong Gon ; Cho, Hee Yoon. Retina. November 2011;32(10):2044-2049 (s12)

Commotio retinae is characterized by transient whitening at the level of the deep sensory retina. It was originally postulated that the opacity was caused by extracellular edema. However, histopathologic studies have suggested that disruption of the photoreceptor outer segment may cause the opacity, and a lack of real edema was noted in many cases. The purpose of this study was to characterize retinal changes in areas of commotio retinae using spectral-domain optical coherence tomography (SD-OCT). This is a retrospective observational case series. Fourteen eyes of 14 patients who had experienced blunt ocular trauma underwent SD-OCT and fundus photography. The retinal thickness and volume of eyes with commotio retinae were compared with fellow eyes. Fundus images obtained by spectral-domain OCT were compared with fundus photographs. Seven of the 14 eyes showed commotion retinae involving the macula. Macular thickness and volume were not increased in eyes with commotio retinae involving the macula. There was photoreceptor outer segment hyperreflectivity corresponding to the area of retinal opacity which recovered with the disappearance of retinal opacity over time.

Functional and Anatomic Consequences of Subretinal Dosing in the Cynomolgus Macaque. Nork TM, Murphy CJ, Kim CBY et al. Arch Ophthalmol 2012;130(1):65-75. (s12)

Objective: To characterize functional and anatomic sequelae of a bleb induced by subretinal injection.

Methods: Subretinal injections (100 microliters) of BSS were placed in the supretemporal macula of 1 eye in 3 cynomolgus macaques.

Results: Retinas were reattached by 2 days postinjection (by OCT). Multifocal ERG amplitudes were nearly recovered by 90 days. Spectral domain OCT inner segment-outer segment line had decreased reflectivity at 92 days. Transmission EM revealed disorganization of the outer segment rod but not cone discs.

Conclusion: Subretinal injection is a promising route for drug delivery to the eye. Three months post-subretinal injection, retinal function was nearly recovered, although reorganization of the outer segment rod disc remained disrupted. Understanding the functional and anatomic effects of subretinal injection is important for interpretation of the effects of compounds delivered to the subretinal space.

Comment: Subretinal gene therapy trials in animals and humans thus far have depended on injection of the vector in a bleb of fluid under the retina. This bleb flattens rapidly over a few

days. This study shows that while mfERG goes back to normal in 90 days in the bleb area, the outer segments of rods remain disorganized. Long term electrophysiologic and anatomic/histologic changes are important to document so the outcomes of gene therapy can be correctly interpreted.

Edaravone-Loaded Liposome Eyedrops Protect against Light-Induced Retinal Damage in Mice

Hiroki Shimazaki, Kohei Hironaka, Takuya Fujisawa, Kazuhiro Tsuruma, Yuichi Tozuka, Masamitsu Shimazawa, Invest Ophthalmol Vis Sci. 2011;52:7289–7297
DOI:10.1167/iovs.11-7983 (s12)

PURPOSE. To investigate the pharmacologic effects of eyedrops containing liposomes loaded with edaravone (3-methyl-1-phenyl-2-pyrazolin-5-1) against light-induced retinal damage in mice.

METHODS. Edaravone was incorporated into submicron-sized liposomes (ssLips) by the calcium acetate gradient method. Retinal damage in mice was induced in dark-adapted mice by exposure to white light at 8000 lux for 3 hours. Edaravone-loaded ssLips were dropped into the left eye just before and after light exposure and then three times daily for 5 days after light exposure. Retinal damage was evaluated by recording the scotopic electroretinogram (ERG) and measuring the thickness of the outer nuclear layer (ONL) and by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining. The scavenging capacity of reactive oxygen species (ROS) of edaravone-loaded ssLips was determined using a murine cone photoreceptor cell line (661W). The human corneal and conjunctival cell lines were exposed to edaravone-loaded ssLips to determine cytotoxicity.

RESULTS. Eyedrop administration of edaravone-loaded ssLips significantly prevented both the decrease in a- and b-wave amplitudes of flash ERG and the shrinkage of the ONL compared with the control group (treated with empty ssLips) after 5 days of light exposure. The edaravone-loaded ssLips prevented the increase in the numbers of TUNEL-positive cells after 48 hours of light exposure. This marked protection was not found in the group treated with free edaravone. Edaravone loaded ssLips showed a stronger inhibition of in vitro light induced ROS production and cell death than did free edaravone. The ssLips showed little cytotoxicity toward ocular cell lines.

CONCLUSIONS. Edaravone-loaded ssLips protected against light-induced retinal dysfunction by eyedrop administration. Liposomal eyedrops may become one of the therapeutic candidates for drug delivery to posterior eye segments.

Comment: Light has been found to be a co-factor in progression of retinal degeneration in many forms of retinitis pigmentosa. There are mice models of light induced retinal damage which can be used to test treatment of this disorder. In this study an eyedrop delivering a liposome carrying the drug edaravone showed efficacy in preventing light toxicity to the retina. This might be developed into a treatment that could slow progression of retinal degeneration in humans.

Asymmetry of familial exudative vitreoretinopathy.

Shukla SY , Kaliki S , Shields CL . J Pediatr Ophthalmol Strabismus. 2012 Feb 28;49 (s12)

A 2-month-old male infant presented with unilateral leukocoria suspected to be retinoblastoma. Fundus examination and fluorescein angiography confirmed the diagnosis of bilateral familial exudative vitreoretinopathy with markedly asymmetric presentation (Stage 3/Type 5 in the right eye and Stage 2/Type 3 in the left eye).

Comment: This study highlights the importance of knowing that FEVR can be very asymmetric, and can have many different presentations. It can be inherited as AR, AD or X-linked. There are at least 3 genes that are associated with FEVR, and commercial testing is available.

XIX ORBIT

Functional results of the surgical repair of a lacerated canaliculus in children.

Kwitny A, Baker J. JPOS 2011;48:117-119. (March-April) (f11)

Purpose: examines the functional success of surgical repair of lacerated canaliculi in a pediatric population.

Methods: retrospective review of 46 patients who had repair of a lacerated canaliculus. Success was defined as no tearing or discharge.

Results: 44 of 46 patients had repair with a Crawford tube. Of these, 39 presented for post-operative follow-up. Two patients had some tearing at the time of tube removal.

Conclusion: supports previous studies reporting a high rate of success in repair of canalicular laceration utilizing Crawford tubes. Excellent results were obtained regardless of whether the cut ends of the duct were sutured.

Comment: None of the patients whose tubes fell out at a mean of 39 days following surgical repair complained of symptoms after the tube was out. Suggests tubes may be removed earlier than 3-6 months as commonly practiced. It would be interesting to compare monocanicular stent placement with Crawford tubes with early removal in this clinical setting.

Microbiology and antibiotic management of orbital cellulitis. Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J.Pediatrics. 2011 Mar;127(3) (f11)

Orbital infections caused by methicillin-resistant Staphylococcus aureus (MRSA) may be increasing. The authors reviewed the microbiology and antibiotic management of children hospitalized with orbital cellulitis and abscesses.

This study was a retrospective chart review of all 94 patients admitted to a tertiary care children's hospital between 2004 and 2009 with orbital infections confirmed by a computed tomography scan. Patients with preceding surgery or trauma, anatomic eye abnormalities, malignancy, immunodeficiency, or preseptal infections were excluded. A true pathogen was recovered in 31% of patients. The most commonly identified bacteria was the *Streptococcus anginosus* group (14 of 94 patients [15%]). *Staphylococcus Aureus* (1 patient with MRSA) was identified in 9% of patients. Combination antimicrobial agents were frequently used (62%), and Vancomycin use increased from 14% to 57% during the study period. Patients treated with a single antibiotic during hospitalization (n = 32), in contrast to combination therapy (n = 58), were more likely to be discharged on a single antibiotic (P < .001). Twenty-five (27%) patients were discharged on combination antibiotics. Thirteen (14%) patients were discharged on intravenous therapy. The authors conclude that the *Streptococcus anginosus* group is an emerging pathogen in pediatric orbital infections. Although MRSA was uncommon, patients frequently received Vancomycin and combination antibiotics. Because of the infrequency of MRSA, the authors recommend a simplified antibiotic regimen, which may also help limit the development of resistant organisms and facilitate transition to an oral agent.

Clinical Relevance of Thyroid-Stimulating Immunoglobulins in Graves' Ophthalmopathy

Katharina A Ponto, Michael Kanitz, Paul G Olivo , Suzanna Pitz, et al.

Ophthalmology, 2011 November: 118; 2279-2285 (November) (s12)

Cross sectional trial involving 108 untreated patients with Graves' ophthalmopathy (GO). The purpose of the study is to evaluate clinical relevance of thyroid stimulating immunoglobulins (TSI) as potential mediators for GO.

Thyroid-stimulating immunoglobulins, activity and severity of GO were the main outcome measures.

Thyroid stimulating immunoglobulins (TSI) show more significant association with clinical features of GO than Thyrotropin Receptor (TSHR) binding inhibitory immunoglobulins (TBII) and may be regarded as functional biomarkers for GO.

Commercially available assays are not yet available.

Study performed at the Department of Ophthalmology, University Medical Center, Mainz, Germany

COMMENT: Hopefully this research will result in inexpensive, commercially available biomarker serology to help us manage difficult thyroid eye disease.

XX PLASTICS

Treatment of Acute Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Using Amniotic Membrane: A Review of 10 Consecutive Cases

Darren G Gregory, Ophthalmology Volume 118, Number 5, May 2011 (f11)
Prospective case series of 10 consecutive patients treated by 1 surgeon

Study Objectives and Design

The purpose of the study was to describe the clinical course, treatment and outcome of 10 consecutive patients treated with amniotic membrane transplantation applied to the eyelid margins, palpebral conjunctiva and ocular surface during the acute phase of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Key Study Conclusions

Acute Stevens-Johnson syndrome and toxic epidermal necrolysis, amniotic membrane transplantation is an affective treatment for severe ocular surface and eyelid inflammation greatly decreasing the risk of significant ocular and visual sequelae.

Importance for Pediatric Ophthalmologists

This is the second use of amniotic membrane in the pediatric/strabismus population. Amniotic membrane obtained commercially from Amniograft, Bio-Tissue, Miami, Florida. It was sewn to the lid margins and palpebral conjunctiva as described by Kobayashi et al, and summarized by Gregory in 2008. Amniotic membrane is also used in restrictive strabismus caused by fat adherence syndrome, conjunctival scarring (secondary to inflammation such as Stevens-Johnson or toxic epidermal necrolysis). Review of the photographs shows very significant clinical and surgical results.

Pearls

The fundamental tenets of treatment of Stevens-Johnson disease are unchanged but for cases with severe denuding disease of the cornea and conjunctiva, surgical interventions with amniotic membrane transplantation may be helpful.

Incidence and Demographics of Childhood Ptosis

Gregory J Griepentrog, Nancy N. Diehl, Brian G. Mohny,
Ophthalmology Volume 118, Number 6, June 2011 (f11)

Type of Study

Retrospective, population-based cohort study evaluating potential cases of ptosis utilizing resources of the Rochester Epidemiology Project from Olmsted County, Minnesota.

Study Objectives and Design

The Purpose of this study was to report the incidence and demographics of childhood ptosis diagnosed over a 40 year period in a well defined population confined to Olmsted County, Minnesota.

A total of 107 children were diagnosed with ptosis during a 40 year period between January 1, 1965, and December 31, 2004. The total incidence of ptosis during this time was 7.9 per 100,000 in patients younger than 19 years of age. Ninety-six of the 107 patients (89.7%) had congenital onset ptosis. Eighty-one of the 107 patients (75%) had simple congenital ptosis. The prevalence of the condition was 1 in 842 births. A family history of childhood ptosis was present in 12% of the queried patients with simple congenital ptosis. Four percent of the simple congenital ptosis was bilateral and 68% with unilateral ptosis involved the left upper lid.

Key Study Conclusions

Childhood ptosis was diagnosed in 7.9 per 100,000 patients younger than 19 years of age. Simple congenital ptosis was the most prevalent form occurring in 1 out of 842 live births. Sixty-eight percent of the cases of unilateral ptosis involved the left upper lid.

Left eye predominance in unilateral simple congenital ptosis has not been previously reported. Distribution of childhood ptosis (males, n = 54 [56%]; females, n = 42 [44%]) of simple congenital ptosis (males 57% and females 43%). Family history of childhood ptosis was noted in 11.7% patients with simple congenital ptosis.

In this study unilateral ptosis was defined as either a measured palpebral fissure asymmetry of 1mm or more between the 2 upper eyelids or marginal reflex distance of less than 2.5mm. Bilateral ptosis was defined as a marginal reflex distance of less than 2.5mm in both eyes. Patients were considered to have a “congenital form” of ptosis if they sought treatment from a physician within the first months of life or could produce photographs demonstrating ptosis during the first few months of life.

Importance for Pediatric Ophthalmology

This is the first major epidemiologic study for childhood ptosis performed in the United States. This study was compared to a 10 year review of 155 children in the United Kingdom performed by Barry-Brincat and Willshaw in 2009.

Pearls

Palpebral fissure asymmetry of 1mm or more between the 2 upper lids or a marginal reflex distance of less than 2.5mm defined unilateral ptosis. Bilateral ptosis is defined as a marginal reflex distance of less than 2.5mm in both eyes.

Cost-effectiveness of 2 Approaches to Managing Nasolacrimal Duct Obstruction in Infants: The Importance of the Spontaneous Resolution Rate.

Kevin D. Frick, PhD; Luxme Hariharan, MD, MPH; Michael X. Repka, MD, MBA; Danielle Chandler, MSPH; B. Michele Melia, ScM; Roy W. Beck, MD, PhD; for the Pediatric Eye Disease Investigator Group (PEDIG). Arch Ophthalmol. May. 2011;129(5):603-609. (f11)

The purpose of this paper was to assess the impact of the rate of spontaneous resolution of congenital nasolacrimal duct obstruction on the relative cost-effectiveness of deferred nasolacrimal duct probing in a surgical facility (DFPS) compared with an immediate office-based probing surgery (IOPS). Data from the literature, Medicare 2009 fee schedule, and

consensus assumptions were combined to populate a model of outcomes of 2 treatment strategies: immediate office-based probing (IOPS) and deferred facility-based probing (DFPS) (deferred for 6 months). Sensitivity analyses were conducted, varying the 6-month spontaneous resolution rate from 50% to 90%. Additional factors varied during analyses included surgical cost and each procedure's probability of success. Outcomes measured were overall cost of treatment, chance of cure, and months of symptoms avoided by 18 months of life. The authors found that under the base case, assuming a 75% spontaneous resolution rate during 6 months prior to deferred probing, IOPS is more expensive (\$771 vs \$641) and slightly less effective (93.0% vs 97.5%) than DFPS, although IOPS costs only \$44 per month of symptoms avoided. At spontaneous resolution rates between 50% and 68%, IOPS costs less than DFPS (from \$2 to \$342 less), although it also is slightly less effective (from 2.0% to 3.8% less). At a 90% spontaneous resolution rate, IOPS costs \$169 per month of symptoms avoided. As the rate of spontaneous resolution falls, the cost per additional success for DFPS increases to \$16 709 at a 50% spontaneous resolution rate. The authors concluded that the relative cost-effectiveness of these strategies for treatment of nasolacrimal duct obstruction depends on the spontaneous resolution rate after diagnosis.

Oral Propranolol for Treatment of Periocular Infantile Hemangiomas.

Tara G. Missoi, MD; Gregg T. Lueder, MD; Kenneth Gilbertson, MD; Susan J. Bayliss, MD. Arch Ophthalmol. July 2011;129(7):899-903. (f11)

The purpose of this paper was to evaluate the efficacy and adverse effects of oral propranolol for treatment of periocular infantile hemangioma. In this study, participants were treated with oral propranolol 3 times daily, with outpatient monitoring of adverse effects. The starting dosage was 0.5 mg/kg/d for 1 week, then 1 mg/kg/d for the following week, then 2 mg/kg/d for the remaining duration of treatment. Serial examinations and external photography documented the size of the hemangiomas. Complete ophthalmic examinations included assessing for amblyopia with cycloplegic refraction and visual diagnostic testing. Amblyopia was treated with part-time occlusion therapy. Nineteen periocular hemangiomas from 17 children (71% girls) were studied. The median age at the start of treatment was 4.5 months (interquartile range, 2.2-5.6 months). The median treatment duration was 6.8 months (interquartile range, 4.1-7.2 months). Treatment with oral propranolol reduced the size of all hemangiomas. Median change in the surface area was 61% (interquartile range, 32%-64%) of the original size. Mild rebound growth that did not necessitate retreatment was found in 2 patients (12%). One patient (6%) experienced a benign episode of bradycardia. Seven patients (41%) had amblyopia. The authors concluded that oral propranolol for treatment of infantile hemangiomas was effective in all patients, with 33% reduction in astigmatism and 39% reduction in surface area. Vision equalized in all but 1 child, who receives ongoing amblyopia therapy. The authors suggest that early treatment with propranolol is remarkably effective in treating and preventing loss of visual acuity associated with periocular infantile hemangiomas.

The association of refractive error, strabismus, and amblyopia with congenital ptosis

Srinagesh V, Simon JW, Meyer DR, and Zobal-Ratner J, J AAPOS. 2011 Dec;15(6):541-4 (s12)

A chart-review disclosed 99 patients seen over a 5-year period with congenital ptosis. Seven patients were excluded. Follow-up ranged from 1 month to 16 years (mean 45 +/- 32 months). 87/92 patients had unilateral or asymmetric ptosis. Amblyopia was identified in 22 patients. 20 of the 22 cases of amblyopia occurred in the eye with the more severe ptosis. The amblyopic group had a greater mean upper eyelid asymmetry. 9 of the 87 patients had documented strabismus. 17 of 87 children had anisometropia with 16 of the 17 developing amblyopia. Of these 16, amblyopia occurred in the eye with the more severe ptosis in 15 cases. Over time, the more ptotic eyes of amblyopic patients demonstrated an increase in mean cylinder power. The results of this studies must be viewed in the context of its retrospective nature from a single-site. However, the study strongly shows ptosis can cause amblyopia, almost always coexistent with anisometropia or strabismus in the more severely ptotic eye. Strong with-the-rule cylinder power is particularly problematic. These children need to be watched carefully.

Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol.

Snir M, Reich U, Siegel R, Zvulunov A, Friling R, et al *Eye (Lond)*. December 2011;25(12):1627-34. (S12)

Children diagnosed with infantile capillary hemangioma from 2008-2010 at a tertiary pediatric medical center were studied while on oral propranolol treatment of 2 mg/kg/day. The main outcome measures were changes in lesion size and refraction before and after treatment.

A total of 30 patients (8 male; mean age at diagnosis, 1.6±2.8 months) participated. The hemangiomas were primarily periorbital (83%) rather than orbital. Propranolol was started at mean age 5.0±4.5 months, 3.3±4.3 months from disease onset. The patients were followed on propranolol for 7.3±3.5 months. Side effects occurred in 11 patients and warranted a dose reduction (to 1 mg/kg per day) in 3 and treatment termination in 1

Of the 30 treated patients, 24 had digital photographs of sufficient quality for lesion size calculation, and 21 had cycloplegic refractions. Findings were significant for post-treatment reduction in involved extraocular area (12.7±21.7cm² before therapy and 6.0±9.5cm² after therapy, P<0.0001) and for post-treatment reduction in mean cylindrical power in involved eyes (1.0±1.1 to 0.6±0.7, P=0.02).

The use of propranolol in the management of periocular capillary haemangioma--a systematic review.

Spiteri Cornish K, Reddy AR. *Eye (Lond)*. October 2011; 25(10):1277-83. (s12)

Capillary hemangioma or infantile hemangioma is the most common congenital vascular tumor in the periocular region. Propranolol has recently been reported to be an effective and safe alternative to steroid treatment. A systematic review of literature was carried out by two independent reviewers.

A total of 100 cases of oral propranolol use in periorbital or orbital capillary hemangiomas have been documented in the literature. The commonest dose used was 2 mg/kg/day. Adverse events were documented in one-third of cases (including hypoglycemia, hypotension and wheezing); in most cases these were minor, as termination of propranolol was only required in 5 (5%) cases. Improvement or complete resolution of the lesions occurred in 96% of cases, but studies used different definitions for improvement. Hemangioma recurrence was noted in one-fifth of cases.

Propranolol has shown a lot of promise in the therapy of infantile hemangioma

Periocular Port Wine Stain: The Great Ormond Street Hospital Experience

Ayman Khair, Ken K Nischal, Marcela Espinosa, Bal Manoj,

Ophthalmology 2011 November;118; 2274-2278 (s12)

Retrospective, case-control study involving a large cohort of patients with Port Wine stain (PWS), designed to identify risk factors for the development of glaucoma.

216 patients with a mean age at presentation of 2.9 years and a mean follow-up of three years were studied.

Iris heterochromia is associated with the development of early glaucoma in patients with PWS. Patients who do not have lid involvement or episcleral hemangioma has a lower risk of developing glaucoma and can be watched less frequently.

The study was performed at the Great Ormond Street Hospital for Children, London, United Kingdom., but its effectiveness has not yet been studied in a randomized controlled trial.

XXI. GLAUCOMA

Home Tonometry for Management of Pediatric Glaucoma

Flemmons MS, Hsiao YC, Dzau J, Asrani S, Jones S, Freedman SF.

Am J Ophthalmol. 2011 Sep;152(3):470-478 (f11)

Purpose

To use iCare rebound tonometry in the home setting for documentation of diurnal intraocular pressure (IOP) fluctuations in children.

Design

Nonrandomized, prospective clinical study.

Methods

Pediatric ophthalmology clinic patients were recruited between October 2009 and February 2010 who were able to cooperate with IOP measurement by iCare rebound tonometry and whose caregiver was willing and able to obtain iCare measurements at home. The child's IOP

was measured first by iCare tonometry followed by a second method (Goldmann applanation [GAT]). The caregiver was instructed on the use of the iCare tonometer. The subject's IOP was measured by the caregiver at home at designated time periods for at least 2 consecutive days.

Results

Seventeen children (17 eyes) with known or suspected glaucoma and 11 normal children were included. Excellent reliability was obtained by caregivers in 70% of iCare measurements. Mean difference between iCare and GAT in clinic was 2.0 ± 4.0 mm Hg, $P = .08$. Daily IOP fluctuation occurred in both subjects with glaucoma and normal subjects. In children with known or suspected glaucoma, relative peak and trough IOPs occurred in the early morning (45%) and late evening (43.5%), respectively. Comparison of the peak IOP measured at home vs in the clinic was >6 mm Hg in 5 of 16 subjects (31%) and affected glaucoma management in several subjects.

Conclusions

In selected children with glaucoma, home tonometry by iCare rebound tonometry was reliable, easily performed by caregivers, and well tolerated, and offered IOP information valuable in clinical management.

Reviewer Comment

Home monitoring using the Icare could be particularly useful for children with severe glaucoma, particularly if they have significant diurnal fluctuations.

Infantile aphakic glaucoma: a proposed etiologic role of IL-4 and VEGF.

Michael I, Walton DS, Levenberg S. JPOS 2011;48:98-107. (March-April) (f11)

Purpose: to identify the factors secreted by lens epithelial cells (LEC) responsible for the altered trabecular meshwork (TM) cells and to compare their effect on monocultured TM cells with that of TM cells co-cultured with LECs.

Methods: factors were identified using cytokine antibody array membranes and their effect on TM cells was assessed by analyzing changes in morphology and gene expression.

Results: Transforming growth factor beta-2, interleukin-4 (IL-4), and vascular endothelial growth factor (VEGF) are presented as candidate cytokines responsible for the observed changes in LEC-TM co-cultures.

Conclusion: suggests a possible explanation for the development of infantile aphakic glaucoma following the removal of congenital cataract.

Comment: In addition to an extensive basic science analysis, this article offers a practical explanation of an increasingly recognized problem in pediatric ophthalmology, provides an excellent bibliography, and suggests a possible basis for new treatment modalities in preventing infantile aphakic glaucoma.

Central corneal thickness in children and adolescents with pediatric glaucoma and eye disorders at risk of developing glaucoma.

Lopez J, Freedman S, Muir K et al. JPOS 2011;48:108-116. (March-April) (f11)

Purpose: to investigate central corneal thickness (CCT) in children with glaucoma and at risk for glaucoma.

Methods: study included 271 children (139 with glaucoma, 66 at risk for glaucoma, and 66 normal children). CCT was measured by ultrasound pachymetry and intraocular pressure by applanation.

Results: CCT was significantly higher for 141 eyes with glaucoma and 76 eyes at risk for glaucoma than for 66 normal eyes. No significant difference was observed between at-risk and glaucoma eyes.

Conclusion: suggests caution in application of standard formulas for IOP-to-CCT correction when evaluating children with glaucoma.

Comment: this study, the largest series of CCT in pediatric glaucoma and related disorders, reports a very wide variation in CCT in pediatric patients (0.387 to 0.85mm) and suggests that another clinical tool is needed to assess true IOP in eyes with extremely abnormal corneal thickness.

Longitudinal study of optic cup progression in children.

Park H-J, Hampp C, Demer J. JPOS 2011;48:151-156. (May-June) (f11)

Purpose: to determine the normal rate of cup-to-disc ratio progression in children and the effect of prematurity and low birth weight on this rate.

Methods: 184 eyes in 92 patients were examined by serial ophthalmoscopy over a five year period by a single examiner. No patients had optic nerve disease or had undergone intraocular surgery.

Results: Progressive optic nerve cupping at a rate increase of .0075 was observed in term children with a rate double this amount (.016) noted in children born preterm. A similar, non-significant trend was observed when comparing low birth weight to normal children.

Conclusion: Prematurity and low birth weight are associated with an increased rate of cupping in children. Cup-to-disc progression is not a specific sign of glaucoma in children

Comment: . Measurements in this patient cohort were determined by indirect ophthalmoscopy (20D), which, although not quantitative, did demonstrate a measurable trend over the study period by a single observer. The mechanism of this observed phenomena remains unknown and is discussed further in this excellent review of the subject.

Measurement of intraocular pressure with pressure phosphene tonometry in children.

Fan D, Chiu T, Congdon N et al. JPOS 2011;48:167-173. (May-June) (f11)

Purpose: to compare the accuracy and acceptability of IOP measurement in children utilizing pressure phosphene tonometry, non-contact tonometry, and Goldmann tonometry.

Methods: 50 children (aged 5-14 years) were studied prospectively by three masked examiners. IOP was measured by pressure phosphene tonometry, non-contact tonometry, and Goldmann tonometry. Degree of discomfort was graded from 0 (no discomfort) to 5 (most discomfort).

Results: Mean difference between pressure phosphene tonometry and Goldmann tonometry was 2.9mm Hg and that between non-contact tonometry and Goldmann tonometry was 2.1 mm Hg. Mean discomfort rating for pressure phosphene tonometry was significantly less (0.6) than for either non-contact (2.0) or Goldmann (2.3) tonometry.

Conclusion: Pressure phosphene tonometry was less accurate than non-contact tonometry when compared with Goldmann tonometry. However, pressure phosphene tonometry was most acceptable to children by a significant margin.

Comment: Pressure phosphene tonometry requires subjective input by the patient to provide an accurate endpoint for IOP measurement. However, it is applied through the eyelid without topical anesthetic, is portable, requires no power, and in this study showed a high specificity of elevated IOP. Thus, it may represent an alternative method of IOP measurement in selected pediatric patient populations.

Icare rebound tonometry in children with known and suspected glaucoma.

Flemmons MS, Hsiao Y, Dzau J, et al. Apr. J AAPOS 2011;15:153-157 (f11)

The Icare rebound tonometer does not require topical anesthesia for use. This paper compared readings obtained with this instrument to Goldman applanation in children with known or suspected glaucoma. The intraocular pressure (IOP), of 71 eyes of 71 subjects was measured with the Icare tonometer. Subsequently, an examiner masked to those results measured the IOP with Goldman applanation. The IOP measurements differed by a statistically significant amount (19mm Hg vs 17mm Hg, respectively). This difference was present regardless of whether the IOP was low, normal, or elevated. In over 1/3 of children, the IOP difference was >3mm Hg. This study is not able to discern which method is the more accurate one. Also, this study did not assess reproducibility of Icare tonometry measurements. The fact that Icare readings were always taken prior to Goldman readings might affect obtained values. It is possible that the relationship between the IOP readings found in the two groups might be changed if the order was reversed or randomized.

Long-term outcome of primary congenital glaucoma. De Silva DJ, Khaw PT, and Brookes JL.

Apr. J AAPOS 2011;15:148-152 (f11)

The goal of this paper was to evaluate the long-term outcome, acuity and risk of progression in patients with primary congenital glaucoma (PCG). Sixteen patients with at least 22 years of follow-up were included. Probability of stability was 90.3% at 1 year, 70.8% at 10 years, and under 50% at 40 years. Glaucomatous progression can occur many years after stability, highlighting the need for continued follow-up. These patients were followed over decades. Because of advances in surgery, medications, and diagnostic testing, the data from this paper is unlikely to be applicable to a patient who is newly diagnosed with PCG.

Surgical outcomes with 360-degree suture trabeculotomy in poor-prognosis primary congenital glaucoma and glaucoma associated with congenital anomalies or cataract surgery. Beck AD, Lynn MJ, Crandall J, and Mobin-Uddin O. Feb. J AAPOS 2011;15:54-58.

This paper reports the results of 360-degree suture trabeculotomy in a group of children with poorer-prognosis infantile glaucoma. Thirty-three eyes of 33 patients were included for analysis. Surgical success rates were fairly good, but were lower than published rates of success in patients with primary congenital glaucoma presenting after birth and before 1 year of age. Cumulative success rates declined over time from 87% at 6 months, to 58% at 2 years. Study groups were small so statistical analysis in this study is problematic. The study was retrospective and patients were placed into small categories.

Comparison of Latanoprost and Timolol in Pediatric Glaucoma: A Phase 3, 12-week Randomized, Double –Masked Multicenter Study

Tomoko Maeda-Chubachi, Katherine Chi-Burris, Brad D Simons, Sharon F. Freedman, Peng T Khaw, et al. for the A6111137 Study Group

Ophthalmology 2011; 118: 2014-2021 (October) (s12)

Prospective, randomized, double masked, 12 week, multicenter study designed to compare the efficacy of latanoprost versus timolol in pediatric patients with glaucoma. 137 patients were enrolled in the study. They were stratified by age, diagnosis and intraocular pressure. Latanoprost was administered at 8pm and timolol was administered at 8am and 8pm over a three month period.

This was a non inferiority study which showed that latanoprost 0.005% was “not inferior” (that is, either more or similarly effective) to timolol (0.5% and 0.25%) and produces clinically relevant IOP reductions across pediatric patients with and without pediatric congenital glaucoma.

Both latanoprost and timolol had favorable safety profiles over the duration of this three month study.

Study was funded by Pfizer and performed at the Duke University Eye Center and other centers in Florida and London, United Kingdom.

COMMENT: One of the first randomized clinical trials comparing the efficacy of these two common anti-glaucoma medication in children with all types of pediatric glaucoma.

Latanoprost Systemic Exposure in Pediatric and Adult Patients with Glaucoma: A Phase 1, Open-Label Study

Susan Raber, Racel Courtney, Tomoko Maeda-Chubachi, Brad D. Simons, Sharon Freedman, Barbara Wirostko, for the A6111139 Study Group

Ophthalmology 2011; 118:2022-2027 (October) (s12)

Phase 1, open-label, multicenter study for pediatric patients of three age groups and adults greater than 18 years of age to evaluate the pharmacokinetics of latanoprost in children who received the same dose of latanoprost as the adult population.

latanoprost acid systemic exposure was greater in young children than adolescents and adults (lower body mass) however there were no associated toxicities or adverse effects reported.

This pilot study suggests that the adult dose of latanoprost is safe and efficacious in children.

Multicenter trial sponsored by Pfizer and performed at different sites in the United States of America

COMMENT: First trial to demonstrate safety of latanoprost in children.

Shrinkage of the Scleral Canal During Cupping Reversal in Children

Hidekei Mochizuki, Ashley G. Lesley, James D. Brandt,

Ophthalmology 2011; 118:2008-2013 (October) (s12)

A retrospective, single center, observational case series of 29 eyes in children who underwent incisional pediatric glaucoma surgery at the University of California, Davis.

RetCam photographs were used to analyze optic disc changes. Special software was used to analyze and manually outline the optic nerve and adjacent nerve fiber layer.

Cupping reversal in children reflects elasticity in the scleral ring that responds to pressure lowering surgery. On the other hand when the cupping reversal does not occur, the scleral ring continues to enlarge, indicating ongoing stress on the optic nerve. Adults have lower elasticity and therefore do not show as much cup reversal with effective pressure lowering surgery.

Study performed at the Department of Ophthalmology, University of California, Davis

COMMENT: Excellent photos showing cup reversal with virtually all types of pediatric glaucoma surgery

XXII. CONGENITAL INFECTION

Oral acyclovir suppression and neurodevelopment after neonatal herpes.

Kimberlin DW, Whitley RJ, Wan W, Powell DA, et al National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med.* October 2011;365(14):1284-92. (s12)

Poor neurodevelopmental outcomes and recurrences of cutaneous lesions are frequent among survivors of neonatal herpes simplex virus (HSV) disease. The authors studied two groups of infants: those with central nervous system involvement and those with skin, eye and mouth involvement due to HSV. After completing a regimen of 14 to 21 days of intravenous acyclovir, the infants were randomly assigned to immediate acyclovir suppression (300 mg per square meter of body-surface area per dose orally, three times daily for 6 months) or placebo. This was a double masked study involving multiple clinical centers.

A primary outcome measure was a neurodevelopmental assessment performed at the age of 12 months. This was completed by only 28 of the 45 infants with CNS involvement (62%), but infants assigned to acyclovir performed better than those assigned to placebo (P=0.046). A secondary outcome was having at least two sets of HSV skin lesion recurrences, at which time the patients exited the study and were allowed to take open label acyclovir. The infants treated with acyclovir fared better than those treated with placebo. Of 74 infants having either CNS involvement or SEM disease, those taking placebo had two skin recurrences of HSV 2.5 months earlier than those taking acyclovir (P=0.009). When the SEM group of 29 infants was analyzed separately, the trend was in the same direction (placebo group had two skin recurrences 1.7 months earlier than acyclovir group) but was not statistically significant (P = 0.24).

Acyclovir prophylaxis continued for six months after neonatal HSV CNS disease or SEM disease improves neurodevelopmental outcomes and decreases the likelihood of skin lesion recurrence. No information re: eye disease or recurrences was provided by the authors. We as pediatric ophthalmologists may see these patients in the neonatal intensive care unit or as outpatients, and we should consider treating survivors of neonatal HSV with oral acyclovir for 6 months.

XXIII. PEDIATRICS

Pediatric ophthalmology: The oldest ophthalmology subspecialty

Natarajan S.

Indian J Ophthalmol 2011;59:419-20 (Nov-Dec) (s12)

This is an introduction to this issue which focuses on pediatric ophthalmology. It summarizes the history of pediatric ophthalmology, beginning with Dr. Costenbader who limited his practice to pediatrics in 1943, at a time when there were no other sub-specialties in ophthalmology. The Strabismological Society of India was founded in 1982 and has meetings yearly. In India 320,000 children are blind (prevalence 0.8%) with the major causes being corneal scarring secondary to vitamin A deficiency, congenital cataract, Retinopathy of Prematurity (ROP), and congenital glaucoma. **Comment** ORBIS has launched the 'India Childhood Blindness Initiative' to overcome this crisis. They have planned to develop 50 Pediatric Ophthalmology Centers across the country by 2012, with ORBIS-trained staff in place to treat childhood blindness.

Anesthesia in children--limitations of the data on neurotoxicity

Glass NL, Malviya S.N Engl J Med. 2011 Apr 14;364(15):1466-7 (f11)

This is a correspondence for the above article. Although the authors shared the same concern over the possible developmental delays due to early anesthesia exposure, they cited two studies which did not support the causative effects of anesthesia on developmental delays. In the first study, twins who were exposed to discordant amounts of anesthesia did not show any differences in educational outcomes. In the second study 2500 children between the ages of 15 and 16 who had inguinal herniorrhaphy did not show any delays compared to age matched controls. The authors feel that based on the available data, it would be inappropriate to deny or delay necessary surgery for fear of unknown consequences. The authors urge prospective studies to help elucidate the possible causative effects of anesthesia on young children and to define biomarkers to identify individuals susceptible to potential adverse effects of anesthetics.

Defining safe use of anesthesia in children

Rappaport B, Mellon RD, Simone A, Woodcock J. N Engl J Med. 2011 Apr 14;364(15):1387-90 (f11)

Studies in rodents have found that exposure to anesthetic agents during sensitive periods of brain development results in widespread neuronal apoptosis and functional deficits later in development. No safe doses or safe durations of administration have been defined. Recent studies by the National Center for Toxicology Research of the FDA have demonstrated similar cell death in non-human primate infants. Retrospective studies of human children who underwent general anesthesia show varying results. 383 children who underwent inguinal herniorrhaphy during the first 3 years of life were twice as likely as controls to be given a diagnosis of a developmental or behavioral disorder. A different retrospective study examined the educational and medical records of children who were given a single, two, or more anesthetic agents. This study did not show increased delays with a single agent but did show a delay with two or more agents. The authors recommend that further studies are warranted.

.XXIV. INFANTILE DISEASES

XXV SYSTEMIC

Retinal Arteriolar Tortuosity is Associated With Retinopathy and Early Kidney Dysfunction in Type 1 Diabetes. Am J Sasongko MB, Wong TY, Donaghu KC, et al. *Ophthalmol* January 2012;153(1):176-83. (s12)

This cross-sectional study examined the association of retinal vessel tortuosity with diabetic retinopathy and early nephropathy in children with type 1 diabetes. A total of 1159 participants with type 1 diabetes aged 12 to 20 years, attending diabetes clinics in Children's Hospital at Westmead, Sydney, Australia between 1990 and 2002, were included. Retinal photography and clinical examinations were performed during the baseline visit to assess diabetic retinopathy and albumin excretion rate (AER). Retinal vessel tortuosity was measured from digitized retinal photographs using a semi-automated computer program by a single grader masked to participants' characteristics. Diabetic retinopathy was defined as ETDRS level ≥ 21 (mild nonproliferative retinopathy) and early kidney dysfunction was defined as AER ≥ 7.5 $\mu\text{g}/\text{min}$. Of 944 patients (81.4%), 85 (9.0%) had signs of retinopathy only, 250 (26.5%) had early kidney dysfunction only, and 85 (9.0%) had both retinopathy and early kidney dysfunction. In multivariate analysis, higher arteriolar tortuosity was associated with retinopathy (odds ratio [OR] 2.01, 95% confidence interval [CI] 1.23-3.29, the highest quartile vs the remaining 3 quartiles), early kidney dysfunction (OR 1.56, 95% CI 1.06-2.28, per standard deviation [SD] increase), or coexistence of both complications (OR 1.96, 95% CI 1.21-3.24, the highest quartile vs the remaining 3 quartiles).

The authors concluded that retinal arteriolar tortuosity was independently associated with retinopathy and early stage of nephropathy in type 1 diabetes. These findings may offer the potential of quantitative measurement of retinal vessel tortuosity for diabetic complication risk assessment.

This paper is important to clinicians who screen children with Type I diabetes. If retinal tortuosity is detected, endocrinologists and other treating physicians can be made aware and screening for early nephropathy performed.

Corneal biomechanical properties and intraocular pressure measurement in Marfan patients

Necip Kara, Ercument Bozkurt, Okkes Baz, Hasan Altinkaynak, *J Cataract Refract Surg*. February 2012; 38:309–314 (s12)

This is a study of the in vivo biomechanical properties of the cornea in 39 patients with Marfan syndrome and healthy controls. The authors used an instrument called an Ocular Response Analyze to study the biomechanical properties of the cornea: corneal hysteresis and corneal resistance factor, and to measure intraocular pressure. They found that corneal biomechanical parameters were not significantly different between the study group and the control group; however, they were significantly different between Marfan eyes with ectopia lentis and Marfan eyes without ectopia lentis. The authors present several plausible explanations for this observation, including the possibility that the same fibrillin defects leading to lens subluxation may cause abnormalities in the structural integrity of the cornea

(fibrillin is a major component of corneal stroma). Corneal biomechanical properties influence intraocular pressure measurement. The authors suggest that due to corneal biomechanical properties, intraocular pressure measurements Goldman tonometry may be artificially low in Marfan eyes with ectopia lentis.

Lack of Ocular Side Effects After 2 years of Topical Steroids for Allergic Rhinitis

Emin Ozkaya, Mustafa Ozkaya, Faith Mete, Journal of Pediatric Ophthalmology and Strabismus September 2011; 48: 311-317 (s12)

A safe and effective treatment for Allergic Rhinitis is intranasal corticosteroids (INS). It is considered a first line treatment for moderate to severe persistent allergic rhinitis. As the ocular side effects for systemic, topical and periocular are well known, there is a protocol in terms of checking for these effects. There has not been any documentation of ocular side effects associated with INS. The results of chronic, intermittent use of intranasal budesonide is presented. Questions as to dose and duration of use were addressed. A 2 year treatment of children with allergic rhinitis prescribed intermittent intranasal budesonide at an average daily dose of 100ug was not found to be associated with ocular side effects.