

What's New and Important in Pediatric Ophthalmology and Strabismus for 2011

**American Association for Pediatric Ophthalmology
Annual Meeting**

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**American Association for Pediatric Ophthalmology and
Strabismus – Professional Education Committee**

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I. AMBLYOPIA

Charlie Brown, amblyopia, and me: A (not so short) personal history of the past forty years of diagnosing and treatment amblyopia.

FRANCE TD: *Am Orthopt J* 2010; 60: 73-81.

This article is based on the John Pratt-Johnson Annual Lecture, presented at the annual meeting of the Canadian Orthoptic Society (TCOS), Toronto, Ontario, Canada 2009. The author reviews the history of amblyopia research and treatment, from 1950 to the present day, beginning with the publication of "Security is an Eye Patch", a pamphlet distributed by the U.S. Department of Health and Welfare featuring Charlie Brown and his sister, Sally, who was diagnosed with amblyopia. Reviewed are developments in preschool screening techniques, diagnostic tools such as Teller Acuity cards, sweep VEP, and neutral density filters, and treatment such as patching, atropine penalization, and optical penalization. The author concludes with a brief discussion of the future of amblyopia detection and treatment.

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Atropine treatment of amblyopia: is a swap in fixation necessary?

Leone J, Georgievski Z, Koklanis K. *JPOS* 2010;47:270-276. (September/October)

Purpose: To investigate the impact of fixation on vision outcomes in amblyopic children undergoing atropine treatment and to validate the "cyclo-swap test" (CST) in predicting atropine efficacy.

Methods: Fixation and CST was assessed in 16 children at 1/3 m, 6m and less than 1/3m.

Children were treated for 10 weeks and assessed at 5 week intervals with cessation of atropine 4 days prior. Children demonstrating no fixation swap were observed after one week of atropine cycloplegia.

Results: Eight children demonstrated a fixation swap (FS) at either 1/3 or 6m and eight demonstrated no fixation swap (NFS). Both groups demonstrated a mean visual improvement of between 2 and 3 lines. Six of 8 children in the NFS group demonstrated visual improvement, all of whom also demonstrated a fixation swap at some stage.

Conclusions: Vision improvement seen in patients using atropine is likely to be attributable to a fixation swap which occurs during the treatment phase. The CST has little predictive value in determining visual improvement when performed at 1/3 and 6m; however, when performed at less than 1/3 m it may provide valuable clinical information regarding atropine efficacy.

Comment: This study demonstrates that the cyclo-swap test when performed at less than 1/3 m may provide additional information regarding atropine efficacy. Previous studies noting visual improvement without a fixation swap at 1/3 or 6m may have not detected a fixation swap at less than 1/3m.

The effect of recent amblyopia research on current practice in the UK

D Newsham *Br J Ophthalmol* 2010 94: 1352-1357.

Background/aims Several studies have recently provided insights into how amblyopia may be most

effectively managed. Despite the new evidence, a US study reported that a recent randomized controlled trial had made little influence on clinical practice. The aims of this research are to assess current practice of amblyopia management in the UK and to determine the comparability with the evidence-based recommendations.

Methods A questionnaire was constructed to assess current amblyopia management practice, particularly in relation to areas investigated by recent research and emailed to every head orthoptist within the UK.

Results: There was a great deal of variability in the amount of occlusion that was prescribed for moderate and severe amblyopia. Sixty per cent of clinicians indicated that the maximum they would prescribe was in excess of the 6 h recommended by research. Atropine was rarely recommended as a first-line treatment, with occlusion generally being considered to be more effective. Despite recommendations regarding education as a means of reducing non-compliance, only 39% of clinicians always gave written information, although various other methods of enhancing compliance were used. A period of refractive adaptation was allowed by most clinicians but often far less than recommended.

Conclusion: The uptake of recent research evidence into clinical practice is sporadic and incomplete with one third of respondents indicating that following the studies, they had made no changes whatsoever to their practice. This is similar to other areas of medicine; the reasons are likely to be varied, and is an area that would benefit from greater attention.

Review: This is an interesting study showing the practice patterns of clinicians in UK with regards to publications in amblyopia. The good thing about this study is that many parameters of amblyopia treatment are studied.

Vision therapy and orthoptics.

SHAINBERG MJ: *Am Orthopt J* 2010; 60: 28-32.

This article was based on a presentation made as part of a symposium held at the Joint Meeting of the American Orthoptic Council, the American Association of Certified Orthoptists, and the American Academy of Ophthalmology in San Francisco, CA, October 2009. The author compares and contrasts orthoptic therapy and behavioral vision therapy (BVT) and discusses the limited quality evidence in support of each. Though often used interchangeably and intentionally or unintentionally equated in the literature, these two terms refer to two very different treatment methods, with different goals and utilized for two very different patient populations. Orthoptic therapy is used to restore single binocular vision and improve control over a latent or intermittent deviation. Patients in need of orthoptic therapy have strabismus, diplopia, and other disorders of binocular vision, particularly convergence insufficiency. Multicentered treatment trials have provided evidence that convergence therapy can improve the symptoms and signs of convergence insufficiency. In contrast, BVT is typically used either prophylactically to prevent refractive, binocular, or accommodative anomalies in children, or to treat non-ocular, non-visual conditions such as learning disability and juvenile delinquency. The author notes that BVT is not supported by randomized, controlled studies. Rather, the literature consists of case studies, and observational studies, or small studies fraught with various types of bias.

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Effect and sustainability of part-time occlusion therapy for patients with anisometric amblyopia aged >8 years D J Hwang, Y J Kim, J Y Lee

Br J Ophthalmol 2010 94: 1160-1164

Aims To study the effect and long-term sustainability of part-time occlusion therapy for anisometric

amblyopia after 8 years of age.

Methods: A total of 41 anisometropic amblyopes aged > -8 years were analysed. In six patients, best-corrected visual acuity (BCVA) of amblyopic eye improved more than two lines within 2 weeks of full-time spectacle wear. The remaining patients were assigned to perform part-time patching during out-of-school hours. Long-term results were assessed in patients who were observed over 1 year after the end of the treatment.

Results: Among 35 patients, four dropped out, refusing further treatment, and one changed to atropine penalisation. The part-time patching schedule was completed in 30 patients. 90% of patients (27/30) complied well. Mean BCVA in the amblyopic eye improved significantly ($p < 0.001$), and 96.7% of patients (29/30) achieved the final BCVA of 0.1 logMAR or better. In long-term results, 87% preserved the BCVA of 0.1 logMAR or better. None of four dropouts achieved the BCVA of 0.1 logMAR or better in long-term results even on the continuous spectacle wear.

Conclusions: The part-time occlusion treatment in school-aged amblyopes, which had been carried out after school hours, was successful and the effect was sustained in most cases.

Review: No new information and very small sample size from single referral center. This may not represent the general population, as most of the cases are referred.

Randomized Controlled Trial of Patching vs Acupuncture for Anisometropic Amblyopia in Children Aged 7 to 12 Years

Jianhao Zhao, MD; Dennis S. C. Lam, MD, FRCOphth; Li Jia Chen, PhD; Yunxiu Wang, BMed; Chongren Zheng, DEpid; Qiaoer Lin, DN; Srinivas K. Rao, FRCS; Dorothy S. P. Fan, FRCS; Mingzhi Zhang, MD; Ping Chung Leung, MD; Robert Ritch, MD, FRCOphth

Arch Ophthalmol. December 2010;128(12):1510-1517. doi:10.1001/archophthalmol.2010.306

This study compares the effectiveness of 2-hour daily patching with the effectiveness of acupuncture in treating anisometropic amblyopia in children aged 7 to 12 years who have worn optimal spectacles for at least 16 weeks. This was a single-center randomized controlled trial involving 88 eligible children. The children had an amblyopic eye with best spectacle-corrected visual acuity (BSCVA) of 0.3 to 0.8 logMAR at baseline and were randomly assigned to receive 2 hours of patching of the sound eye daily or 5 sessions of acupuncture weekly. All participants in the study received constant optical correction, plus 1 hour of near-vision activities daily, and were followed up at weeks 5, 10, 15, and 25. The main outcome measure was BSCVA in the amblyopic eye at 15 weeks. The mean BSCVA of the amblyopic eye at 15 weeks improved from baseline by 1.83 and 2.27 lines in the patching and acupuncture groups, respectively. After baseline adjustment, the mean difference of BSCVA between the 2 groups was 0.049 logMAR (95% confidence interval, 0.005-0.092; $P = .03$), meeting the definition of equivalence (difference within 1 line). The BSCVA had improved by 2 lines or more in 28 (66.7%) and 31 (75.6%) eyes in the patching and acupuncture groups, respectively. Amblyopia was resolved in 7 (16.7%) and 17 (41.5%) eyes in the patching and acupuncture groups, respectively. The authors conclude that acupuncture produced equivalent treatment effect for anisometropic amblyopia, compared with patching, and was statistically superior. They do note that further studies are warranted to investigate its value in the treatment of amblyopia but suggest that acupuncture could potentially become an alternative treatment to occlusion therapy for amblyopia.

Neonatal Dacryostenosis as a Risk Factor for Anisometropia

Joshua T. Piotrowski, BA; Nancy N. Diehl, BS; Brian G. Mohny, MD

Arch Ophthalmol. September 2010;128(9):1166-1169.

The purpose of this paper is to determine whether there is a relationship between congenital nasolacrimal duct obstruction (CNLDO) and subsequent refractive error disorders in children. This was a retrospective review of the medical records of children 5 years and younger diagnosed as having CNLDO between January 1, 2000, and December 31, 2007. Three hundred five consecutive children were diagnosed as having CNLDO at a median age of 12.3 months (range, 0.8 months to 4.8 years). Thirty children (9.8%) were diagnosed as having anisometropia with ($n = 16$) or without ($n = 14$) amblyopia at a median age of 19.2 months (range, 3.6 months to 7.4 years). Twenty-six of the 30 patients had hyperopic anisometropia; more severe hyperopia occurred in the eye with CNLDO in 23 patients (88.5%), 2 patients had more severe hyperopia in the fellow eye and 1 patient had bilateral CNLDO. The median initial ($P = .005$) and final ($P < .001$) refractive error was significantly more hyperopic in those with both CNLDO and anisometropia compared with those with CNLDO alone. The authors conclude that the development of anisometropia with or without amblyopia seems to be more frequent in children examined by an ophthalmologist for CNLDO compared with that reported for the general public. The laterality of more severe hyperopia and amblyopia is generally on the side of the previous dacryostenosis.

Pilot Study of Levodopa Dose as Treatment for Residual Amblyopia in Children Aged 8 Years to Younger than 18 Years

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Arch Ophthalmol. September 2010;128(9):1215-1217

Prior studies have evaluated levodopa as an adjunct to occlusion therapy in the treatment of amblyopia. Improvement in visual acuity after completion of a course of levodopa has been reported; however, regression has occurred in several studies after stopping the medication. Reported adverse effects of levodopa were mild. They have included nausea, headache, fatigue, mood changes, emesis, dizziness, dry mouth, decreased appetite, and nightmares. The authors conducted a prospective randomized in preparation for conducting a phase 3 randomized trial. They enrolled a small cohort to gain experience with the drug, define the treatment dose for a future trial, and develop study procedures. The results suggested that levodopa-carbidopa therapy for residual amblyopia in older children and teenagers is well tolerated and may improve visual acuity. There was a suggestion of partial regression of the improvement in visual acuity after treatment was discontinued. No serious adverse effects were noted. Headache and nausea were infrequent. Without a patching-only control group, no conclusions about the efficacy, safety, or frequency of adverse effects associated with this treatment were able to be made. The authors conclude that a placebo-controlled trial is necessary to determine whether levodopa can successfully augment occlusion therapy in the treatment of amblyopia.

Randomized Evaluation of Spectacles Plus Alternate-Day Occlusion to Treat Amblyopia

Agervi P., et al.

Ophthalmology 2010; 117:381-387 (February)

Purpose: To compare spectacles plus patching ≥ 8 hours daily 6 days a week with spectacles plus patching ≥ 8 hours on alternate days to treat amblyopia in children 4 to 5 years of age. Prospective, randomized clinical trial in Stockholm, Sweden of forty children with untreated amblyopia.

Methods: Refractive correction was provided, and the children were randomized.

Main Outcome Methods: Median change in VCVA of the amblyopic eye after 1 year.

Results: The median change in BCVA of the amblyopic eye did not differ significantly between the 2 groups. Binocular function improved in both groups with no significant differences between the groups at 1 year. The median spherical equivalent refractive error did not change significantly during the study period in the amblyopic eyes in either group; however, a significant increase was found in the fellow eyes in both groups.

Conclusions: The improvement in visual acuity is a combined effect of spectacle wear and occlusion therapy.

Reviewer's Comments: Does duration or schedule of patching matter at all??

A new interocular suppression technique for measuring sensory eye dominance.

YANG E, BLAKE R, MCDONALD JE *Invest Ophthalmol Vis Sci* 2010; 51: 588-593.

The authors devised a new test of sensory eye dominance based on binocular rivalry. The apparatus presents dissimilar images dichoptically, using liquid crystal shutter glasses. One eye perceives visual noise, while the fellow eye perceives an arrow in the middle of a gray field. The contrast over the eye presented with visual noise is gradually reduced as the contrast over the eye presented with the arrow is increased until the subject perceives the arrow and is able to identify the direction in which it is pointing. This test was given to 88 normal volunteers who also underwent visual acuity testing, and a sighting dominance measure (the hole-in-the-card test).

The new test was simple and quick to do, and showed good test-retest reliability. Results showed 62% of subjects with right eye dominance, which is consistent with other reports using different dominance tests. There was a poor correlation with dominance as measured with the rivalry technique and dominance using a sighting technique, and there was also no correlation with visual acuity. This is also consistent with earlier studies. Only 38% of subjects showed a strong sensory dominance. Strong sensory dominance was more likely in those with left eye dominance. Individuals with strong dominance are less likely to do well with monovision.

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The prevalence of anisometropia, amblyopia and strabismus in schoolchildren of Shiraz, Iran.

YEKTA AA, FOTOUHI A, HASHEMI H, DEGHANI C, OSTADIMOGHADDAM H, HERAVIAN J, DERAKHSHAN A, YEKTA R, REZVAN F, BEHNIA M, KHABAZKHOOB M: *Strabismus* 2010; 18: 104-110.

The aim of this study was to determine the prevalence of amblyopia, anisometropia, and strabismus in school children of Shiraz, Iran. A random cluster sampling was used in a cross-sectional study on school children in Shiraz. Cycloplegic refraction was performed on subjects in elementary and middle school, but high school students had an uncorrected refraction. Uncorrected and best corrected visual acuity were recorded and alignment assessed. The mean age of the 2,638 schoolchildren was 12.5 years \pm 3.00 years (range 7-17 years). Prevalence of anisometropia was 2.31% and prevalence of amblyopia was 2.29% (males 2.32% and females 2.26%). Anisometropic amblyopia accounted for 58.1% of the amblyopic subjects. Two percent of the school children had strabismus (1.3% had exodeviations and 0.59% had esodeviations). Strabismus was more prevalent in students aged 15 and older (3.04% had exodeviations and 1.79% had esodeviations). Population based studies have shown prevalence of amblyopia as 0.2%-5% and of strabismus as 0.01%-4%. Therefore, results of this study showed that the prevalence of anisometropia, amblyopia, and strabismus in Shiraz, Iran are within reported frequencies. The etiology of the amblyopia was usually refractive and exodeviations were the most common type of strabismus.

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A Randomized Trial Comparing Bangerter Filters and Patching for the Treatment of Moderate Amblyopia in Children.

Pediatric Eye Disease Investigator Group Writing Committee
Ophthalmology 2010; 117:998-1004 (May)

Design: Randomized, clinical trial of 186 children, 3 to <10 years old, with moderate amblyopia (20/40-20/80).

Methods: Children were randomly assigned to receive either daily patching or use a Bangerter filter on spectacle lens in front of the fellow eye. Study visits were scheduled at 6, 12, 18, and 24 weeks.

Results: At 24 weeks, amblyopic eye improvement averaged 1.9 lines in the Bangerter group and 2.3 lines in the patching group. Similar percentages of subjects in each group improved ≥ 3 lines or had $\geq 20/25$ amblyopic eye acuity (36% vs. 31%, respectively). There was a lower treatment burden in the Bangerter group as measured with the Amblyopia Treatment Index. With Bangerter filters, neither a fixation switch to the amblyopic eye nor induced blurring in the fellow eye to worse than that of the amblyopic eye was required for visual acuity improvement.

Reviewer's Comments: Bangerter filter treatment is a reasonable option when initiating treatment.

Editorial: Amblyopia treatment: do we have enough evidence for a treatment plan? Stewart CE. Br Ir Orthopt J 2010; 7:1-2. (Jul)

This recent editorial begins by comparing the 'plethora of treatment trials' that have been conducted since a systematic review by Snowden et al in 1997 concluded that the 'evidence for amblyopia therapy falls far short of showing that treatment works.' This threatened the standard practice methods of most pediatric ophthalmologists and orthoptists and called for more evidence-based studies. One opinion is that children are being overtreated. Another opinion places much emphasis on the role of refractive errors in amblyopia therapy.

There is unconvincing and contradictory evidence to support the long-held clinical belief that amblyopia therapy is more successful at earlier stages of visual development. The author gives excellent references and discusses the information in each of the major amblyopia treatment trials that have been undertaken in the UK and US. There are other articles on this topic in the same journal and the author refers to them and gives the references.

This is a short but thought-provoking article and acts a springboard for several other articles in the same issue of this journal.

Review of amblyopia treatment: Are we overtreating children with amblyopia? Clarke MP. Br Ir Orthopt J 2010; 7: 3-7 (Jul)

This excellent article discusses the difficulty most clinicians have in deciding when to stop amblyopia treatment. Most children undergo far more than the published suggestions for duration of therapy. One study (reference given) states that beyond 150-250 hours of patching, little further improvement occurs. This author discusses the age at which patching should be discontinued and refers to other studies.

Clarke believes that the terms organic and functional amblyopia should be abandoned. He gives 7 other key points, in particular, how to avoid overtreating the amblyopia, and backs up these opinions with 39 references.

A comparison of the effect of 3M Fresnel prisms and Trusetal prism foils on visual function. Cotton HC, Griffiths HJ. Br Ir Orthopt J 2010; 7: 45-48.

I was unfamiliar with the Trusetal prism foils and would have liked a photograph comparing them with the more familiar 3M Fresnel prism. Most patients will note some decrease in visual acuity and contrast sensitivity through a Fresnel prism. Stimulated by the statement by the German manufacturer Trusetal that their prism foils have a 'superb optical quality' and a similar claim by the distributor in the UK for the 3M Fresnel prism ('the best in terms of performance, optical clarity, thickness and adherence to lenses') the authors decided to compare these commercially available press-on prisms. They performed a prospective well-designed study to compare these different devices to determine whether there were any significant differences in visual acuity and contrast sensitivity.

Sixteen university students were enrolled and the right eye was tested in random fashion with previously prepared plano lenses fitted with 0, 10, 20, and 30 diopter prisms. As expected, the visual acuity decreased and there was a gradual decline in contrast sensitivity also with increasing prism strength. This was true for both types of prisms. There were no statistical

differences between the two types of prism until 30 diopters when the Trusetal allowed 6.5 more letters to be read. The 30 diopter Fresnel prism was actually thinner.

The authors also compared the composition of the material in each prism, the number of bases and the relative flexibility and concluded that the 3M Fresnel prism was easier to use, but that the Trusetal should be considered for amounts exceeding 30 diopters.

The accuracy of binocular fixation preference for the diagnosis of strabismic amblyopia. Procianoy, L MD, PhD, and Procianoy, E MD, PhD. *J AAPOS* 2010; 14:205-210. (Jun)

Clinicians commonly use the binocular fixation preference test to diagnose amblyopia in the preverbal child. The accuracy of this test is unclear and reported results vary greatly in different studies. This study determined the accuracy of different scales for the binocular fixation preference test and the 10 prism diopter fixation test. 221 patients from 6 to 38 years old were examined with slightly less than half having amblyopia. The study found a strong correlation of each scale with the interocular visual acuity difference. There was no benefit found to combining the binocular fixation preference test and the 10 prism diopter fixation test, and there was no benefit of one of these tests over the other. Strong fixation preference showed strong evidence of amblyopia. Alternating fixation freely showed moderate evidence of symmetric acuity. Intermediate findings were less helpful. This test is probably best utilized when the data is combined with the overall clinical examination findings, rather than as a stand alone diagnostic test.

Johnny Wu, MBBS, MMedSc, FRANZCO; Fariba Nazemi, MD, FRCSC; Jennifer Schofield, CO; Giuseppe Mirabella, PhD; Agnes M. F. Wong, MD, PhD, FRCSC. Effectiveness of Telescopic Magnification in the Treatment of Amblyopia: A Pilot Study. *Arch Ophthalmol.* 2010; 128(3):297-302. doi:10.1001/archophthalmol.2009.400

The purpose is to compare the effectiveness of patching plus telescopic magnification vs. patching alone in treating refractory amblyopia. Children aged 4 to 17 years who failed previous amblyopia treatment were recruited into this prospective study. Subjects were randomly assigned to either 30 minutes per day of patching of the fellow eye only ($n = 7$) or 30 minutes per day of patching of the fellow eye plus concurrent use of a telescope in the amblyopic eye ($n = 8$). The treatment outcome was best-corrected logMAR visual acuity score of the amblyopic eye after 17 weeks of treatment. Both treatment groups demonstrated significant improvement in visual acuity in the amblyopic eye after 17 weeks ($P = .001$). Improvements in the patching-only group were slightly greater over the course of treatment, but this difference was not statistically significant ($P = .06$). At 17 weeks, mean visual acuity improvement from baseline was 0.14 logMAR (SD, 0.13 logMAR) in the patching-only group and 0.06 logMAR (SD, 0.17 logMAR) in the patching plus telescope group ($P = .11$). The 17-week visual acuity was at least 0.2 logMAR and/or improved from baseline by at least 0.2 logMAR in 2 patients in the patching-only group and none in the patching plus telescope group ($P = .08$). Treatment of refractory amblyopia in children using telescopic magnification did not appear to confer any additional benefits over patching alone.

Ophthalmic assessment of children with Down syndrome: is England doing its bit?

CREAVIN AL, BROWN RD: *Strabismus* 2010; 18: 142-145.

Guidelines exist for ophthalmic care for people with Down syndrome (Down's Syndrome Medical Interest Group UK), but in North Staffordshire, there is no formal program in place. The authors reviewed hospital records from 1996 to 2008 to identify children with Down syndrome. Retrospective data were extracted to determine which children had been seen by ophthalmic services, the mode of assessment used, and the frequency of ophthalmic disorders. Ninety-six children (age 0-16 years) with Down syndrome were identified and of these, 59 (62%) were referred to an ophthalmologist. Of these, notes were only obtained for 53. The children who received ophthalmic care had a mean age of 2.5 years at the first exam. Ninety-six percent had at least one ophthalmic abnormality, with hyperopia being the most common diagnosis (83%). Of these, glasses were prescribed for 38%. Sixty-five percent had strabismus, with the majority having an esodeviation (77%). Nineteen percent of children received no follow up. For those who did, the follow up visit interval was exceeded by a mean of 47 weeks later than requested. The authors concluded that a local screening program might have had a beneficial impact on the vision of children with Down syndrome.

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How Dutch orthoptists deal with noncompliance with occlusion therapy for amblyopia.

TJAM AM, ASJES-TYDEMAN WL, HOLTSLAG G, LOUDON SE, SINO O MM, SIMON SZ HJ:
Strabismus 2010; 18: 146-166.

In a previous study, the authors found that compliance with occlusion therapy for amblyopia is poor, especially among children of non-native (Netherlands) parents who spoke Dutch poorly and who had low socioeconomic status. In the current study, the authors investigated conception of, awareness of, attitude toward, and actions used to deal with noncompliance among Dutch orthoptists. Nine orthoptists working in non-native, low socioeconomic (SES) areas were studied and compared to 23 orthoptists working elsewhere in the Netherlands. Orthoptists were observed for one day in their practice, asked to complete a structured questionnaire, and participated in an interview. Also, a short survey was sent to all working orthoptists in the Netherlands (151 were returned).

Major differences were found between the non-native, low SES areas and the rest of the country. Opinions differed on what should be defined as noncompliance (patched less than 85% of the prescribed time vs. only if 0% patching) and what causes noncompliance. Almost all orthoptists (30/32) thought that the success of occlusion therapy lies both with the parents and the orthoptist.

In non-native, low SES areas, 22% of families spoke Dutch moderately to none. The allotted time for a patient's first visit was 21 minutes and time spent explaining amblyopia therapy to the parents was 2 minutes 30 seconds and 10 seconds to the child. In comparison, at the practices of the other 23 orthoptists, only 6% of families spoke Dutch moderately to none ($p < 0.0001$), the time for a patient's first visit was 27 minutes 24 seconds ($p = 0.47$) and explanation to parents took 2 minutes 51 seconds ($p = 0.59$) and 26 seconds ($p = 0.17$) to the child. Orthoptists estimated patients' compliance at 69.3% in the non-native, low SES areas. Actual compliance was measured electronically at 52%. Compliance was estimated at 74.1% by the other 23 orthoptists throughout the Netherlands. Actions to improve compliance varied, as some orthoptists increased occlusion hours whereas others decreased hours to avoid failure due to excessive demands on the family. In non-native, low SES areas, time spent on explanation was shorter, despite a lower fluency in Dutch among the patients. The authors suggested that more communication with the parent and child may increase compliance.

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II. VISION SCREENING

Predictors of Early Acceptance of Free Spectacles Provided to Junior High School Students in China

Lisa Keay, PhD, BOptom; Yangfa Zeng, MD; Beatriz Munoz, MD; Mingguang He, MD, PhD; David S. Friedman, MD, PhD

Arch Ophthalmol. October 2010; 128(10):1328-1334

This paper examines factors influencing adherence to spectacle wear and perceived value within a prospective 1-month trial of ready-made and custom spectacles in school-aged children with uncorrected refractive error in urban China. A total of 428 students aged 12 to 15 years with at least 1 diopter of uncorrected refractive error were given free spectacles and evaluated 1 month later at an unannounced visit. Demographic factors, vision, optical effects, and perceptions were modeled as predictors of observed use and perceived value using logistic regression adjusted for spectacle allocation. Of 415 students, 388 (93.5%) planned to use their spectacles, 227 (54.7%) valued their spectacles highly, 204 (49.2%) had their spectacles on hand, and 13 (3.0%) were lost to follow-up. Female students were 1.72 times (95% confidence interval [CI], 1.10-2.68), students from lower income households were 1.78 times (1.32-2.39), and those not concerned over appearance were 2.04 times (1.25-3.36) more likely to have spectacles on hand. Students with a pupil size of 4 mm or greater were 2.55 times (95% CI, 1.61-4.03) and students with

spectacle vision worse than 20/20 were 2.06 times (1.20-3.49) more likely to have spectacles on hand. Self-report of high perceived value was 2.23 times (95% CI, 1.30-3.80) more likely with 20/20 spectacle vision, 1.63 times (1.06-2.52) more likely with base-in prismatic effects of 0.5 prism diopters or more, 3.52 times (2.03-6.13) more likely when students would not tolerate blur to avoid wearing spectacles, and 2.16 times (1.24-3.76) more likely with disbelief that spectacles would make vision worse. Spectacle type had no effect. In conclusion, although most students planned to use their spectacles, only half were observed using them. Day-to-day use might increase if students were less concerned over appearance. Optical factors and beliefs surrounding spectacles are also predictive of acceptance. These findings provide further understanding of spectacle acceptance in teenagers.

Comparison of the Plusoptix SO4 binocular autorefractor with cycloplegic refraction performed by an ophthalmologist. Gilmartin LM. Br Ir Orthopt J 2010; 7: 59-61. (Jul)

The author designed a study to determine the accuracy of the autorefractor when compared to cycloplegic refraction. Fifty-two children under the age of 8 were tested. Results showed that the autorefractor agreed with an ophthalmologist's cycloplegic refraction in 88 percent of anisometric and astigmatic refractions. However, the spherical results were less reliable with only 67 percent agreeing.

The authors concluded that the autorefractor did not replace a formal cycloplegic evaluation performed by an ophthalmologist.

Performance of the plusoptiX S04 photoscreener for the detection of amblyopia risk factors in children aged 3 to 5. Matta, NS CO, CRC, Singman, EL MD, PhD, Silbert, DI MD, FAAP. J AAPOS 2010; 14:147-149. (Apr)

This photoscreener provides an instant image and autorefraction (noncycloplegic). The study looked at this device's ability to detect amblyopia risk factors, compared to cycloplegic examinations. A retrospective chart review of 3-5 year olds who underwent a cycloplegic refraction and photoscreening yielded 153 patients. The plusoptiX S04 photoscreener displayed a sensitivity of 99%, specificity of 82%, false-positive of 18%, false-negative of 1.2% and a positive predictive value of 86%. The ophthalmologist was not masked to the results of the photoscreening, and the positive predictive value is artificially high because of the greater prevalence of amblyopia in this cohort than in the general population. The machine was found to be easy to use, reliable and provide data quickly.

Longitudinal follow-up of hypermetropic children identified during preschool vision screening. Colburn, J.D. MD, Morrison, D.G. MD, Estes, R.L. MD, et al. J AAPOS 2010; 14:211-215. (Jun)

This paper evaluates moderate-to-high hypermetropes identified by preschool vision screening. One purpose of the study was to determine the natural history of the condition. Another purpose of the study was to evaluate whether the prevalence of strabismus and amblyopia is altered by prescribing spectacles. Children ages 1 to 6 years were screened. Over 200,000 children were screened. 149 children met inclusion criteria and follow-up information was available for 108 children. 19% of

children presented with amblyopia and of the remaining group 24% developed amblyopia during follow-up. 32% of children presented with strabismus and of the remaining group 33% developed strabismus during follow-up. Patients developed amblyopia at a lower rate if treated with spectacles versus observation alone during the course of the study but the difference was not statistically significant. Prescribing spectacles for hypermetropia did not reduce the % of patients who developed accommodative esotropia during follow-up versus observation alone. This study was not randomized and follow-up length was variable. Also patients with anisometropia were excluded.

Ophthalmic assessment of children with Down syndrome: is England doing its bit?

CREAVIN AL, BROWN RD: *Strabismus* 2010; 18: 142-145.

Guidelines exist for ophthalmic care for people with Down syndrome (Down's Syndrome Medical Interest Group UK), but in North Staffordshire, there is no formal program in place. The authors reviewed hospital records from 1996 to 2008 to identify children with Down syndrome. Retrospective data were extracted to determine which children had been seen by ophthalmic services, the mode of assessment used, and the frequency of ophthalmic disorders. Ninety-six children (age 0-16 years) with Down syndrome were identified and of these, 59 (62%) were referred to an ophthalmologist. Of these, notes were only obtained for 53. The children who received ophthalmic care had a mean age of 2.5 years at the first exam. Ninety-six percent had at least one ophthalmic abnormality, with hyperopia being the most common diagnosis (83%). Of these, glasses were prescribed for 38%. Sixty-five percent had strabismus, with the majority having an esodeviation (77%). Nineteen percent of children received no follow up. For those who did, the follow up visit interval was exceeded by a mean of 47 weeks later than requested. The authors concluded that a local screening program might have had a beneficial impact on the vision of children with Down syndrome.

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III. Refractive Error

Hypo-accommodation responses in hypermetropic infants and children. Anna M Horwood and Patricia M Riddell *Br J Ophthalmol* 2011 95: 231-237

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 underaccommodated 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.

Prevalence and causes of decreased visual acuity in Singaporean Chinese preschoolers M Dirani, B Zhou, D Hornbeak, et al 24, 2010 *Br J Ophthalmol* 2010 94: 1561-1565

Aims To describe the prevalence and causes of decreased visual acuity (VA) in Singaporean Chinese children.

Methods A population-based survey of Singaporean Chinese children aged 6 to 72 months was conducted. Participants underwent an orthoptic evaluation, cycloplegic refraction and biometric measurements. A sub-group of children aged 30 to 72 months with presenting logMAR VA were included in this analysis.

Retesting was performed on the same day or another day by predefined criteria with best refractive correction. Decreased VA was defined as worse than 20/50 (0.4

logMAR) for ages 30 to 47 months and worse than 20/40 (0.3 logMAR) for ages 48 to 72 months.

Results The study examined 3009 children (participation rate 72.3%) of which 2017 children aged 30 to 72 months were eligible for VA testing and completed in 1684 (83.5%). In children aged 30e47 months, the prevalence of decreased presenting VA was 2.1%, and in children 48e72 months, it was 2.05%, with no significant difference between boys and girls in both age groups ($p = 1/40.15$ and $p = 1/40.85$). Causes for decreased presenting VA in those 30e47 months were refractive error (7/11, 63.6%), amblyopia (1/11, 9.1%) and “no explanation” (3/11, 27.3%), and 17/24 (70.8%), 5/24 48e72 months. The types of refractive error were astigmatism (15/24, 62.5%), myopia (6/24, 25.0%), hyperopia (2/24, 8.3%) and hyperopia with astigmatism (1/24, 4.2%).

Conclusions: The prevalence of decreased VA among Singaporean Chinese preschoolers is low, with uncorrected refractive error being the main cause in both children 30e47 and 48e72 months.

Sampling and measurement methods for a study of childhood refractive error in a UK population. L O'Donoghue, K J Saunders, J F McClelland, et al. *Br J Ophthalmol* 2010 94: 1150-1154

Background: There is a paucity of data describing the prevalence of childhood refractive error in the United Kingdom. The Northern Ireland Childhood Errors of Refraction study, along with its sister study the Aston Eye Study, are the first population-based surveys of children using both random

cluster sampling and cycloplegic autorefraction to quantify levels of refractive error in the United Kingdom.

Methods: Children aged 6e7 years and 12e13 years were recruited from a stratified random sample of primary and post-primary schools, representative of the population of Northern Ireland as a whole. Measurements included assessment of visual acuity, oculomotor balance, ocular biometry and cycloplegic binocular open-field autorefraction. Questionnaires were used to identify putative risk factors for refractive error.

Results 399 (57%) of 6e7 years and 669 (60%) of 12e13 years participated. School participation rates did not vary statistically significantly with the size of the school, whether the school is urban or rural, or whether it is in a deprived/non-deprived area. The gender balance, ethnicity and type of schooling of participants are reflective of the Northern Ireland population.

Conclusions The study design, sample size and methodology will ensure accurate measures of the prevalence of refractive errors in the target population and will facilitate comparisons with other population based refractive data.

Refractive error and visual impairment in school children in Northern Ireland L O'Donoghue, J F McClelland, N S Logan, et al *Br J Ophthalmol* 2010 94: 1155-1159

Aims To describe the prevalence of refractive error (myopia and hyperopia) and visual impairment in a representative sample of white school children.

Methods: The Northern Ireland Childhood Errors of Refraction study, a population-based cross-sectional study, examined 661 white 12e13-year-old and 392 white 6e7-year-old children between 2006 and 2008.

Procedures included assessment of monocular logarithm of the minimum angle of resolution (logMAR), visual acuity (unaided and presenting) and binocular open-field cycloplegic (1% cyclopentolate) autorefraction. Myopia was defined as ≥ 0.50 DS or more myopic spherical equivalent refraction (SER) in either eye, hyperopia as $\geq +2.00$ DS SER in either eye if not previously classified as myopic. Visual impairment was defined as >0.30 logMAR units (equivalent to 6/12).

Results Levels of myopia were 2.8% (95% CI 1.3% to 4.3%) in younger and 17.7% (95% CI 13.2% to 22.2%) in older children: corresponding levels of hyperopia were 26% (95% CI 20% to 33%) and 14.7% (95% CI 9.9% to 19.4%). The prevalence of presenting visual impairment in the better eye was 3.6% in 12e13-year-old children compared with 1.5% in 6e7-year-old children. Almost one in four children fails to bring their spectacles to school.

Conclusions This study is the first to provide robust population-based data on the prevalence of refractive error and visual impairment in Northern Irish school children. Strategies to improve compliance with spectacle wear are required.

Review: This is good population based study pertaining to Northern Ireland, though may not representative of the whole of UK.

Paediatric retinal detachment: comparison of high myopia and extreme myopia.

Wang NK, Chen YP, Lai CC, et al.

Br J Ophthalmol 2009 May; 93(5):650-5.

Aims: To compare the clinical features and surgical outcomes of paediatric retinal detachment (RD) in high myopia and extreme myopia.

Methods: The clinical charts of 107 children who experienced RD and had a spherical equivalent (SE) of at least 6.00 dioptres (D) were reviewed. The patients were separated into a high myopia group (SE 6.0 to 10.0 D) and extreme myopia group (SE >10.0 D). RD characteristics and outcomes were compared between these two groups.

Results: There were significant differences between the two groups in total RD ($p=0.001$), the presence of posterior staphyloma ($p=0.001$) and some types of breaks. More eyes in the extreme myopia group required vitrectomy after the initial RD repair. In the high myopia group, retinal reattachment was achieved in 79 eyes (97.5%) at the end of the intervention, whereas in the extreme myopia group, retinal reattachment was achieved in 22 eyes (73.3%). Multiple logistic regression showed that a higher refractive error was the only negative predictor of surgical outcome ($p=0.026$).

Conclusions: Due to differences in aetiologies, clinical characteristics, required surgical procedure after initial repair, surgical and functional outcomes, paediatric RD with extreme myopia should be addressed differently from paediatric RD with high myopia.

Note: The strengths of this study include the large numbers of high and extreme myopic patients, and the long follow-up. The study's limitations include the fact that this is a nonrandomized retrospective review, and the patient population was based on referrals. They recommend a thorough retinal examination in extremely myopic children, especially in anisometropic and amblyopic children.

Height, stunting, and refractive error among rural Chinese schoolchildren: the See Well to Learn Well project.

[Sharma A](#), [Congdon N](#), [Gao Y](#), [Lu Y](#), [Ye Y](#), [Wu J](#), [Lam DS](#), [Li L](#), [Wu J](#), [Tse YK](#), [Zhang M](#), [Song Y](#), [Griffiths S](#).

[Am J Ophthalmol](#). 2010 Feb; 149(2):347-353.e1. Epub 2009 Oct 29.

PURPOSE: To evaluate the hypothesis that changes in nutritional status could be partly responsible for observed increases in myopia prevalence among Chinese children.

METHODS: Rural Chinese secondary school children participating in a study of interventions to promote spectacle use were randomly sampled (20% of children with uncorrected vision >6/12 bilaterally, and 100% of remaining children) and underwent cycloplegic refraction with subjective refinement and measurement of height and weight. Stunting was defined according to the World Health Organization standard population.

RESULTS: Among 3226 children in the sample, 2905 (90.0%) took part. Among 1477 children undergoing refraction, 1371 (92.8%) had height and weight measurements. These children had a mean age of 14.5 +/- 1.4 years, 59.8% were girls, and mean spherical equivalent refraction was -1.93 +/- 1.82 diopters. Stunting was present in 87 children (6.4%). While height was inversely associated with refractive error (RE) (taller children were more myopic) among boys ($r = -0.147$, $P = .001$), this disappeared when adjusting for age, and no such association was observed among girls. Neither girls nor boys with stunting differed significantly in refraction from children without stunting, and neither stunting nor height was associated with RE when adjusting for age, height, and parental education. The power of this study to have detected a 0.75 diopters difference in RE between children with and without stunting was 0.96.

CONCLUSION: Results from this cross-sectional study are not consistent with the hypothesis that nutritional status is a determinant of RE in this setting.

The development of myopia among children with intermittent exotropia.

[Ekdawi NS](#), [Nusz KJ](#), [Diehl NN](#), [Mohney BG](#).

[Am J Ophthalmol](#). 2010 Mar;149(3):503-7.

PURPOSE: To describe the long-term refractive error changes in children diagnosed with intermittent exotropia (IXT) in a defined population.

METHODS: Using the resources of the Rochester Epidemiology Project, the medical records of all children (<19 years) diagnosed with IXT as residents of Olmsted County, Minnesota, from January 1, 1975 through December 31, 1994 were retrospectively reviewed for any change in refractive error over time.

RESULTS: One hundred eighty-four children were diagnosed with IXT during the 20-year study period; 135 (73.4%) had 2 or more refractions separated by a mean of 10 years (range, 1-27 years). The Kaplan-Meier rate of developing myopia in this population was 7.4% by 5 years of age, 46.5% by 10 years, and 91.1% by 20 years. There were 106 patients with 2 or more refractions separated by at least 1 year through 21 years of age, of which 43 underwent surgery and 63 were observed. The annual overall progression was -0.26 diopters (SD +/- 0.24) without a statistically significant difference between the observed and surgical groups (P = .59).

CONCLUSION: In this population-based study of children with intermittent exotropia, myopia was calculated to occur in more than 90% of patients by 20 years of age. Observation versus surgical correction did not alter the refractive outcome.

Age-related changes in accommodative dynamics from preschool to adulthood.

ANDERSON HA, GLASSER A, MANNY RE, STUEBING KK: *Invest Ophthalmol Vis Sci* 2010; 51: 614-622.

The purpose of this study was to investigate the effect of age on dynamic accommodative measures. The latency and peak velocity of accommodation and disaccommodation, as well as microfluctuations in accommodative effort were studied using a dynamic infrared photorefractor in 41 normal volunteers, aged 3 to 38 years.

Accommodation and disaccommodation latencies were found to decrease linearly with increasing age. Mean latency was not significantly different for accommodation vs. disaccommodation.

Accommodative response amplitude was low compared to demand in all age groups, and the difference between stimulus and response increased with an increase in demand. Microfluctuations in accommodative response to a sustained accommodative stimulus were found in all subjects, with the youngest subjects having the greatest fluctuations. Peak velocity of accommodation also changed with age. Velocities were significantly slower in the older age groups. In contrast, there were no age-related differences in disaccommodation. There was, however, a significant linear relationship between peak velocity and amplitude for disaccommodation.

To summarize, the onset of the accommodative response and the accuracy of the response improves, while the velocity decreases over the first 40 years of life. However, in all age groups, the amount of accommodation exerted is less than the accommodative demand of the stimulus. The authors conclude that some aspects of accommodation and disaccommodation change with age, while others remain stable during the first four decades of life.

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Onset and progression of with-the-rule astigmatism in children with infantile nystagmus syndrome.

WANG J, WYATT LM, FELIUS J, STAGER DR Jr, STAGER DR Sr, BIRCH EE, BEDELL HE. *Invest Ophthalmol Vis Sci* 2010; 51: 594-601.

With-the-rule (WTR) astigmatism has been reported in children and adults with Infantile Nystagmus Syndrome (INS). The authors studied the onset and progression of astigmatism in a group of 95 infants and children with albinism, and 106 infants and children with idiopathic INS using both cross-sectional and longitudinal data. These data were compared to a group of age-matched normal children. Both the albinism and the idiopathic INS groups had significant WTR astigmatism that increased with age. The age of onset was significantly younger, and the severity of WTR astigmatism was significantly greater in the albinism group. In contrast, the mean amount of astigmatism in the normal group was significantly lower and tended to be against-the-rule (ATR). Children in the INS groups tended towards compound hyperopic astigmatism. While the children in the normal group showed evidence emmetropization, the patients in both INS groups remained hyperopic and tended to develop more astigmatism with time. The authors hypothesized that INS may interfere with emmetropization by smearing the vertically oriented images and by degrading visual acuity. Both of these effects will result in blurred retinal images, which interfere with emmetropization.

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Treatment of accommodative insufficiency with plus lens reading addition: Is +1.00D better than +2.00D?

WAHLBERG M, ABDI S, BRAUTASET R. *Strabismus* 2010; 18: 67-71.

This study evaluated whether a +2.00 D lens reading addition is as effective as +1.00D reading addition in the treatment of accommodative insufficiency (AI). Criteria for inclusion were history of blur and/or headache with near tasks, a phoria < 6 prism diopters (PD) at near and < 2PD at distance, and a near point of accommodation less than $100/[15D-(0.4 \text{ age})]$ on the RAF rule. Those taking medications with known effects on accommodation were excluded. Twenty-two subjects (mean age 11.8 years, $SD \pm 3.54$) with AI were included in this study. Treatment was randomized, with 11 subjects receiving +1.00D readers and 11 receiving +2.00D readers for 8 weeks. The Visual Analogue Scale (VAS) was used to evaluate the subjective degree of asthenopia before and after treatment. The VAS grades symptoms on a scale of 0 to 10, with 10 signifying the most severe symptoms. In spite of the randomization, the mean pre-treatment VAS score of the two groups were not statistically equal. The group prescribed the stronger lens had worse symptoms at presentation. The +1.00D group scored 5.4, compared to 7.4 for the +2.00D group.

There was a statistically significant improvement in accommodative amplitude in the +1.00D group after 8 weeks of treatment ($p < 0.05$). In the +2.00D group the improvement of accommodative amplitude was not significant. The mean post-treatment VAS score improved in both treatment groups, and was statistically equivalent at the conclusion of treatment (+1.00D = 3.21 units lower; +2.00D = 5.57 units lower). The authors concluded that, while both reading additions improved symptoms, +2.00D reading addition was not as effective in the treatment of AI because it did not exercise the accommodative system as effectively as +1.00D reading addition.

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Longitudinal changes in refractive error of children with infantile esotropia.

[Birch EE](#), [Stager DR Sr](#), [Wang J](#), [O'Connor A](#). *Eye*. 2010 Dec; 24(12):1814-21.

The aim of this study was to quantify changes in refractive status over time in children with infantile esotropia (ET) and to analyse a number of clinical factors associated with infantile ET to determine how they may affect emmetropization.

Longitudinal cycloplegic refraction data were collected for 5-12 years from 143 consecutive children enrolled in a prospective study of infantile ET by 6 months of age. 55% had low to moderate hypermetropic on the initial visit ($< +3.00$ D). Although the initial refractive error is similar to normative data, the rapid decrease in hypermetropic that characterizes normal development during the first 9 months of life is absent in children with infantile ET. After 9 months of age, children with infantile ET follow a developmental course which is similar to the normative course: there is little change in hypermetropic during years 1-7. This is followed by a decline of approximately -0.5 D/year beginning at age 8 years. The presence or absence of amblyopia did not have a statistically significant effect on the course of refractive changes with age.

Undercorrection of hyperopia in spectacles did not effect the rate or amount of emmetropization.

Dietary Factors, Myopia, and Axial Dimensions (AL) in Children

Lim LS., et. al.

Ophthalmology 2010; 117:993-997 (May)

Design: Cross-sectional study of 851 Chinese schoolchildren from the Singapore Cohort Study of Risk Factors for Myopia.

Results: The mean age was 12.81 years, (73.8%) children had myopia.

Conclusions: Higher saturated fat and cholesterol intake are associated with longer AL in otherwise healthy Singapore Chinese schoolchildren.

Review's Comments: Large, population – based sample but not statistically significant.

Breastfeeding and association with refractive error in young Singapore Chinese children.

[Sham WK](#), [Dirani M](#), [Chong YS](#), [Hornbeak DM](#), [Gazzard G](#), [Li J](#), [Saw SM](#). *Eye* 2010 May 24(5), 875-880.

Strabismus, amblyopia, and refractive errors in Singaporean preschoolers (STARS) is a cross-sectional population-based study of Chinese children aged 6-72 months conducted between June 2006 and September 2008 in Singapore. Parents were asked about the history of breastfeeding. All 2639 children (52% male, 48% female) included in this study had a cycloplegic refraction.

RESULTS: Out of those who were breastfed, 41% were breastfed for more than 3 months and 29% were breastfed longer than 6 months. The prevalence of myopia, defined as the spherical equivalent refraction of the right eye of at least -0.5 diopters (D), was 11% (95% CI). The mean spherical equivalent refraction of breastfed children was 0.12 D higher (less myopic) than that of children who were not breastfed ($p=0.03$). Children who were breastfed some, but less than 3 months, were 0.16 D less myopic than children who were never breastfed ($p=0.01$). Children that were breastfed more than 3 months were marginally less myopic, 0.06 D, than children who were never breastfed. This difference was not statistically significant.

CONCLUSIONS: The results show that breastfeeding is associated with more hyperopic spherical equivalent refraction in young Chinese children in Singapore.

Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children **Br J Ophthalmol 2010;94:1012-1016 (Aug)**

This paper investigated the risk factors for myopia, including near work and outdoor activity, in Singapore Chinese preschool children. This was a cross-sectional study, with disproportionate random sampling by 6-month age groups, of 3009 Singapore Chinese children aged 6–72 months. Information on family history, near work and outdoor activity was obtained. Spherical equivalent refraction was assessed. They found children with two myopic parents were more likely to be myopic (adjusted OR=1.91; 95% CI 1.38 to 2.63) and to have a more myopic spherical equivalent (regression coefficient=-0.35; 95% CI -0.47 to -0.22) than children without myopic parents. For each 1 cm taller height, the spherical equivalent was more myopic by 0.01 dioptres. Neither near work nor outdoor activity was associated with preschool myopia. The authors concluded that a family history of myopia was the strongest factor associated with preschool myopia. In contrast, neither near work nor outdoor activity was found to be associated with early myopia. These data suggest that genetic factors may play a more substantial role in the development of early-onset myopia than key environmental factors.

IV NEURO

The Evaluation of Horner Syndrome. Trobe J. J Neuro-ophthalmol 2010; (Mar) 30 :(1) 1-2.

This is a comprehensive editorial article containing a step-by-step approach to the differential diagnosis of Horner Syndrome. Editor Jon Trobe first summarizes the results reported in the article in the same issue by Almog et al. (See below.) Using this “real world” information, adding data from previous studies as well as his own expertise, he outlines each step along the way to the correct diagnosis. He includes practical tips on which pharmacological agents to use and when, and mentions those that are a “waste of time.” He describes the pathways of the oculosympathetic nerves, and describes how accidental or surgical trauma to the neck, upper spine or chest can explain the syndrome and must be ruled out. If none can explain the entity, then imaging should be pursued.

The editorial discusses the type of imaging to consider and what to order. These include a vascular study of the neck, CT and CT angiography (CTA) and MRI/MRA but points out the expense and possible delay in obtaining the latter. He also discusses the urgency of imaging and explains which signs and symptoms are urgent and which can wait. In children with clinical features of Horner syndrome under one twelve months of age, he recommends using topical cocaine in preference to apraclonidine. [20 refs]

Diagnostic value of imaging in Horner syndrome in adults. Almog Y, Gepstein R, Kesler A. J Neuro-ophthalmol 2010; (Mar) 30 :(1) 7-11.

This is an excellent retrospective chart review from Israel. The authors note that a comprehensive work-up of Horner syndrome often includes expensive imaging tests that are unrevealing and that the yield from imaging these cases has been explored only in children. They studied 52 adults with Horner syndrome to determine 1) to what extent the etiology could be determined during the initial examination, and 2) what information could be revealed by imaging testing when the etiology is unclear at the initial clinical visit.

Results of the study were divided into three groups. In 32 (62%) of patients in the first group, the etiology was already known from other factors, the most prevalent being surgical trauma. In 11 (21%) of patients in the second group, enough clinical information was present to justify a targeted imaging study and in 7 of the 11 patients the etiology was revealed. Most common were carotid dissection and cavernous sinus lesions. In the smallest third group of 9 (17%) patients, not enough clinical information was elicited to offer a targeted imaging evaluation and the etiology was determined by non-targeted imaging in only one patient in this group (thyroid malignancy.)

The results of this study show that the diagnosis is known in almost two-thirds of Horner syndrome patients at the initial visit. In the remaining one-third, enough information is available to allow a targeted imaging evaluation to define the etiology. In a very small group,

the neuro-ophthalmology examination did not provide enough information to guide targeted imaging studies. [Refs 12]

Non-organic (psychogenic) visual loss in children: A retrospective series. Toldo I, Pinello L, Suppiej A, Ermani M, Cermakova I, Zanin E, Sartoris S, Battistella PA. *J Neuro-ophthalmol* 2010; (Mar) 30:(1) 26-30.

Few published studies of non-organic (psychogenic) visual loss in children provide a systematic investigation of prognostic parameters. This retrospective study from Padua, Italy studied the clinical characteristics, outcome and prognostic indicators in 58 children under 16 with a diagnosis of non-organic visual loss. Girls were affected more than boys (2:1) and the mean age at onset was 9.6 years. All patients underwent full ophthalmologic, neurologic and orthoptic examination. Many patients had undergone electrophysiological testing as part of the initial evaluation. Some patients were referred for neuroimaging or psychiatric evaluation, if indicated.

Most of the patients presented with vision deficits such as reduced visual acuity (76%) or visual field defects (48%) with bilateral involvement in 71%. Associated symptoms included headache, abdominal pain and limb pain. There was a 3.1 month duration between onset and diagnosis and a 7.4 month period from onset to resolution of symptoms. They identified several psychosocial stressors that may have precipitated the onset of the condition.

The authors conclude that nonorganic visual loss in children generally resolves spontaneously within one year, consistent with the findings of other authors. They also conclude that no major psychiatric disorders were associated with the nonorganic visual loss, nor were any likely to develop after a child had an episode of the condition. [18 refs, all in English.]

Abducens ocular neuromyotonia in a patient with nasopharyngeal carcinoma following concurrent chemoradiotherapy. Kau H-C, Tsai C-C. *J Neuro-ophthalmol* 2010; (Sept) 30:(3) 266-267.

This short case report from Taiwan should be included in our overall review because it adds another instance of ocular neuromyotonia to the body of published cases of this uncommon entity. In this paper, or clinical observation, the muscle affected is the lateral rectus. The authors describe a 47-year-old woman treated six years previously for nasopharyngeal carcinoma by concurrent chemoradiotherapy. She presented with a 3-year history of intermittent diplopia. On examination she had a small 14 diopter left esotropia in primary gaze that increased on left gaze and decreased on right gaze, consistent with a mild partial left VI nerve palsy. She was seen again three months later and although the esotropia only measured 10 diopters in primary gaze, the incomitant pattern was unchanged. After sustained leftward gaze for more than a minute, she reported a pulling sensation in her left eye. When asked to look into primary gaze, she developed a large left esotropia exceeding 50 diopters, and on right gaze this was associated with globe retraction, narrowing of the palpebral fissure and a downshoot resembling Duane syndrome. The authors emphasize that diplopia in patients with nasopharyngeal should raise suspicion of tumor recurrence or

radiation-related cranial neuropathy, ONM must also be considered in the differential diagnosis. A video link is provided to view episodes of this unusual entity. [4 refs.]

Prevalence and risk factors for disrupted circadian rhythmicity in children

with optic nerve hypoplasia S A Rivkees, C Fink, M Nelson, et al. *Br J Ophthalmol* 2010 94: 1358-1362

Background/aims Children with optic nerve hypoplasia (ONH) have visual impairment and may have hypopituitarism and developmental delay. Children with ONH have also been reported to have abnormal sleepwake cycles. We assessed the incidence and nature of sleepwake abnormalities in children with ONH.

Methods Resteactivity patterns were assessed in 23 children with ONH using actigraphy, which is a noninvasive method for continuously monitoring activity. The children also had formal assessment of pituitary function, visual acuity measurements, assessment of papillary responsiveness; MRI scans of the head and assessment of neurocognitive function.

Results Sufficient actigraphy data were obtained on 19 of the children. Analysis of expressed rhythmicity revealed normal resteactivity patterns in 13 children (68%). Of the six children (32%) with abnormal rhythmicity, three had fragmented sleep, one had free running resteactivity cycles and two were arrhythmic. Of the children with normal rhythmicity, the following were found: hypoplastic corpus callosum in 30%, growth hormone deficiency in 53%, hypothyroidism in 23%, adrenal insufficiency in 30%, diabetes insipidus in 0% and developmental delay in 15%. Of the children with abnormal rhythmicity, the following were found: hypoplastic corpus callosum in 66% ($p > 0.05$), severe visual impairment in 100% ($p = 1/40.006$), abnormal papillary responsiveness in 85% ($p = 1/40.0084$), cognitive impairment in 100% ($p = 1/40.04$) and multiple hormonal deficiencies in 66% ($p = 1/40.03$).

Conclusions Abnormal resteactivity rhythmicity patterns are present in 30% of children with ONH. The best predictors of abnormal rhythmicity are severe vision impairment, abnormal pupillary responsiveness, developmental delay and multiple hormonal deficiencies.

Review: This article shows good evidence to show the sleep abnormality in a subset of Optic Nerve hypoplasia patients.

Eye movement recordings to investigate a supranuclear component in chronic progressive external ophthalmoplegia: a cross-sectional study

A E Ritchie, P G Griffiths, P F Chinnery, et al. *Br J Ophthalmol* 2010 94: 1165-1168

Background It has been postulated that eye movement disorders in chronic progressive external ophthalmoplegia (CPEO) have a neurological as well as a myopathic component to them.

Aim To investigate whether there is a supranuclear component to eye movement disorders in CPEO using eye movement recordings.

Methods Saccade and smooth pursuit (SP) characteristics together with vestibulo-ocular reflex (VOR) gain and VOR suppression (VORS) gain in 18 patients with CPEO and 34 normal patients were measured using Eyelink II video-oculography.

Results The asymptotic values of the peak velocity main sequence curves were reduced in the CPEO group compared to those of normal patients, with a mean of 1618/s (95% CI 1268/s to 1978/s) compared with 4538/s (95% CI 430 to 4758/s), respectively. Saccadic latency was longer in CPEO (263 ms; 95% CI 250 to 278), compared to controls (185 ms; 95% CI 181 to 189). Smooth pursuit and

VOR gains were impaired in CPEO, although this could be explained by non-supranuclear causes. VORS gain was identical in the two groups.

Conclusions This study does not support a supranuclear component to the ophthalmoplegia of CPEO, although the increased latencies observed may warrant further investigation.

Review: This study is interesting in the sense that it showing some new concept behind the CPEO. Inaccuracies associated with eye movements should be taken into consideration when interpreting the results.

Clinical electrophysiology and visual outcome in optic nerve hypoplasia Br J Ophthalmol 2010;94:1017-1023 (Aug)

This paper investigated the prognostic value of visual electrodiagnostic tests in infants and toddlers with ONH by comparison with visual outcome. They examined 85 patients with ONH by performing electroretinogram (ERG) and visual-evoked potential (VEP) testing to flash and to pattern-reversal checks and ocular fundus photography prior to 36 months of age. These initial measures were compared with visual acuity outcomes at 5 years of age in the better-seeing eye. The visual outcomes ranged from normal to no light perception. Electrodiagnostic tests with prognostic value were: the amplitude of the flash VEP (Spearman's rank correlations, $p < 0.001$), the threshold category of stimulus (flash or check size) that elicited a VEP ($p < 0.001$) and the amplitude of the N95 component of the pattern ERG (PERG) to 4-degree checks ($p < 0.02$). Optic nerve size and co-existing pallor were also significant correlates. Stepwise regression analysis composed a best prediction model from VEP threshold category, optic nerve size and optic disc pallor ($R^2 = 58\%$; $p < 0.001$). The authors concluded that optic disc diameter, observation of disc pallor, VEP and PERG testing in infancy are useful for establishing the visual prognosis at 5 years of age in children with ONH. This is consistent with the notion that these parameters are related to the anatomic and functional preservation of retinal ganglion cells.

The functional significance of stereopsis.

O'Connor AR, et al. Invest Ophthalmol Vis Sci 2010; 51:2019-23. (Apr 2010)

Purpose: Development or restoration of binocular vision is one of the key goals of strabismus management; however, the functional impact of stereoacuity has largely been neglected.

Methods: Subjects aged 10 to 30 years with normal, reduced, or nil stereoacuity performed three tasks: Purdue pegboard (measured how many pegs placed in 30 seconds), bead threading (with two sizes of bead, to increase the difficulty; measured time taken to thread a number of beads), and water pouring (measured both accuracy and time). All tests were undertaken both with and without occlusion of one eye.

Results: One hundred forty-three subjects were recruited, 32.9% ($n = 47$) with a manifest deviation. Performances on the pegboard and bead tasks were significantly worse in the nil stereoacuity group when compared with that of the normal stereoacuity group. On the large and small bead tasks, those with reduced stereoacuity were better than those with nil stereoacuity (when the Preschool Randot

Stereoacuity Test results were used to determine stereoacuity levels). Comparison of the short-term monocular conditions (those with normal stereoacuity but occluded) with nil stereoacuity showed that, on all measures, the performance was best in the nil stereoacuity group and was statistically significant for the large and small beads task, irrespective of which test result was used to define the stereoacuity levels.

Conclusions: Performance on motor skills tasks was related to stereoacuity, with subjects with normal stereoacuity performing best on all tests. This quantifiable degradation in performance on some motor skill tasks supports the need to implement management strategies to maximize development of high-grade stereoacuity.

Comment: This is an interesting paper that is worth a read by all strabismus surgeons, and perhaps by policy-makers. Many decisions regarding strabismus management are based on the assumption that stereopsis is beneficial, yet there is little literature in this area. Data in this study support the notion that stereopsis should be maintained at the highest level possible, with some stereoacuity resulting in better functional performance than little stereopsis. Data in this study also argue against the premise that patients without any stereopsis will adapt in the long-term without any detriment to motor skills.

Changes to control of adaptive gait in individuals with long-standing reduced stereoacuity.

Buckley JG, et al. Invest Ophthalmol Vis Sci 2010; 51:2487-95. (May 2010)

Purpose: Gait during obstacle negotiation is adapted in visually normal subjects whose vision is temporarily and unilaterally blurred or occluded. This study examines whether gait parameters in individuals with long-standing deficient stereopsis are similarly adapted.

Methods: Twelve visually normal subjects and 16 individuals with deficient stereopsis due to amblyopia and/or its associated conditions negotiated floor-based obstacles of different heights (7–22 cm). Trials were conducted during binocular viewing and monocular occlusion. Analyses focused on foot placement before the obstacle and toe clearance over it.

Results: Across all viewing conditions, there were significant group-by-obstacle height interactions for toe clearance ($P < 0.001$), walking velocity ($P = 0.003$), and penultimate step length ($P = 0.022$). Toe clearance decreased (~0.7cm) with increasing obstacle height in visually normal subjects, but it increased (~1.5 cm) with increasing obstacle height in the stereo-deficient group. Walking velocity and penultimate step length decreased with increasing obstacle height in both groups, but the reduction was more pronounced in stereo-deficient individuals. Post hoc analyses indicated group differences in toe clearance and penultimate step length when negotiating the highest obstacle ($P < 0.05$).

Conclusions: Occlusion of either eye caused significant and similar gait changes in both groups, suggesting that in stereo-deficient individuals, as in visually normal subjects, both eyes contribute usefully to the execution of adaptive gait. Under monocular and binocular viewing, obstacle-crossing performance in stereo-deficient individuals was more cautious when compared with that of visually normal subjects, but this difference became evident only when the subjects were negotiating higher obstacles; suggesting that such individuals may be at greater risk of tripping or falling during everyday locomotion.

Comment: This study examines the question of whether/how reduced or absent stereopsis affects day-to-day control of body movement. This is clearly an interesting question for strabismus surgeons, whose goal is to maximize ocular alignment and cooperation. Results from this study show that stereo-deficient subjects were more cautious during adaptive gait when compared to normal controls, although this became apparent only when subjects were negotiating higher obstacles. This implies that

there might be an association with tripping & falling during day-to-day walking. The authors point out that this association has also been found in previous studies involving the association between falls and decreased vision, cataract, or asymmetry in visual acuity between the eyes.

Stephen J. Smith, BS; Nancy Diehl, BS; Jacqueline A. Leavitt, MD; Brian G. Mohney, MD. Incidence of Pediatric Horner Syndrome and the Risk of Neuroblastoma: A Population-Based Study. *Arch Ophthalmol.* 2010;128(3):324-329. doi:10.1001/archophthalmol.2010.6

The purpose is to describe the incidence of pediatric Horner syndrome and the risk of occult malignancy in a population-based cohort. The medical records of all pediatric patients (aged <19 years) residing in Olmsted County, Minnesota, who received diagnoses of Horner syndrome from January 1, 1969, through December 31, 2008, were retrospectively reviewed. Horner syndrome was diagnosed in 20 pediatric patients during the 40-year period, yielding an age- and sex-adjusted incidence of 1.42 per 100 000 patients younger than 19 years of age (95% confidence interval [CI], 0.80-2.04). Eleven of the 20 patients (55%) had a congenital onset, for a birth prevalence of 1 in 6250 (95% CI, 3333-10 000), while the remaining 9 (45%) had acquired syndromes. Seven of the 11 (63.6%) patients with congenital cases had a history of birth trauma, while the remaining 4 (36.4%) had no identifiable cause. Six of the 9 (66%) acquired cases occurred following surgery or trauma, while the remaining 3 (33%) had no known etiology. None of the 20 patients (95% CI, 0.0%-16.8%) were found to have a neuroblastoma or other malignancy during a mean follow-up of 56.5 months (range, 0-256.9 months). The incidence of pediatric Horner syndrome in this population was 1.42 per 100 000 patients younger than 19 years, with a birth prevalence of 1 in 6250 for those with a congenital onset. Birth, surgical, or other trauma occurred in 13 (65%) of the patients, while none were found to have an underlying mass lesion, suggesting a need for reappraising current recommendations for extensive evaluations in these patients.

Who sees visual impairment following stroke?

ROWE FJ: *Strabismus* 2010; 18: 37-40.

A number of national guidelines for stroke are available in the United Kingdom, including the National Service Framework for Older Persons (NSF). In none of these guidelines was the role of the orthoptist mentioned, and vision assessment received very little mention. The purpose of this study was to determine the extent of orthoptic involvement in stroke services through the UK and to define what constitutes a vision assessment. A questionnaire was sent to 134 orthoptic departments in the UK asking for information on stroke services in their trust, including utilization of orthoptic evaluation and vision assessments. The return rate was 42% (56 questionnaires). Eighty-four percent of departments reported a designated stroke service in their trust and 62% were aware of adherence to the NSF guidelines on stroke services. Fifty-five percent confirmed that a vision assessment was provided by orthoptists, occupational therapists, physicians, or nurses. Orthoptic screening provided quantitative assessment of visual acuity, ocular motility, and visual fields. The remaining 15% of examinations

were basic qualitative assessments of vision only. The author recommends that each specialist stroke rehabilitation center should have easy access to orthoptic services as part of the stroke team.

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Ethnic differences in optic nerve head and retinal nerve fibre layer thickness parameters in children
Br J Ophthalmol 2010;94:871-876 (July)

This paper examined ethnic differences in optic nerve head and retinal nerve fibre layer (RNFL) parameters between European Caucasian and East Asian children aged 6–12 years. 4,118 children were examined in the Sydney Childhood Eye Study (incorporating the Sydney Myopia Study) from 34 randomly selected primary and 21 secondary schools during 2003–5. 3,382 (82.1%) had optical coherence tomography (OCT; Zeiss Stratus) data suitable for analysis. ‘Fast’ optic disc and RNFL scans were used. Ethnicity was defined only when both parents were of the same ethnicity. They found that East Asian children tended to have a lower birth weight, were shorter with a smaller body mass index and were less hyperopic than European Caucasian children of the same age. After adjusting for age, gender, axial length, birth weight and optic-disc area, East Asian children had similar mean vertical disc diameters to European Caucasians ($p=0.38$, $p=0.64$ for 6–12 years, respectively) but a 30–43% larger mean vertical cup diameters ($p<0.0001$ for both), resulting in larger mean cup/disc ratios ($p<0.0001$ for both). Compared with European Caucasians (101.95 μm and 104.57 μm , respectively), East Asian children had thicker mean average RNFL (105.45 μm and 107.92 μm , respectively; $p=0.0006$ and 0.0001) and thicker non-nasal RNFL quadrants in both ages. The authors concluded that compared with European Caucasian children, East Asian children generally had thicker RNFL and larger mean cup/disc ratios. Given the relatively lower prevalence of open angle glaucoma in Asians, these anatomical variations could contribute to better understanding of apparent racial differences in glaucoma susceptibility.

The management of strabismus in patients with chronic progressive external ophthalmoplegia.

TINLEY C, DAWSON E, LEE J: *Strabismus* 2010; 18: 41-47.

This retrospective study describes the clinical profiles and results of surgical and nonsurgical interventions of patients with strabismus associated with chronic progressive external ophthalmoplegia (CPEO). Twenty-eight patients were included in this study, 12 male and 16 female (mean age 43 years; range 3 to 78 years), of which 14 presented with a chief complaint of diplopia, and 11 with a chief complaint of noticeable strabismus. Three patients had symptoms unrelated to strabismus and were excluded. Eighty-eight percent had exotropia (mean 47 prism diopters), and 11 of these patients also had a vertical deviation. Management consisted of prisms (3 cases), occlusion (3 cases),

botulinum toxin (7), and surgery (8). The most effective procedure for exotropia was maximal bilateral lateral rectus recessions with medial rectus resections using adjustable sutures. Patients who had less than maximal horizontal muscle surgery were under-corrected and long term stability of measurements was rarely achieved. Patients who underwent botulinum toxin injection for large angle exotropia had little to no effect. Those with moderate angles had mixed results. The authors conclude that in some patients with CPEO and exotropia, maximal bilateral surgery significantly improves ocular alignment and may relieve symptoms of diplopia, but strabismus often recurs.

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V. ROP

Contrast sensitivity thresholds in children with autistic spectrum disorder. Milne E, Buckley D. *Br Ir Orthopt J* 2010; (June) 7: 62-65.

Very little is known about the basic visual system in children with autism spectrum disorder. There is current interest in atypical visual perception that seems to be a secondary symptom of ASD. The literature contains reports of atypical gaze, visual self-stimulation and enhanced perception of local detail. A few studies suggest evidence of oculomotor dysfunction such as hypometric saccades and reduced saccadic velocity, atypical OKN and a higher incidence of strabismus.

This article reports a study designed to evaluate whether contrast sensitivity is normal in ASD compared with normal (typically developing) children. There were four studies within the overall research project. Children with ASD use high-spatial frequency cues when matching pictures of faces compared to normal controls who use low-spatial frequency cues. Sixty children were included in the study; 30 with ASD and 30 TD controls. The results showed that the contrast sensitivity thresholds of ASD children do not differ from TD controls when tested at 3, 6, 12 and 18 cpd. The study concluded that at a gross level, the visual system of children with ASD is intact and that if an autistic child does exhibit reduced contrast sensitivity

when tested in the studied ranges that it may be indicative of a visual problem unrelated to autism. [Includes an interesting selection (34) of refs.]

ROP: A cautionary tale: What we know and what we think we know.

REYNOLDS JD: *Am Orthopt J* 2010; 60: 9-16.

This article was based on a presentation made as part of a symposium held at the Joint Meeting of the American Orthoptic Council, the American Association of Certified Orthoptists, and the American Academy of Ophthalmology in San Francisco, CA, October 2009. Retinopathy of Prematurity (ROP) is a unique condition in that it was the first in the field of pediatric ophthalmology to be extensively studied with multicenter, randomized trials. Four NEI-funded studies, CRYO-ROP, STOP-ROP, LIGHT-ROP, and ET-ROP, published from 1988 to 2000, represent our main source of reliable evidence-based medicine and have had an enormous impact on the classification, screening, and treatment of ROP. In this study, the author described what these studies have taught us with regards to classification, natural history, incidence, screening, treatment, and the role of oxygen. He also discusses what we still do not know, and what we think we know which may or may not be correct. He concludes that the reader of even these “gold standard” clinical trials must critically review each, and maintain a healthy level of skepticism when interpreting the results.

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Treatment for retinopathy of prematurity in infants born before 27 weeks of gestation in Sweden. Dordi Austeng, Karin B M Ka'llen, Uwe W Ewald, Agneta Wallin, Gerd E Holmstro'm *Br J Ophthalmol* 2010 94: 1136-1139 (Sep)

ABSTRACT

Aims To study various aspects of treatment for retinopathy of prematurity (ROP) in a Swedish population of extremely preterm infants born before 27 weeks of gestation.

Methods A national, prospective and population-based study was performed in Sweden from 1 April 2004 to 31 March 2007. The criteria for the treatment of ROP accorded with the recommendations of the Early Treatment for Retinopathy of Prematurity Cooperative Group.

Results Twenty per cent of the infants (99/506) were treated for ROP. The likelihood of reaching treatment criteria nearly doubled for each week of reduction in gestational age at birth. The first treatment was performed at an earlier postmenstrual age in the most immature infants. One third of the infants had more than one session of laser treatment.

Conclusions A high percentage of these extremely preterm infants required treatment for ROP. The likelihood of reaching treatment criteria increased with a decline in gestational age at birth. Although only a few infants progressed to ROP stages 4 and 5, the findings of this study indicate a potential for improvement in the treatment routines, both regarding the timing and number of laser spots at the first treatment.

Review:

The present study gives us new insight major aspects regarding the treatment of ROP in extremely preterm infants. First, the number of infants treated was high, 20%, in this strictly population-based study, with a high survival of extremely preterm infants born before 27 weeks of gestation.

Second, the present study shows that infants run a higher risk of reaching the criteria for treatment with a lower gestational risk of reaching the threshold with an increase in the gestational age at birth. The third major insight from our study concerns the timing of the first treatment of extremely preterm infants. In addition to the increased risk of reaching treatment criteria, we found that the most immature infants reached these criteria earlier than the more mature infants.

Predicting Proliferative Retinopathy in a Brazilian Population of Preterm Infants With the Screening Algorithm WINROP

Anna-Lena Hård, MD, PhD; Chatarina Löfqvist, PhD; Joao Borges Fortes Filho, MD, PhD; Renato Soibelman Procionoy, MD, PhD; Lois Smith, MD, PhD; Ann Hellström, MD, PhD

Arch Ophthalmol. November 2010;128(11):1432-1436.

The purpose of this study was to retrospectively validate the WINROP (weight, insulinlike growth factor I, neonatal, retinopathy of prematurity [ROP]) algorithm in a Brazilian population. WINROP aims to predict ROP and is based on longitudinal weight measurements from birth until postmenstrual age 36 weeks. WINROP has predicted 100% of severe ROP in 3 neonatal intensive care unit settings in the United States and Sweden. The study involved children admitted to the neonatal intensive care unit at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, from April 2002 to October 2008, weight measurements had been recorded once a week for children screened for ROP, 366 of whom had a gestational age of 32 weeks or less. The participating children had a median gestational age of 30 weeks (range, 24-32 weeks) at birth and their median birth weight was 1215 g (range, 505-2000 g). For 192 of 366 children (53%), no alarm or low-risk alarm after postmenstrual age 32 weeks occurred. Of these, 190 of 192 did not develop proliferative disease. Two boys with severe sepsis who were treated for ROP received low-risk alarms at postmenstrual age 33 and 34 weeks, respectively. The remaining 174 children (47%) received high- or low-risk alarms before or at 32 weeks. Of these infants, 21 (12%) developed proliferative ROP. The authors conclude that in this Brazilian population, WINROP, with limited information on specific gestational age and date of weight measurement, detected early 90.5% of infants who developed stage 3 ROP and correctly predicted the majority who did not. Adjustments to the algorithm for specific neonatal intensive care unit populations may improve the results for specific preterm populations.

Natural History of Retinopathy of Prematurity in Infants Born Before 27 Weeks' Gestation in Sweden

Dordi Austeng, MD, PhD; Karin B. M. Källen, PhD; Ann Hellström, MD, PhD; Kristina Tornqvist, MD, PhD; Gerd E. Holmström, MD, PhD

Arch Ophthalmol. October 2010;128(10):1289-1294. doi:10.1001/archophthalmol.2010.234

This paper investigate the natural history of retinopathy of prematurity (ROP) in 506 extremely preterm infants born before 27 weeks' gestation in Sweden during a 3-year period. A national population-based study was performed in Sweden from April 1, 2004, to March 31, 2007. According to the study protocol, initial eye examinations were to be performed at postnatal week 5, and examinations were repeated until the retina was completely vascularized or until criteria for treatment were met. The examinations were to be performed weekly, enabling study of the course and severity of ROP. In infants without ROP or with mild ROP without progression during the latest examinations, further examinations were performed weekly or every other week from

postmenstrual age 35 weeks. During the study, 368 infants (72.7%) developed ROP. Postmenstrual age at onset of ROP was significantly related to severity of ROP, even when controlling for gestational age (ie, the earlier the onset of ROP, the higher the risk of developing severe ROP). Site of onset of ROP was significantly related to gestational age at birth. The risk of nasal onset was almost doubled for every week of decrease in gestational age at birth. Nasal onset was associated with severe ROP, even after adjusting for gestational age at birth. This population-based study confirms results of the Cryotherapy for Retinopathy of Prematurity study and shows new correlations regarding time and site of onset of ROP, both of which are associated with disease severity.

Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. Law, J.C. MD, Recchia, F.M. MD, Morrison, D.G. MD, et al. J AAPOS 2010;14:6-10. Feb

Aggressive, posterior retinopathy of prematurity (AP-ROP) is associated with a worse prognosis and less favorable response to laser therapy. Bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, was used to treat 13 eyes of seven infants in whom conventional laser therapy was not possible (but was performed after the injection), or in whom disease progressed despite treatment with laser therapy. No systemic complications of treatment occurred. Many patients achieved rapid regression of anterior segment vascular activity and increased pupil dilation (allowing laser treatment to occur). Complete regression of ROP occurred in some cases, but some eyes did go on to develop retinal detachment. Caution is necessary because bevacizumab can cause rapid fibrosis and contraction of the posterior hyaloid, leading to a tractional or rhegmatogenous retinal detachment. A prospective, randomized clinical trial, may be necessary to determine the true change in outcomes with the adjunctive use of this medication.

Rebecca S. Braverman, MD; Robert W. Enzenauer, MD, MPH, MBA. Socioeconomics of Retinopathy of Prematurity In-Hospital Care. Arch Ophthalmol. 2010;128(8):1055-1058.

The purpose is to determine if there was any uniform experience across the United States relative to retinopathy of prematurity (ROP) services provided, reimbursement, and malpractice insurance coverage. This study consisted of an online pediatric ophthalmology listserv poll queried pediatric ophthalmologists regarding ROP screening, reimbursement, malpractice insurance, and call and consult coverage. The findings were that compensation for providing ROP services is quite variable around the United States. The Southern respondents reported the highest contract income while the Northeast reported the lowest. The mean annual contract income was \$63 753 and the median annual contract income was \$39 000. There was an even distribution between physicians vs hospitals providing malpractice coverage. There was also a fairly even distribution between physicians who do and do not provide consult and call coverage. In summary, nationwide, there is no standard rate of compensation for ROP in-hospital care, coverage of liability insurance, or providing additional consult or on-call services. Income generation performing ROP screening examinations is roughly half what a pediatric ophthalmologist can generate by seeing patients in the clinic or performing surgery.

The Early Treatment for Retinopathy of Prematurity Cooperative Group. Final Visual Acuity Results in the Early Treatment for Retinopathy of Prematurity Study. *Arch Ophthalmol.* 2010;128(6):663-671.

The purpose is to compare visual acuity at 6 years of age in eyes that received early treatment for high-risk prethreshold retinopathy of prematurity (ROP) with conventionally managed eyes. Infants with symmetrical, high-risk prethreshold ROP ($n = 317$) had one eye randomized to earlier treatment at high-risk prethreshold disease and the other eye managed conventionally, treated if ROP progressed to threshold severity. For asymmetric cases ($n = 84$), the high-risk prethreshold eye was randomized to either early treatment or conventional management. The main outcome measure was ETDRS visual acuity measured at 6 years of age by masked testers. Retinal structure was assessed as a secondary outcome. Analysis of all subjects with high-risk prethreshold ROP showed no statistically significant benefit for early treatment (24.6% vs 29.0% unfavorable outcome; $P = .15$). Analysis of 6-year visual acuity results according to the Type 1 and 2 clinical algorithm showed a benefit for Type 1 eyes (25.1% vs 32.8%; $P = .02$) treated early but not Type 2 eyes (23.6% vs 19.4%; $P = .37$). Early-treated eyes showed a significantly better structural outcome compared with conventionally managed eyes (8.9% vs 15.2% unfavorable outcome; $P < .001$), with no greater risk of ocular complications. Early treatment for Type 1 high-risk prethreshold eyes improved visual acuity outcomes at 6 years of age. Early treatment for Type 2 high-risk prethreshold eyes did not. Type 1 eyes, not Type 2 eyes, should be treated early. These results are particularly important considering that 52% of Type 2 high-risk prethreshold eyes underwent regression of ROP without requiring treatment.

Devon H. Ghodasra, BS; Karen A. Karp, BSN; Gui-Shuang Ying, PhD; Monte D. Mills, MD; Clare Wilson, MRCOphth; Alistair R. Fielder, FRCOphth; Jeffery Ng, PhD; Graham E. Quinn, MD, MSCE. Risk Stratification of Preplus Retinopathy of Prematurity by Semiautomated Analysis of Digital Images. *Arch Ophthalmol.* 2010;128(6):719-723.

The purpose of this paper is to determine whether quantitative analysis of retinal vessel width and tortuosity from digital images discriminates which eyes with preplus retinopathy of prematurity (ROP) progress to treatment severity. Posterior pole images of eyes at first clinical diagnosis of preplus ROP were obtained using a 30°-field, noncontact fundus camera. Width and tortuosity of retinal vessels were analyzed from digital images using computer-assisted image analysis software. Mean width and tortuosity of venules and arterioles were compared in 19 preplus eyes that regressed spontaneously and 11 preplus eyes that progressed to treatment severity. Receiver operating characteristic curve analysis was performed to assess whether width and tortuosity discriminated between groups. Mean widths of venules alone, arterioles alone, and the 3 widest vessels were higher in preplus progressed eyes ($P < .04$). Mean tortuosity of the 3 most tortuous vessels was higher in preplus progressed than in preplus regressed eyes ($P = .01$). Most vessel width and tortuosity variables predicted which eyes with preplus progressed to treatment moderately well, with an area under the receiver operating characteristic curve of 0.72 to 0.82. Digital image analysis of retinal vessel width and tortuosity may be useful in predicting which preplus ROP eyes will require treatment. Because vascular abnormalities are a continuum and clinical diagnosis is subjective, quantitative analysis may improve risk stratification for ROP.

Stephen P. Christiansen, MD; Velma Dobson, PhD; Graham E. Quinn, MD; William V. Good, MD; Betty Tung, MS; Robert J. Hardy, PhD; John D. Baker, MD; Robert O. Hoffman, MD; James D. Reynolds, MD; Paul J. Rychwalski, MD; Michael J. Shapiro, MD; for the Early Treatment for Retinopathy of Prematurity Cooperative Group. Progression of Type 2 to Type 1 Retinopathy of Prematurity in the Early Treatment for Retinopathy of Prematurity Study. *Arch Ophthalmol.* 2010;128(4):461-465.

The purpose of this manuscript is to examine the frequency and timing of progression from type 2 to type 1 retinopathy of prematurity (ROP) in the Early Treatment for Retinopathy of Prematurity Study. Infants with prethreshold ROP that was no worse than low risk in 1 or both eyes, based on the RM-ROP2 model, were examined every 2 to 4 days for at least 2 weeks. Using the Early Treatment for Retinopathy of Prematurity Study–defined classification of eyes as having type 1 or type 2 prethreshold ROP, we analyzed the time to conversion from type 2 to type 1. Data were analyzed for 1 randomly selected eye for each child. Of 294 eyes at first diagnosis of type 2 ROP, 65 (22.1%) progressed to type 1 (mean [SD] interval, 9.0 [6.6] days; median, 7.0 days). Of 217 eyes with type 2 ROP that had an examination in less than 7 days, 25 (11.5%) were diagnosed with type 1 ROP in less than 7 days. Of 200 eyes that continued to have type 2 disease at the first follow-up examination and underwent a subsequent examination, 24 (15.7% of the 153 eyes that had an examination in <7 days) developed type 1 ROP in less than 7 days. The risk of progression from type 2 to type 1 in less than 7 days was greatest between 33 and 36 weeks' postmenstrual age, regardless of zone of retinopathy. Type 1 ROP can be identified with weekly examinations in most eyes with initial diagnosis of type 2 ROP; a small subset progresses to type 1 in less than 7 days.

Telemedical diagnosis of retinopathy of prematurity: accuracy of expert versus non-expert graders

Br J Ophthalmol 2010;94:351-356 (Mar)

This paper reported the accuracy of telemedical retinopathy of prematurity (ROP) diagnosis by trained non-expert graders compared with expert graders. They used eye examinations (n=248) from 67 consecutive infants captured using the Ret Cam II. Non-expert graders attended two 1-h training sessions on image-based ROP diagnosis. Using a web-based telemedicine system, 14 non-expert and three expert graders provided a diagnosis for each eye: no ROP, mild ROP, type 2 pre-threshold ROP or treatment-requiring ROP. All diagnoses were compared with a reference standard of dilated indirect ophthalmoscopy by an experienced paediatric ophthalmologist. The results showed for detection of type 2 or worse ROP, the mean (range) sensitivities and specificities were 0.95 (0.94–0.97) and 0.93 (0.91–0.96) for experts, 0.87 (0.71–0.97) and 0.73 (0.39–0.95) for resident non-experts, and 0.73 (0.41–0.88) and 0.91 (0.84–0.96) for student non-experts, respectively. For detection of treatment-requiring ROP, the mean (range) sensitivities and specificities were 1.00 (1.00–1.00) and 0.93 (0.88–0.96) for experts, 0.88 (0.50–1.00) and 0.84 (0.71–0.98) for resident non-experts, and 0.82 (0.42–1.00) and 0.92 (0.83–0.97) for student non-experts, respectively. The authors concluded that the mean sensitivity and specificity of trained non-experts were lower than that of experts, although several non-experts had high accuracy.

Gonzalez, VH et al. Confluent Laser Photocoagulation for the Treatment of Retinopathy of Prematurity. JPOS March-April 2010; 47: 81-85.

100 eyes from 51 patients treated between 2003 and 2006 with confluent laser treatment anterior to the ridge were included. Mean gestation age was 28 weeks and mean birth weight was 1065 grams. Mean follow-up was 13 months. Progression to stage 4 or 5 occurred in only 6 eyes. Previous studies have suggested that confluent laser treatment is associated with an increased risk of anterior segment ischemia, cataract, and vitreous hemorrhage. Findings in this study did not show a significant increase in complications compared with previous studies that used laser burns 0.5 to 1.5 burn widths apart. The need for additional laser treatment and the rate of progression to stage 4 or 5 ROP were slightly lower than in prior reports.

Effects of elevated thyroid hormone on adult rabbit extraocular muscles.

HARRISON AR, LEE MS, MCLOON LK: *Invest Ophthalmol Vis Sci* 2010; 51: 183-191.

Elevated levels of thyroid hormone are known to have catabolic (destructive) effects on skeletal muscle by degrading muscle proteins, impairing their ability to generate force, and by affecting mitochondrial function within the muscle cell. The unique anatomy and physiology of extraocular muscle (EOM) make it particularly susceptible to damage from elevated thyroid hormone levels. The authors studied the effects of one month of elevated thyroid hormone levels on the EOM of adult rabbits.

Compared to those of euthyroid rabbits, EOM exposed to elevated thyroid hormone was thinner, with reduced cross-sectional area and number of myofibers. The normal ratio of fast and slow muscle fibers was altered, with a decrease in fast fibers, and an increase in slow fibers. There were no alterations in connective tissue, and no evidence of inflammatory cell infiltrate, fiber necrosis, or fibrosis. All rectus muscles were affected, both orbital and global layers from insertion to the midbelly region, though the changes were more pronounced in superior and lateral rectus muscles.

The authors conclude that hyperthyroidism leads to significant changes in EOM metabolism and function. They hypothesize that the increased myofiber loss plays a role in the inflammatory response that leads to the clinical picture of thyroid eye disease.

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VI. PREMATURITY

An analysis of neonatal risk factors associated with the development of ophthalmologic problems at infancy and early childhood: a study of premature infants born at or before 32 weeks of gestation.

Saldir M, Sarici S, Mutlu F, et al. *JPOS* 2010;47:331-337. (November/December)

Purpose: To determine the frequency of ophthalmologic problems occurring in premature infants with a gestational age of 32 weeks or less.

Methods: Premature infants examined at a neonatal intensive care unit between January 2002 and March 2006 were included. Control ophthalmologic exam performed at 10 months of age. Primary ocular morbidities were studied.

Results: 169 premature infants were included in the study and were examined at a mean age of 25.85 +/- 11.79 months (range 10-42 months). There was blindness in one (0.6%) case, strabismus in 15 (8.9%) cases, and refractive errors in 10 (5.9%) cases. Short gestational age, low birth weight, and the presence of ROP requiring retinal surgery during the neonatal period were determined to be significant risk factors for the development of vision loss, strabismus, and refractive errors.

Conclusions: Neonates with a gestational age of 32 weeks or less should not only be screened for ROP in the neonatal period but should also have regular follow-up exams to check for the development of other ophthalmologic problems during early childhood.

Comment: Premature infants with a gestational age of 32 weeks or less need regular ophthalmologic follow-up regardless of whether or not they develop ROP.

Interexpert Agreement in the Identification of Macular Location in Infants at Risk for Retinopathy of Prematurity

Michael F. Chiang, MD; Preeti J. Thyparampil, MD; Daniel Rabinowitz, PhD

Arch Ophthalmol. September 2010;128(9):1153-1159.

The objective of this paper was to characterize variability in the identification of the macular center among retinopathy of prematurity (ROP) experts. The authors looked at a printed set of 25 wide-angle retinal images which were compiled from infants at risk for ROP using a commercially available camera. Ten recognized ROP experts were asked to mark the macular center on each image. For each image, they measured the distance from the optic disc center to the marked macular center. Distances were standardized by normalizing the horizontal optic disc diameter in each image to 0.93 mm. In images with visible peripheral disease, interexpert agreement on the presence of zone I disease was also determined. For the image with the least variability among experts, mean (SD) distance from the optic disc to the macular center was 3.69 (0.21) mm (range, 3.13-3.81 mm). For the image with the greatest variability among experts, distance from the optic disc to the macular center was 4.32 (1.19) mm (range, 3.21-7.19 mm). In 7 of 21 images (33%) with visible peripheral disease, there would have been disagreement among experts in the diagnosis of zone I disease based on identification of the macular center. Among the 10 experts, in 17 of 25 images (68%), 1 expert identified the distance between the optic disc and macular center to be greater than 1 SD from the mean. Significant variability exists among experts in identification of the macular center from wide-angle images, which raises concerns about the reliability of zone I ROP diagnosis.

Ophthalmic artery blood flow in very-low-birth-weight preterm infants.

Soares CRS, et al. *Invest Ophthalmol Vis Sci* 2010; 51:708-11. (Feb 2010)

Purpose: To evaluate normal blood flow velocity and Doppler indices of the ophthalmic arteries from birth to hospital discharge of inborn infants at birth weights between 500 and 1500 g and gestational age \leq 32 weeks.

Methods: A longitudinal prospective study with Doppler ultrasound was conducted in both eyes at 24 hours, 7 and 28 days, and hospital discharge for systolic and diastolic velocities, pulsatility, and

resistance indices. Retinopathy of prematurity stage 2 and higher, peri-intraventricular hemorrhage grades 3 and 4, and death were excluded.

Results: The authors studied 46 very-low-birth-weight infants (92 eyes; birth weight, 1215 ± 202 g; gestational age, 30.4 ± 1.3 weeks). Both eyes had similar Doppler findings at each study interval. Systolic velocity increased significantly from birth to hospital discharge ($P = 0.001$; right eye, 17.85 ± 5.3 cm/s and 23.18 ± 4.88 cm/s; left eye, 17.78 ± 5.19 cm/s and 23.51 ± 5.63 cm/s), as did diastolic velocity ($P = 0.02$; right eye, 6.17 ± 1.13 cm/s and 6.76 ± 1.12 cm/s; left eye, 6.34 ± 1.26 cm/s and 6.9 ± 1.53 cm/s). Pulsatility and resistance indices did not change during the entire period.

Conclusions: There is a typical pattern of ophthalmic artery systolic and diastolic blood flow velocities, and pulsatility and resistance indices during the neonatal period in very-low-birth-weight infants.

Comment: This study is clinically-relevant because peri-intraventricular hemorrhage and ROP are vascular-circulatory disorders related to altered blood flow. Studies have suggested that changes in retinal blood flow are involved in ROP pathogenesis by causing abnormal growth of vessels in the immature retina. In this paper, the authors present data about normal ranges for ophthalmic artery blood flow in preterm infants without significant ROP or peri-intraventricular hemorrhage.

Ophthalmic artery blood flow in very-low-birth-weight preterm infants.

Soares CRS, et al. Invest Ophthalmol Vis Sci 2010; 51:708-11. (Feb 2010)

Purpose: To evaluate normal blood flow velocity and Doppler indices of the ophthalmic arteries from birth to hospital discharge of inborn infants at birth weights between 500 and 1500 g and gestational age ≤ 32 weeks.

Methods: A longitudinal prospective study with Doppler ultrasound was conducted in both eyes at 24 hours, 7 and 28 days, and hospital discharge for systolic and diastolic velocities, pulsatility, and resistance indices. Retinopathy of prematurity stage 2 and higher, peri-intraventricular hemorrhage grades 3 and 4, and death were excluded.

Results: The authors studied 46 very-low-birth-weight infants (92 eyes; birth weight, 1215 ± 202 g; gestational age, 30.4 ± 1.3 weeks). Both eyes had similar Doppler findings at each study interval. Systolic velocity increased significantly from birth to hospital discharge ($P = 0.001$; right eye, 17.85 ± 5.3 cm/s and 23.18 ± 4.88 cm/s; left eye, 17.78 ± 5.19 cm/s and 23.51 ± 5.63 cm/s), as did diastolic velocity ($P = 0.02$; right eye, 6.17 ± 1.13 cm/s and 6.76 ± 1.12 cm/s; left eye, 6.34 ± 1.26 cm/s and 6.9 ± 1.53 cm/s). Pulsatility and resistance indices did not change during the entire period.

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Inhibitory effects of maternal smoking on the development of severe retinopathy of prematurity.

[Hirabayashi H](#), [Honda S](#), [Morioka I](#), [Yokoyama N](#), [Sugiyama D](#), [Nishimura K](#), [Matsuo M](#), [Negi A](#). *Eye* 2010 June 24(6),1024-1027

The records of 86 newborn infants with an estimated postmenstrual age of 32 weeks or less were reviewed. ROP grading was evaluated in accordance with the International Classification of Retinopathy of Prematurity. Severe ROP was diagnosed when it progressed to stage 3 with plus disease. The factors were first evaluated using a univariate logistic regression analysis between the groups of severe and non-severe ROP, followed by a multivariate logistic regression analysis.

RESULTS: A low birth weight, a long duration of artificial ventilation and oxygen supplementation, presence of chronic lung disease, and ABSENCE of maternal smoking were found to be significantly associated with severe ROP in the univariate logistic regression analysis. Of the children whose mothers smoked during gestation, 25% had non-severe ROP and only 4% had severe ROP. In the multivariate logistic regression analysis, maternal smoking was revealed as a significant factor independently associated with the incidence of severe ROP.

CONCLUSIONS: Surprisingly, an inhibitory effect of maternal smoking against developing severe ROP is suggested. The authors suggest that smoking inhibits the development of the fetal central nervous system and may also inhibit neuroretinal development and limit the demand for oxygen. This would attenuate the stress the of hypoxia and reduce the production of angiogenic factors participating in the development of severe ROP. The mechanism by which smoking may reduce the incidence of severe ROP needs to be further investigated.

The authors do not recommend maternal smoking because of other known adverse systemic effects to both mother and child. However, they feel this finding may provide meaningful insights into the pathogenesis of severe ROP.

Carolyn Wu, MD; Deborah K. VanderVeen, MD; Ann Hellström, MD, PhD; Chatarina Löfqvist, PhD; Lois E. H. Smith, MD, PhD. Longitudinal Postnatal Weight Measurements for the Prediction of Retinopathy of Prematurity. *Arch Ophthalmol.* 2010;128(4):443-447.

The purpose is to validate longitudinal postnatal weight gain as a method for predicting severe retinopathy of prematurity (ROP) in a US cohort. Both ROP evaluations and weekly weight measurements from birth to postmenstrual week 36 for 318 infants were entered into a computer-based surveillance system, WINROP. This system signaled an alarm when the rate of weight gain decreased compared with control subjects. Infants were classified into 3 groups: (1) no alarm, (2) low-risk alarm, or (3) high-risk alarm. Maximum ROP for each infant was categorized as (1) no ROP (immature or mature vascularization), (2) mild ROP (stage 1 or 2 ROP in zone II or III, without plus disease), or (3) severe ROP (any prethreshold, any

stage 3, or threshold ROP). A high-risk alarm identified infants at risk for developing severe ROP. A high-risk alarm occurred in 81 infants (25.5%) and detected all infants who developed severe ROP a median of 9 weeks before diagnosis. The remaining infants received no alarm or a low-risk alarm. None of these infants developed more than mild ROP. Longitudinal postnatal weight gain may help predict ROP. In a US cohort, the WINROP system had a sensitivity of 100% and identified infants early who developed severe ROP. With further validation, WINROP has the potential to safely reduce the number of ROP examinations.

Morrison, DG et al. Risk of Refractive Pathology After Spontaneously Regressed ROP in Emmetropic Patients. JPOS May-June 2010; 47: 141-144.

226 children with a history of spontaneously regressed ROP who had a cycloplegic refraction prior to 18 months of age were examined by a pediatric ophthalmologist. Of the 226 children, 87 had a second cycloplegic refraction 2 years after the initial visit. In 63 of these children, the second examination remained normal. Overall, the authors found that the risk of developing ametropia in these children is similar to that of the general population and suggest follow-up ocular examination at 3 to 4 years of age by the pediatrician. These findings suggest a possible reduction in the need for frequent ocular examinations by the pediatric ophthalmologist during the first 2 to 3 years of life in children with spontaneously regressed ROP.

VII. STRABISMUS

The effect of Fresnel prisms on dynamic visual acuity. Maconachie G, Griffiths H, Buckley D. Br Ir Orthopt J 2010; (June) 7: 49-53.

In this well-designed study the authors showed that base-out Fresnel prisms of increasing strength have a deleterious effect on the dynamic visual acuity in a healthy student cohort with normal ocular function. Dynamic visual acuity can be tested by moving the optotypes with an immobile head, or moving the participant's head with an immobile object. The participants were tested viewing a Landolt C optotype with the gap orientation aligned either horizontally or vertically and wearing a plano (0), 5, 15, or 30 diopter Fresnel prism over one eye with the opposite eye occluded. Of note, the 5 prism diopter test results showed a significantly worse performance than no prism. Several studies suggest that, even in adults, the prism amount be split between both eyes, rather than the norm of placing the full strength over one eye. However, this has produced conflicting results.

The current study showed that as prism strength increases, then the percentage correct response decreases. The responses are better for static stimuli when compared to moving stimuli. The authors conclude by suggesting a study to investigate dynamic visual acuity in a patient population wearing a Fresnel prism over one eye or splitting the amount between each eye to represent the normal patient experience. [26 refs.]

Enhancement of quality of life in progressive supranuclear palsy: a review of clinical practice elements. Pickett L, Rowe FJ. *Br Ir Orthopt J* 2010;(June) 7:14-19.

This review article addresses the diagnostic and management issues affecting patients with PSP and to what extent this debilitating disease affects quality of life. The condition has similarities with Parkinson's disease, and is often misdiagnosed in the early stages. One study found that 4.7 years passed between the onset of symptoms and the correct diagnosis. With the population in the developed countries getting older, conditions such as PSP will be more prevalent. A recent study found that 6.4 per 100,000 would be affected. PSP is a common motor-neuron disease, and the second most common form of degenerative neuro-disorder after PD. However, the public is far less aware of it. Since the onset is insidious, and the symptoms progress more quickly and with poorer outcomes than PD, early and accurate diagnosis is crucial in providing a realistic prognosis for patients and their families. A multidisciplinary approach to the diagnosis, management and adjustment to daily living is required.

Precise measurements of saccadic velocities may permit differential diagnosis between PD and PSP. Other studies suggest that rehabilitation exercises may help improve the role between vision and locomotion in these impaired patients. [48 references.]

Magnetic Resonance Imaging of Tissues Compatible with Supernumerary Extraocular

Muscles Monica R. Khitri, Joseph L. Demer *American Journal of Ophthalmology* Volume 150, Issue 6, Pages 925-931.e2 (December 2010)

Purpose: To determine by magnetic resonance imaging (MRI) the prevalence and anatomy of anomalous extraocular muscle (EOM) bands.

Design: Prospective, observational case series.

Methods: High-resolution, multipositional, surface coil orbital MRI was performed using T1 or T2 fast spin echo weighting with target fixation control under a prospective protocol in normal adult subjects and a diverse group of strabismic patients between 1996 and 2009. Images demonstrating anomalous EOM bands were analyzed digitally to evaluate their sizes and paths, correlating findings with complete ophthalmic and motility examinations.

Results: Among 118 orthotropic and 453 strabismic subjects, 1 (0.8%) orthotropic and 11 (2.4%) strabismic subjects exhibited unilateral or bilateral orbital bands having MRI signal characteristics identical to EOM. Most bands occurred without other EOM dysplasia and coursed in the retrobulbar space between rectus EOMs such as the medial rectus to lateral rectus, from superior to inferior rectus, or from 1 EOM to the globe. In 2 cases, horizontal bands from the medial rectus to lateral rectus muscles immediately posterior to the globe apparently limited supraduction by collision with the optic nerve. All bands were too deep to be approached via conventional strabismus surgical approaches.

Conclusions: Approximately 2% of humans exhibit on MRI deep orbital bands consistent with supernumerary EOMs. Although band anatomy is nonoculorotary, some bands may cause restrictive strabismus.

Comment: This article represents more fascinating work from Dr. Demer's team. Although relatively uncommon, we can add deep orbital bands to our differential diagnosis of strabismus that it restrictive and/or has an unusual motility pattern.

Effect of motion stimulation without changing binocular disparity on stereopsis in strabismus patients.

HANDA T, ISHIKAWA H, NISHIMOTO H, GOSEKI T, ICHIBE Y, ICHIBE H, NOBUYUKI S, SHIMIZU K *Am Orthopt J* 2010; 60: 87-94.

Previous studies have shown that some patients with strabismus with absent static stereopsis, retain dynamic stereopsis. Dynamic stereopsis is the ability to detect motion in depth, and relies upon a different cortical pathway than static stereopsis. While static stereopsis is easily detected and measured with readily available tests such as the Titmus test, no test for dynamic stereopsis has yet been developed for use in the clinic. The authors describe a novel technique for investigating dynamic stereopsis using the PlayStation Portable (PSP, Sony, Japan). The device and the stereo test targets are described in detail in the article. The test was delivered to 120 non-strabismic children and 30 patients, aged 5 to 63 years, with strabismus. Both groups were also tested with the Titmus Stereotest. The normal control group found the PSP test easy to do and enjoyable. Of the strabismic patients who failed the Titmus test, 47.3% had detectable dynamic stereopsis on the PSP. All of these patients had exotropia. The esotropic subjects failed both the Titmus and the PSP tests. The authors discuss previous studies on dynamic stereopsis and compare their results. They present hypotheses to explain the difference in dynamic stereoacuity between eso- and exotropia based on the different pathways used to process static and dynamic stereo signals and the testing apparatus used.

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Persistently recurrent infantile esotropia.

GALLI M, LUEDER GT. *Am Orthopt J* 2010; 60: 95-102.

This retrospective study described 11 patients who required three or more surgeries for recurrent infantile esotropia. The average number of surgeries performed for this cohort was five (range three to nine). Recurrent esotropia was evident within a mean three months post-operatively. Six of the 11 cases were achieved a successful motor and sensory outcome following their last procedure. Another two patients achieved successful motor alignment, but without binocular vision. Two patients eventually developed a consecutive exotropia. The authors discuss several surgical approaches to recurrent esotropia. Previous studies of recurrent esotropia were also reviewed in detail, and results compared to their outcome. They conclude that while developmental delay may have contributed to persistent recurrence in some of their cases, there was no satisfactory explanation for recurrence in most of them. Most significantly, however, they found that delayed correction of the esotropia did not prevent the development of sensory or motor fusion in many of their cases.

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Strabismus-related prejudice in 5- 6-year-old children H Lukman, J E Kiat, A Ganesan, et al. *Br J Ophthalmol* 2010 94: 1348-1351

Aims There is a general consensus that individuals with conspicuous strabismus are perceived more negatively with respect to physical appearance, personality and capability. Such social biases can potentially lead to social alienation and negative psychosocial development, particularly when experienced at a young age. This study aims to explore young children's perception of peers with noticeable exotropia.

Methods 128 children, 5-6 years old, took part in this cross-sectional within-group study. The sample viewed four paired images of peers with orthotropia and exotropia, and chose the image they LIKED and the image they would SHARE their favourite toy with. All images were created using digital morphing technique.

Results Single proportion tests showed that a significantly greater proportion of the sample chose the orthotropic images as the ones they like ($z=1/45.74$, $p<0.001$) and the ones they would share their favourite toy with ($z=1/44.90$, $p<0.001$). Phi coefficient analysis further demonstrated an association between the choice to like and the choice to share ($4(504)/40.34$, $p<0.001$).

Conclusions Children as young as 5 years old are found to have negative social reactions towards peers with noticeable exotropia. These findings imply that children with noticeable strabismus may be subjected to social alienation at an early age.

Review: Good study showing the prejudice in children. This study included only exotropia patients. There is scope to involve other forms of strabismus too.

Prevalence of Amblyopia and Strabismus in Young Singaporean Chinese Children
Chia A, et al. *Invest Ophthalmol Vis Sci* 2010; 51:3411-7. (Jul 2010)

Purpose: To determine the prevalence of amblyopia and strabismus in young Singaporean Chinese children.

Methods: Enrolled in the study were 3009 Singaporean children, aged 6 to 72 months. All underwent complete eye examinations and cycloplegic refraction. Visual acuity (VA) was measured with a logMAR chart when possible and the Sheridan-Gardner test when not. Strabismus was defined as any manifest tropia. Unilateral amblyopia was defined as a 2-line difference between eyes with VA $<20/30$ in the worse eye and with coexisting anisometropia (≥ 1.00 D for hyperopia, ≥ 3.00 D for myopia, and ≥ 1.50 D for astigmatism), strabismus, or past or present visual axis obstruction. Bilateral amblyopia was defined as VA in both eyes $<20/40$ (in children 48-72 months) and $<20/50$ (<48 months), with coexisting hyperopia ≥ 4.00 D, myopia ≤ -6.00 D, and astigmatism ≥ 2.50 D, or past or present visual axis obstruction.

Results: The amblyopia prevalence in children aged 30 to 72 months was 1.19% (95% confidence interval [CI], 0.73–1.83) with no age ($P = 0.37$) or sex ($P = 0.22$) differences. Unilateral amblyopia (0.83%) was twice as frequent as bilateral amblyopia (0.36%). The most frequent causes of amblyopia were refractive error (85%) and strabismus (15%); anisometric astigmatism >1.50 D (42%) and isometric astigmatism >2.50 D (29%) were frequent refractive errors. The prevalence of strabismus in children aged 6 to 72 months was 0.80% (95% CI, 0.51–1.19), with no sex ($P = 0.52$) or age ($P = 0.08$) effects. The exotropia-esotropia ratio was 7:1, with most exotropia being intermittent (63%). Of children with amblyopia, 15.0% had strabismus, whereas 12.5% of children with strabismus had amblyopia.

Conclusions: The prevalence of amblyopia was similar, whereas the prevalence of strabismus was lower than in other populations.

Comment: The Strabismus, Amblyopia, and Refractive Error in Singapore (STARS) study was designed to determine the prevalence of amblyopia and strabismus in young Chinese preschool children in Singapore. Methods and definitions used in the STARS study are similar to those used in BPEDS (Baltimore Pediatric Eye Disease Study) and MEPEDS (Multi-Ethnic Pediatric Eye Disease Study), so that comparisons can readily be made among these studies. In brief, this study shows that the prevalence of amblyopia in the Singaporean Chinese preschool population is similar to what was seen in MEPEDS and BPEDS cohorts (among Latino, white, and African-American children), whereas the prevalence of strabismus was much lower in the STARS cohort.

Fusional vergence measures and their significance in clinical assessment.

ROWE FJ: *Strabismus* 2010; 18: 48-57.

This prospective study evaluated the differences between fusional vergence ranges in eso- and exo-deviations with varying target size. The evaluation included measurement of fusional vergence with prism bars at near and distance with randomization of target size and order of prism base orientation. Subjects had best corrected visual acuity of 6/6 in both eyes, a horizontal phoria of ± 10 prism diopters (PD), and TNO stereo of 60 seconds of arc or better. Twenty-two subjects, 7 esophoric and 15 exophoric, were included in this study. Median prism fusional vergence range at near fixation was 25 base out (BO) to 10 base in (BI) on a small central target and 35BO to 12BI on a large peripheral target. At distance fixation median range was 16BO to 6BI on a small target and 25BO to 6BI on a large target. Esophoric patients had a range shift towards the BO range and exophorics had a shift towards the BI range. When comparing target size there was no significant difference for BI, but for BO a larger range was obtained with a peripheral target at near fixation only (esophoria: $p=0.039$ to $p=0.043$, exophoria: $p=0.016$ to $p=0.046$), although this is not statistically significant. The author concluded that smaller fusional vergence values are obtained with small central targets in comparison to those obtained with larger targets.

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Classifying Stability of Misalignment in Children With Esotropia Using Simulations

B. Michele Melia, ScM; Jonathan M. Holmes, BM, BCh; Danielle L. Chandler, MSPH; Stephen P. Christiansen, MD; for the Pediatric Eye Disease Investigator Group

Arch Ophthalmol. December 2010;128(12):1555-1560.

The purpose of this study is determine the sensitivity and specificity of several classification rules for stability and instability of angle in childhood esotropia. The authors conducted 10 000 Monte Carlo simulations of participants with no actual change in angle of esotropia during follow-up, where "observed" changes in ocular alignment were sampled from a distribution of measurement errors for the prism and alternate cover test. Additional simulations were conducted for a range of "true" changes (1.0, 2.5, 4.2, 5.0, 7.5, and 10.0 prism diopters [PD] per visit) with up to 10 follow-up visits. They then estimated sensitivities and specificities for specific rules for retrospectively classifying stability (all measurements within 0, 5, 10, or 15 PD) and instability (≥ 2 measurements differing by ≥ 10 PD, etc) across a fixed number of visits. Results were extended to classifying ocular alignment stability and instability prospectively based on a varying number of measurements. The authors found: For a series of 4 measurements, the rules that optimized sensitivity and specificity were "all measurements within 5 PD" for stability and "at least 2 measurements differing by 15 PD or more" for instability. For a series of 3 measurements, all 3 measurements needed to be identical to confirm stability. The authors conclude that derived definitions of stability and instability in childhood esotropia using estimates of actual measurement error that may be useful for clinical practice and for future clinical studies of esotropia.

Test-Retest Reliability of Health-Related Quality-of-Life Questionnaires in Adults with Strabismus.

[Leske DA](#), [Hatt SR](#), [Holmes JM](#).

[Am J Ophthalmol](#). 2010 Feb 5. [Epub ahead of print]

PURPOSE: To report the test-retest variability of two health-related quality-of-life instruments: the new Adult Strabismus 20 (AS-20) and the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25), in adults with strabismus.

METHODS: Fifty-five adult patients in a clinical practice with stable strabismus completed the AS-20 and the NEI VFQ-25 at 2 visits, without intervening treatment. Questionnaires were completed the second time either at a subsequent office visit, immediately before surgery, or by mail. Intraclass correlation coefficients were calculated. Ninety-five percent limits of agreement and 95% confidence intervals around the 95% limits of agreement also were calculated.

RESULTS: There was excellent agreement of overall questionnaire scores for the AS-20 (intraclass correlation coefficient, 0.92) and NEI VFQ-25 (intraclass correlation coefficient, 0.94). The 95% limits of agreement for overall scores were 14.3 points (95% confidence interval, 10.9 to 17.7) for the AS-20 and 11.1 points (95% confidence interval, 8.5 to 13.8) for the NEI VFQ-25. The lower test-retest variability of the VFQ-25 seemed to be partly the result of ceiling effects with many scores at the normal end of the range.

CONCLUSIONS: The new AS-20 and the NEI VFQ-25 show excellent test-retest reliability in adults with strabismus. Change exceeding 95% limits of agreement (14 points on the AS-20 and 11 points on the VFQ-25) is indicative of real change in an individual patient. The AS-20 may be more useful than the VFQ-25 because it is less prone to ceiling effects in adults with strabismus.

Incomitant Strabismus :Does Extraocular Muscle Form Denote Function?

Burton J. Kushner, MD

Arch Ophthalmol. December 2010;128(12):1604-1609.

Dr. Kushner writes that the paradigm that an "underacting" extraocular muscle is always atrophic or hypoplastic and that an overacting extraocular muscle should always be enlarged leads to inconsistencies with clinical observations. These include findings of "overacting" inferior oblique muscles, superior rectus muscle overaction or contracture syndrome, and normal extraocular muscle diameters in patients with apparent superior oblique muscle palsy, among other clinical entities. These inconsistencies can be reconciled if one accepts the possibility that extraocular muscle contractile activity may reflect a change in neural input to an anatomically normal muscle or that muscle contractile activity may be altered by shifts in fiber type and distribution within a normal-sized muscle. This remodeling may result from vergence adaptation or from any change in neural stimulus to the muscle. There is substantial evidence to suggest that both of these theoretical possibilities may likely occur.

The psychosocial aspects of strabismus: correlation between the AS-20 and DAS59 quality-of-life questionnaires. Durnian JM, Owen ME, Marsh IB. J AAPOS 2009;13:477-480. Oct

The AS-20 is a twenty item adult strabismus questionnaire. The Derriford Appearance Scale 59 (DAS59) is a well-established research tool looking at overall appearance. This study attempted to determine if there was any correlation between these scales and/or correlation between the subscales of both quality-of-life (QoL) scales. The study also tried to determine if there was a difference between control groups and strabismus groups on these questionnaires. This was a prospective, noninterventional study of adult patients undergoing strabismus surgery (n=34) and a series of random controls (n=30). The study found that both questionnaires were easy to use. There was strong agreement between the scales and the AS-20 was specific for strabismus patients. Strabismus patients were found to have significantly more psychosocial distress than those without strabismus. The problem with this study is that the strabismus patients were self-selected in that they had all chosen to undergo surgery. This may overestimate the distress that patients with strabismus feel because this is biased towards those that elected to correct their strabismus. Also both the AS-20 and the DAS59 had over 10% of patients who either did not fill out the forms correctly or chose not to fill it out at all.

Dynamic Study of the Medial and Lateral Recti Capsulopalpebral Fasciae Using Cine Mode Magnetic Resonance Imaging

Kkakizaki H, Selva D, Leibovitch I.

Ophthalmology 2010;117:388-391 (February)

Design: Observational case series of ten patients (age range 8 – 75 years; mean age, 41.1 years) diagnosed with a unilateral orbital blowout fracture (medial wall, floor, or both) and having a normal contralateral orbit.

Results: In medial gaze, the medial part of the eyelid moves posteromedially, in synchronicity with medial rectus muscle contraction, mediated by the mrCPF. The lateral part of the eyelid moves anteromedially, synchronicity with lateral rectus muscle relaxation, mediated by the lrCPF. In lateral gaze, the lateral part of the eyelid moves posterolaterally, in synchronicity with the lateral rectus muscle contraction, mediated by the lrCPF. The medial

part of the eyelid moves anterolaterally, in synchronicity with medial rectus muscle relaxation, mediated by the mrCPF. These findings were demonstrated in all 10 patients.

Reviewers' Comments: This is a baseline study which may allow a better understanding of the importance of these anatomic structures and may reduce functional and cosmetic complications during common oculoplastic and strabismus surgeries. The authors never distinguished the "why" or the difference in the eyes with a blowout fractures.

The fixation target influences the near deviation and AC/A ratio in intermittent exotropia. Le, T BOrth, Koklanis, K PhD, Georgievski, Z BAppSc(Orth)(Hons). J AAPOS 2010;14:25-30. (Feb)

This study investigates the effect of target size on the AC/A measurement in intermittent exotropes. 25 patients were included. The two targets produced different AC/A ratios by changing the measured exotropia when measured through convex lenses. Categorization of 4 patients as either simulated or true divergence excess type intermittent exotropia changed based on the fixation target used. Twelve patients had a shift in AC/A ratio from low or normal to high. Potential problems with this study include lack of randomization, and that the targets were always presented in the same order. Same order presentation could bias strabismus measurements because of longer disruption of binocularity.

Diplopia and strabismus following ocular surgeries.

Guo S, et al. *Surv Ophthalmol* 2010; 55:335-58. (Jul-Aug 2010)

This article reviews the pathogenesis, clinical features, and management of diplopia and strabismus following ocular surgical procedures: cataract surgery, vitreoretinal surgery, glaucoma surgery, conjunctival surgery, refractive surgery, and orbital decompression surgery. The authors summarize that common underlying mechanisms include sensory disturbance, scarring, direct extraocular muscle injury, myotoxicity from injections of local anesthesia or antibiotics, and malpositioning of extraocular muscles by implant materials. The most common patterns are vertical and horizontal motility disturbance. Treatment options include prisms, botulinum, occlusion, or surgery.

Comment: This is an excellent review article. Strabismus surgeons will have seen some (but probably not all) of the examples described in the paper, but it is an extremely interesting summary and review.

Isolated sixth nerve palsy after intravitreal bevacizumab injection.

ÇAKMAK HB, TOKLU Y, YORGUN A, ŞİMŞEK Ş: *Strabismus* 2010; 8: 18-20.

Bevacizumab is used in the treatment of neovascular age-related macular degeneration (AMD) and other causes of choroidal neovascularization. This was a case study of sixth nerve palsy following intravitreal bevacizumab injection for wet AMD. A 64-year old male presented with a complaint of diplopia seven days after intravitreal bevacizumab injection. He had a 15-year history of well-controlled type II diabetes mellitus, but was otherwise healthy. The patient was examined and diagnosed with an isolated microvascular right lateral rectus paralysis. Measurements were 10 prism diopters (PD) of esotropia in primary position, 30PD esotropia in right gaze, and orthotropia in left gaze. MRI and other neurological exams were normal. The limitation of abduction, the esotropia, and

the diplopia resolved three months post-injection. The authors report that though intravitreal bevacizumab injections are usually well tolerated, there are risks for systemic adverse events to occur, as bevacizumab injected intravitreally could migrate into the bloodstream.

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Diagnostic use of botulinum toxin in patients with Duane syndrome.

DAWSON ELM, MAINO A, LEE JP: *Strabismus* 2010; 18: 21-23.

The authors proposed that botulinum toxin (BT) may be used to assess the likelihood of reducing the abnormal head posture and diplopia with strabismus surgery in patients with Duane syndrome. This article was a retrospective review of 88 patients with Duane Syndrome (48 females) treated with BT between 1980 and 2007. Mean age at injection was 29 years (range 5-68 years). The left eye was affected in 50 patients (57%) and 21 patients (24%) had bilateral Duane syndrome. The average angle of deviation was 28.6 ± 18.4 prism diopters (PD) (range 4PD-100PD) for esotropic patients and 32.5 ± 14.5 PD (range 6PD-55PD) for exotropic patients. All patients underwent a unilateral injection. The medial rectus was injected in 58 patients and the lateral rectus in 30 patients. Of the 73 patients (83%) presenting with an abnormal head posture, 46 showed improvement. Diplopia was reported by 52 patients (59%) pre-operatively, and it was reduced in 34 of these patients following injection. Temporary ptosis was experienced in 11 patients and a transient vertical deviation in 10 patients. Forty-one patients (46.5%) proceeded with strabismus surgery following diagnostic BT, and 12 (14%) continued with maintenance BT injections. This is the first study to explore the diagnostic role of BT in Duane syndrome. The authors conclude that BT is a safe treatment that may also offer long term benefits if used therapeutically.

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The profile of strabismus in stroke survivors.

[Rowe F](#); [VIS group UK](#). *Eye* 2010 April: 24(4), 682-685

The Vision In Stroke (VIS) Group involves 16 recruiting centers in the United Kingdom. This study included 512 patients prospectively over a 2 year recruiting period to evaluate the profile of strabismus that occurs in stroke survivors to determine the relationship between the site of the stroke and symptom of diplopia.

RESULTS: The mean age of the patients was 69 years. 59% were males, 41% were female. 19% of the patients had detectable strabismus after the onset of stroke. Of these strabismic patients, 2.5% had strabismus that pre-existed the onset of stroke; thus, 16.5% of patients had strabismus attributable to the stroke. A total of 70% had strabismus associated with

ocular motility abnormalities (saccadic dysmetria or palsy, third, fourth or sixth cranial nerve palsy, Weber's syndrome, downgaze paresis, INO, gaze palsy) and 30% were in isolation. 24% were associated with brain stem, cerebellar, thalamus or basal ganglia strokes, and 73% with cortical strokes. 52% complained of diplopia, either in isolation or associated with other symptoms (reading difficulty, visual field loss, poor vision or oscillopsia). The remainder had no symptoms related to their strabismus. 100% of the patients who complained of diplopia had associated ocular motility abnormalities. 72% of the patients had exotropia and 77% had impaired convergence. It was not possible to predict from the area of brain injury those patients who complained of diplopia.

Burton J. Kushner, MD. Effect of Ocular Torsion on A and V Patterns and Apparent Oblique Muscle Overaction. *Arch Ophthalmol.* 2010;128(6):712-718.

The purpose is to determine if ocular torsion is a major cause of A and V patterns and oblique muscle overaction or merely a contributing factor. Three separate investigations were conducted. (1) The trajectory of eyes with oblique muscle overaction was plotted across the horizontal field of gaze from videographs to determine if it was linear or curvilinear. (2) The effect of successful Harada-Ito surgery to reduce extorsion on overelevation in adduction in patients with fourth cranial nerve palsy was studied. (3) The effect of successful surgery to treat pattern strabismus in the form of vertical transposition of the horizontal rectus muscles on objective torsion was studied. The results demonstrate that : (1) Three eyes with inferior oblique muscle overaction and 2 with superior oblique muscle overaction had a curvilinear rise or fall (respectively) as they moved into adduction; (2) Surgery that successfully decreased extorsion had a negligible effect on overelevation in adduction in 2 patients; (3) Horizontal rectus muscle transposition that was uniformly successful in eliminating A or V patterns consistently caused an increase in objective torsion in all 5 patients studied. Ocular torsion may contribute to A or V patterns and overelevation or overdepression in adduction, but it is probably not the major cause of these phenomena.

**Dissociated vertical deviation and its relationship with time and type of surgery in infantile esotropia
Br J Ophthalmol 2010;94:740-74 (June)**

This paper investigated the development of dissociated vertical deviation (DVD) in infantile esotropia and its relationship with the infant's age and the surgical intervention technique. The medical records of the patients were reviewed retrospectively. The patients' ages at the time of admission, risk factors, ophthalmological examinations before and after treatment, and treatment mode were recorded and compared. The authors found that DVD developed in approximately one-half of the cases (47.9%) at an average age of 3.2 years (20 months–5.5 years) regardless of the type of treatment. DVD developed in 80.5% of cases that had no surgery and in 37.5% of cases who were surgically treated. On comparison according to age, DVD was seen in 24.1% of the cases that were treated between ages 6 months and 2 years and in 52% of the cases that were treated after age 2 years. This difference was found to be statistically significant ($p < 0.01$). According to the surgical technique used, DVD developed in 34.8% of the cases who had undergone bimedial rectus recession and in 38% of the cases with unilateral recession and resection. This difference was NOT statistically significant ($p > 0.05$). The authors concluded that in the treatment of infantile esotropia, early surgical intervention to obtain binocularity and prevent

amblyopia is associated with a reduced incidence of the development of DVD. They also showed that the incidence of the development DVD increases if surgery is not performed, if performed at a later age, or if additional muscle surgery is needed during follow-up due to undercorrection.

Trochlear palsies caused by isolated trochlear schwannomas.

ELFLEIN HM, THÖMKE F, MÜLLER-FORELL W, PITZ S: *Strabismus* 2010; 18: 83-86.

Schwannomas arising from the ocular motor cranial nerves are extremely rare in patients without neurofibromatosis (NF). The authors describe clinical features and management of four patients without NF suffering from unilateral superior oblique palsies secondary to MRI-documented isolated trochlear nerve schwannomas. All four patients were male, aged 36-72 years (mean 55 years) at initial presentation. History of diplopia prior to presentation ranged from 9 months to 13 years, and follow up was 9 months to 156 months. One patient had remained stable over 9 months of follow-up. A second patient was diagnosed with a fourth nerve palsy 13 years prior to confirmation of a trochlear schwannoma. Both of these patients received no treatment for the fourth nerve palsy or the schwannoma. The third patient underwent eye muscle surgery to alleviate diplopia and improve an abnormal head posture. The fourth patient received stereotactic radiotherapy of an 8mm schwannoma and remained unchanged in his ocular alignment for 3.5 years. None of the four patients developed any additional symptoms or signs of further cranial nerve or central nervous system involvement. The authors concluded that conservative management may be recommended for a trochlear nerve schwannoma as patients can remain unchanged for years.

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Predictive value of age, angle, and refraction on rate of reoperation and rate of spontaneous resolution in infantile esotropia.

SIMONSZ HJ, EIJKEMANS MJC: *Strabismus* 2010; 18: 87-97.

In the Early vs. Late Infantile Strabismus Surgery Study (ELISSS), reoperation rates were 28.7% for children operated on at age 20 months (SD 8.4 months) versus 24.6% for patients operated on at age 4 (SD 12.7 months). The purpose of this study was to compare reoperation rates of the ELISSS study with those from consecutive cases of infantile esotropia in nine university clinics over a one-year time period, and with those found in the literature. The predictive value of age, angle of deviation, and refraction on rate of reoperation was assessed and compared. The rate of spontaneous resolution in infantile esotropia was also investigated. To estimate the chance of spontaneous decrease of the angle without surgery, a random effects model was fitted on the 6 monthly orthoptic measurements of angle and refraction in the ELISSS that preceded surgery, or the final examination at age 6.

One hundred sixty-six patients were included, with a mean age of 4.33 years at the first surgery. Reoperation was performed in 32 (19.3%) of these patients. The reoperation rate was 7.3% for postoperative angle of -4° to $+4^{\circ}$ ($n=82$), 25% for postoperative exodeviations $>5^{\circ}$ and 29% for postoperative esodeviations 10° to 14° . Reoperation rates were between 60% to 80% for children first operated on around age 1 year, and 25% for children operated on around age 4 years. Finally, a small angle at age 1 year and hyperopia of $\geq +4.00$ diopters increased the chance of spontaneous decrease of the angle to a microstrabismus. The authors conclude that early surgery for infantile esotropia is associated with a higher reoperation rate and occasionally a child's angle of strabismus may spontaneously become a microstrabismus if hyperopia is significant.

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VIII. STRABISMUS SURGERY

The Use of Titanium T-Plate as Platform for Globe Alignment in Severe Paralytic and Restrictive Strabismus David T. Tse, Erin M. Shriver, Kenneth B. Krantz, Jeffrey D. Tse, Hilda Capo, Craig A. McKeown American Journal of Ophthalmology

Volume 150, Issue 3, Pages 404-411.e1 (September 2010)

Purpose: To evaluate the long-term effectiveness of improved ocular alignment using a suture/T-plate anchoring platform system.

Design: Retrospective, noncomparative, interventional case series.

Methods: **SETTING:** Institutional. **STUDY POPULATION:** Seven consecutive patients with large angle deviations attributable to paralytic and/or restrictive strabismus managed jointly by orbital and strabismus surgeons. **INTERVENTION PROCEDURE:** The T-plate base is anchored to the orbital rim with the shaft projecting toward the orbital apex to simulate the origin of the affected muscle. A nonabsorbable suture serves as the coupling element linking the muscle insertion to the tip of the T-plate such that the suture coincides with the axis of the dysfunctional muscle and yields a pull vector to simulate the passive tensile force of the muscle. Information analyzed included patient demographics, etiology of strabismus and characteristics, prior muscle surgeries, secondary interventions, subjective appraisal of diplopia, and final ocular alignment measurements. **MAIN OUTCOME MEASURES:** Subjective appraisal of diplopia, final ocular alignment in primary gaze, and late stability.

Results: All 7 patients showed marked reduction in ocular deviation with a median change of 33 prism diopters (PD) and a range of 7 to 72 PD. For the 6 patients with medial rectus dysfunction, the final ocular alignment ranged from 6 to 18 PD of residual exotropia in primary gaze. The patient with sixth nerve palsy had 5 PD of residual esotropia. There were no failures after an average of 59.4 months of follow-up.

Conclusions: A globe tethering technique using a suture/titanium T-plate anchoring platform system effectively treats refractory cases of paralytic and restrictive strabismus with large angles of deviation.

Comment: It is nice to add this technique to our list of options for severe paralytic / restrictive strabismus, since some patients remain undercorrected after maximum extraocular muscle surgery. Most strabismus surgeons will need an orbital surgeon to assist with this procedure.

Functional benefits of adult strabismus surgery.

EDELMAN PM: *Am Orthopt J* 2010; 60: 43-47.

This article was based on a presentation made as part of a symposium held at the Joint Meeting of the American Orthoptic Council, the American Association of Certified Orthoptists, and the American Academy of Ophthalmology in San Francisco, CA, October 2009. In the very recent past, insurance companies often denied claims for strabismus surgery in adults because it was thought to provide only a cosmetic improvement, with no functional benefit. In this article, the author defines and contrasts cosmetic surgery with restorative surgery, and reviews the evidence in the literature for functional improvement following strabismus surgery in adults. Studies have found evidence for restoration of sensory fusion and stereopsis, expansion of the binocular visual field, and improvement in psychosocial and socioeconomic status with restoration of ocular alignment in adult patients. The author concludes that the evidence shows that strabismus surgery in adults is not cosmetic, and has a significant impact on the quality of life in the adult patient.

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Outcome study of graded unilateral medial rectus recession for small to moderate angle esotropia.

Wang L, Nelson LB. *JPOS* 2011;48: 20-24. (January/February)

Purpose: Outcome study of 123 consecutive patients treated by graded medial rectus recession for small to moderate angle esotropia over an eight year period with a minimum follow-up of 6 months.

Methods: Records were reviewed of patients who underwent graded medial rectus recession for unilateral esotropia of 15-35 prism diopters. Successful alignment was defined as +/- 5 PD of orthophoria in primary and lateral gaze while viewing distant and near targets.

Results: The eyes of 96.8% of patients were successfully aligned and the average deviation corrected was 17.3 +/- 1.2 PD for 5mm, 18.6 +/- 2.5 PD for 5.5mm, 23.7 +/- 4.9 PD for 6mm, 26.7 +/- 3.9 PD for 6.5 mm, and 31.9 +/- 3.3 PD for 7mm unilateral medial rectus recession at 6 month follow-up. Seventy-four patients (83.2%) with more than 6 months follow-up achieved successful alignment, 14 (15.7%) were undercorrected, and 1 was overcorrected.

Conclusions: Successful alignment was achieved in most esotropic patients treated by graded unilateral medial rectus recession.

Comment: Provides a reference for the treatment of small to moderate angle esotropia. Advantages included limiting surgery to one eye, decreased anesthesia time and cost, and leaves other muscles untouched for possible future surgery.

Anterior transposition of the inferior oblique muscle in the treatment of unilateral superior oblique palsy.

Keskinbora KH. JPOS 2010;47:301-307. (September/October)

Purpose: To determine whether unilateral inferior oblique anterior transposition alone could be an effective procedure for treating superior oblique palsy with inferior oblique overaction.

Methods: Retrospective review of 38 patients undergoing unilateral inferior oblique anterior transposition for unilateral SOP with IOO were evaluated.

Results: Mean age 29 years, mean follow-up 32 months, mean pre-op hypertropia 14.3 +/- 7.7 PD with mean reduction in post-op hypertropia of 12 PD. Inferior oblique overaction was reduced in all patients. No patients developed primary position hypotropia following surgery. Surgery improved stereoacuity nearly two units using the Titmus stereoacuity scale.

Conclusion: Anterior transposition of the inferior oblique muscle is effective in correcting inferior oblique overaction and primary position hypertropia in the treatment of unilateral superior oblique palsy.

Comment: In this study of adult patients, a single muscle procedure (ATIO) was demonstrated to be sufficient to correct both inferior oblique overaction and primary position hypertropia over a wide range of pre-operative deviations in unilateral SOP. Potentially avoids operating on two vertical muscles in this common muscle palsy.

Comparative study of unilateral and bilateral surgery in moderate exotropia.

Menon V, Singla M, Saxena R, Phulijele S. JPOS 2010;47:288-291. (September/October)

Purpose: To evaluate the surgical outcome of unilateral vs bilateral lateral rectus recession for the correction of moderate exotropia.

Methods: Prospective study of 20 consecutive cases of intermittent exotropia ranging from 15-25 pd randomized into two groups and operated on by a single surgeon.

Results: Mean age, preoperative exotropia, and postoperative deviation were comparable in the two study groups. Consecutive small-angle esotropia was seen in one patient in the bilateral group. There was no significant incomitance at 3 months in either group.

Conclusions: Unilateral and bilateral lateral rectus muscle recession are equally effective in mild to moderate exotropia.

Comment: Confirms several previous studies. There appears to be less likelihood of overcorrection in the unilateral group, but more studies with larger sample size are needed to confirm this assertion.

Delayed adjustable suture technique. S L Robbins, D B Granet, C Burns, *Br J Ophthalmol* 2010 94: 1169-1173

Purpose To characterise the results of the largest patient series to date undergoing closed conjunctival delayed adjustable suture techniques.

Methods A multicentre retrospective review of 440 operations (patients aged 10e91 years) by five surgeons at four centres were evaluated for surgical outcomes

associated with the delayed adjustable suture technique.

Results 26% (116 of 440) of all patients required postoperative manipulation, with individual surgeon rates ranging from 13% to 56%. The majority of these patients did not complain of diplopia in target gaze and/or had satisfactory cosmetic improvement as evaluated at the 1e3 months follow-up visit (84%). Transient complications included dellen, poor conjunctival appearance, filamentary keratitis, infection, granuloma, exposed suture and corneal abrasion. Serious complications were rare.

Conclusions This large multicentred series characterises the closed conjunctival delayed adjustable suture technique for the correction of strabismus. It may present some significant advantages to more traditional adjustable suture techniques.

Review: Delayed adjustment may seem to have an advantage. But its very difficult to prove. May surgeons are involved in the retrospective study.

Surgical procedure for correcting globe dislocation in highly myopic strabismus.

[Yamauchi M](#), [Yokoyama T](#), [Shiraki K](#).

[Am J Ophthalmol](#). 2010 Feb;149(2):341-346.e2. Epub 2009 Nov 24.

PURPOSE: To design a surgical procedure for correcting globe dislocation in strabismus in high myopia (highly myopic strabismus).

METHODS: We examined 36 eyes of 21 patients with highly myopic strabismus and 27 eyes of 27 healthy volunteers as controls at Osaka City General Hospital between 2000 and 2006. Anatomic relationships between the muscle cone and globe were analyzed using magnetic resonance imaging. Ranges of globe movement and angles of ocular deviation were measured quantitatively as angles of maximum abduction and sursumduction and angles of ocular deviation, respectively, using the Goldmann perimeter and alternate prism cover tests. A surgical procedure involving muscle union of the superior rectus and lateral rectus muscles was performed in 23 eyes of 14 patients to restore the dislocated globe back to the muscle cone.

RESULTS: After surgery, the angle of dislocation of the globe, defined as the angle formed by a line connecting the area centroid of the superior rectus muscle and the globe and a line connecting area centroid of the lateral rectus muscle and globe against the supertemporal wall of the orbit, was significantly decreased ($P < .001$), and angles of maximum abduction and sursumduction and the angle of ocular deviation improved significantly ($P < .001$).

CONCLUSIONS: This surgical procedure to restore the dislocated globe back into the muscle cone by uniting muscle bellies of the superior rectus and lateral rectus muscles is effective for highly myopic strabismus.

Br J Ophthalmol 2009;**93**:1616-1619 doi:10.1136/bjo.2008.156687

Residual torticollis in patients after strabismus surgery for congenital superior oblique palsy

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3. K K W Sun²,
4. C B O Yu¹,
5. C Y Wong¹,
6. D S C Lam¹

Abstract

Aim: To study postoperative residual vertical deviation and abnormal head posture (AHP) after surgical treatment for congenital superior oblique palsy (SOP).

Method: Children with both SOP and AHP who underwent extraocular muscle surgery for correction of AHP were recruited. The patients received complete ophthalmic and orthopaedic examinations. Residual AHP was classified according to severity of face turn, head tilt and chin elevation.

Results: Thirty-two children with mean age at operation of 82.6 months were recruited, with mean follow-up of 37.9 months. Of these children, 65.6% had a postoperative vertical deviation of less than three prism dioptres. In addition, 34.4% patients had resolved (0°), 34.4% had mild (1° – 10°), and 31.3% had significant residual torticollis ($>10^\circ$). Of the patients with significant residual torticollis, 33.3% had ocular causes. The mean age at operation for the patients with residual torticollis (95.9 months) was older than those without torticollis (79.9 months) ($p = 0.018$). Residual torticollis was found to be related to sternocleidomastoid muscle tightness ($p = 0.013$).

Conclusion: The success rate for eliminating significant AHP after strabismus surgery for patients with congenital SOP was 68.8%. Early surgery was associated with a better outcome. Association was also found between sternocleidomastoid tightness and AHP. A multidisciplinary approach is recommended in the management of torticollis as ophthalmic and orthopaedic comorbidities can coexist.

Comment: Nice article reporting their results in a series of 32 patients with SOP. Anomalous head position was only relieved in 68% in this series. Residual anomalous head position was associated with tight sternocleidomastoid muscle, therefore these pts should have orthopedic consultation prior to further ophthalmic intervention.

Comparison of sensory outcomes in patients with monofixation versus bifoveal fusion after surgery for intermittent exotropia. Morrison, D MD, MsSwain, W BS, Donahue, S MD, PhD. J AAPOS 2010;14:47-51. (Feb)

The authors postulate that preoperative bifoveal fusion increases the motor and sensory outcomes of strabismus surgery for intermittent exotropia. This was a retrospective review of results of bilateral lateral rectus recessions for intermittent exotropia. 95 children met inclusion criteria. Most children's near stereopsis remained unchanged postoperatively. Children with high-level fusion preoperatively were at low risk of losing this with surgery. Small-angle esotropias that persist beyond the immediate postoperative period can result in loss of stereopsis, despite the fact that they would be considered motor successes. This study has many limitations including: variability in stereoacuity testing, short-followup, retrospective nature, small numbers of patients whose stereoacuity actually changed, only near stereoacuity was evaluated, and lack of ability to detect worsening stereopsis postoperatively in patients with poor or lack of stereopsis preoperatively.

Treatment of "heavy eye syndrome" using simple loop myopexy. Durnian, J.M. FRCOphth, Maddula, S MB, ChB, Marsh, I.B. FRCOphth. J AAPOS 2010;14:39-41. (Feb)

Extreme myopia can produce an elongation of the globe, with resultant progressive esotropia and hypotropia. An effective treatment of this condition is the loop myopexy. The authors used a suture to approximate the superior and lateral rectus muscles without scleral fixation. At six-months follow-up, the esotropia and hypotropia both were significantly improved. Only 5 patients data were included in

the study, and the preoperative deviations were somewhat smaller than is typically reported with the 'heavy eye syndrome'. Diplopia and its treatment, were not addressed in this study, as all patients had very poor preoperative vision in the surgical eye.

Comparison of botulinum toxin with surgery as primary treatment for infantile esotropia. De Alba Campomanes, A.G. MD,MPH, Binenbaum, G MD,MSCE, Campomanes Eguiarte, G MD. J AAPOS 2010;14:111-116. (April)

Botulinum toxin is an alternative treatment of esotropia. Success results have varied widely in prior studies. This study was a nonrandomized, prospective comparison of botulinum toxin and surgery as the primary treatment for esotropia with an onset during the first year of life. Potential causes of bias include surgeons recommending the surgical option for infants who presented at a later age, and parents making the choice of procedure based on the difference in cost. 322 patients underwent injection of botulinum toxin, and 120 had surgery. Patients in the surgery group, on average, were 10 months older at the time of the procedure, and were esotropic longer. Motor success was achieved in 65% of surgical patients and 45% of injection patients. Half of the injection patients required more than one injection. Botulinum injection success was comparable to surgery if the angle of deviation was ≤ 30 PD. This study is limited by the above mentioned bias, lack of randomization, lack of a defined follow-up period, and the different preoperative characteristics of each study group.

Ketamine and botulinum: a safe combination for the management of childhood strabismus. OWEN M, NOONAN CP, AL-KHALID M, ROWE FJ: *Strabismus* 2010; 18: 8-12.

This retrospective study sought to determine the prevalence of ketamine anesthesia side effects in children receiving botulinum toxin (BT) injections for strabismus, and to establish the prevalence, severity and duration of ptosis. The study included children (age 9 months to 16 years, median 6 years) who underwent ketamine anesthesia prior to BT injection to the medial rectus or lateral rectus. A questionnaire regarding occurrences of nightmares, sleeplessness, and hallucinations (ketamine side effects) or ptosis (BT side effect) was sent to parents and examination records were reviewed. Ninety-seven (114 injections, 49 females and 48 males) completed questionnaires were returned. Side effects were reported by 12 patients (12.4%), nine female and three male. Two of these children experienced sleepless nights, nightmares, and hallucinations, and the remaining 10 experienced only one of these ketamine side effects. Eighteen children (15.8% of injections) had ptosis at their 2-week appointment. The ptosis resolved within six weeks for 17 of these cases. Ptosis occurred more frequently when treating esodeviations versus exodeviations ($p=0.001$). The authors concluded that BT injection under intravenous ketamine anesthesia can safely be used for children, but ketamine anesthesia may be associated with side effects, with females being more prone to experiencing these side effects.

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Dose effect of botulinum toxin A in heterotropia and heterophoria.

ROWE FJ, NOONAN CP, BATRA R: *Strabismus* 2010; 18: 3-7.

The authors retrospectively evaluated the short term dose effect of botulinum toxin (Dysport brand) in manifest and intermittent horizontal strabismus, and compared the effect of botulinum toxin (BT) in large (> 20 prism diopters) versus small (≤ 20 prism diopters) deviations. Two units of BT were injected into a single muscle in all cases, and electromyography (EMG) signal was recorded during the procedure. The angle of deviation was measured two weeks after injection.

Sixty-six patients with a mean age of 24 (range 1-79) were included. Thirty-nine had esodeviations (median 25PD at near, 20PD at distance) and 27 had exodeviations (median 30PD at near, 25PD at distance). The change in angle of deviation after BT was significant for both eso- and exo-deviations and at both near and distance fixation ($p=0.0001$ for all parameters). No association was found between reduction of angle and type of deviation ($p=0.134$ at near, $p=0.857$ at distance) or tropia versus intermittent control ($p=0.167$ at near, $p=0.829$ at distance). There was a significant association between larger angle of deviation and greater change in angle with treatment at near and distance ($p=0.001$). The authors caution that measurements at longer follow up periods may show very different angles than the two-week follow up in this study.

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Single medial rectus muscle advancement in stretched scar consecutive exotropia. Tinley, C FRCOphth, Evans, S BM,BS, McGrane, D DBO, et al. J AAPOS 2010;14:120-123 (Apr)

Consecutive exotropia may be seen in the setting of a stretched muscle attachment scar. 11 patients underwent advancement of the medial rectus muscle alone, to treat consecutive exotropia. Follow-up ranged from 4 to 16 months. Only 3 patients achieved the desired postoperative alignment and an exodrift over time was noted. The authors comment that adding a recession of the antagonist is probably necessary to achieve a better final outcome.

Palmaris longus tendon as an autogenous expander for Brown's syndrome: A novel technique. Batal, A MD,FRCS, Batal, O MS, Facharzt. J AAPOS 2010;14:137-141. (Apr)

The authors report the use of Palmaris longus tendon as an autogenous expander to lengthen the superior oblique tendon in cases of moderate to severe Brown syndrome. The surgery was performed on four children, and the tissue was harvested by an orthopedic surgeon. Follow-up ranged from 12-21 months. All patients had improved vertical strabismus and resolved torticollis. No patients developed a superior oblique palsy, and no patients had any functional change in wrist function or grip. The harvest is technically difficult and requires an experienced surgeon. Although no serious complications occurred in this study, there are potentially serious risks, including injury of the median nerve. The need for this procedure is not convincing in light of the fact that other procedures are available to treat this condition.

Surgical management of clinically significant hypertropia associated with exotropia. Struck, M.C. MD, Hariharan, L MPH,MD, Kushner, B.J. MD, et al. J AAPOS 2010;14:216-220 (Jun)

What is the best surgical approach to correcting vertical tropias (not associated with DVD, paresis, or IOOA) in the setting of exotropia? This retrospective study compared results of vertical offsets of the horizontal rectus muscles, versus adding a vertical rectus muscle recession to the horizontal procedure. The groups had comparable postoperative results. A high correlation was found between successful, stable horizontal alignment and successful resolution of the hypertropia. Vertical rectus surgery did produce some vertical overcorrections in patients with intermittent exotropia. The authors recommend preoperative prism adaptation in this group of patients.

Surgical outcome of single-staged three horizontal muscles squint surgery for extra-large angle exotropia.

[Lau FH](#), [Fan DS](#), [Yip WW](#), [Yu CB](#), [Lam DS](#). *Eye* 2010 July 24(7), 1171-1176

This is a prospective case series of 24 consecutive patients with primary exotropia >60 prism diopters (PD) at distant who underwent single-staged three horizontal muscle surgery. Surgery consisted of bilateral lateral rectus recession of 9.0 mm for 50 PD exotropic correction. For every 5 PD exceeding 50 PD, an additional 1.0 mm of unilateral medial rectus resection was added. The mean follow-up period was 15.8 months (range 6-38 months). Results of patients with constant versus intermittent exotropia were evaluated. RESULTS: The mean age at surgery was 31 years old (range 7-78 years old). The mean distant preoperative deviation was 71 PD (range 60-85 PD). No limitation of eye movement or diplopia was found. Success was defined as esodeviation or exodeviation less than 10 PD. The success rate was higher in the intermittent group (88%) than the constant group (43%) (P=0.02) and in cases with preoperative deviation of <80 PD (84%) compared with those with deviation \geq 80 PD (40%) (P=0.042). There were no overcorrections. For the unsuccessful patients, all had an undercorrection with a mean of 32 PD of exotropia (range 16-45 PD). 50% of those patients required a second surgery. In the patients with intermittent exotropia the incidence of stereoacuity greater than 55 seconds of arc increased from 18% to 65%. For patients with constant exotropia, stereoacuity could not be demonstrated either preoperatively or post-operatively.

Clinical audit of horizontal strabismus surgery in children in Maharashtra, India.

GOGATE PM, RISHIKESHI N, TARAS S, AGHOR M, DESHPANDE MD *Strabismus* 2010; 18: 13-17.

This retrospective review audited the results of horizontal strabismus surgery for comitant deviations in the pediatric ophthalmology department in Maharashtra, India from 2004 to 2007. Postoperative deviations and patient satisfaction were assessed. Postoperative deviations \leq 10 prism diopters (PD) were considered good outcomes, 11PD-20PD were considered borderline, and >20PD was considered a poor outcome. Five hundred and twenty-nine children (mean age 9 years) underwent surgery, of whom 461 (87.1%) returned for the 6-week follow up exam. Mean preoperative angle for eso- and exo-deviations was 51.9PD (SD 15.5) and mean postoperative deviation was 12.9PD (SD 11.8). At the 6-week follow-up exam, 56.3% (260/461) had a good outcome, 21.6% (100/461) were borderline, and

21.9% (101/461) had poor outcomes. Of those who underwent bilateral medial rectus recessions for esotropia, 44.6% had a good outcome compared to 61.7% with a good outcome following recess-resect procedure (p=0.062). Bilateral lateral rectus recessions for exotropia resulted in a good outcome in 53.6%, while recess-resect procedures resulted in a good outcome in 55.7% (p=0.97). Satisfaction in the surgical outcome was reported by 93.9% of patients and/or parents at the 6-week follow up. The authors concluded that recess-resect procedures had a better outcome than bilateral rectus recession procedures, although the results were not statistically significant.

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Results following eye muscle surgery for secondary sensory strabismus.

GUSEK-SCHNEIDER G, BOSS A: *Strabismus* 2010; 18: 24-31.

This study reported long term follow up after strabismus surgery for secondary sensory strabismus. Twenty-six patients (10 children, 16 adults) who received strabismus surgery for a sensory deviation were investigated. Seven cases had convergent strabismus (SSC) and 19 had divergent strabismus (SSD). Those with a possible underlying primary motility disorder or mechanical restriction were excluded. Twelve of these patients had sensory strabismus secondary to a congenital disorder, and 12 had sensory strabismus following perforating injury. All patients underwent a single recess-resect procedure. The mean follow up after surgery was 5.67 ± 4 years (range 1.67 to 12.67 years) for SSC and 5.83 ± 3.67 years (range 7 months to 13.25 years) for SSD (p=.086). The distance deviation at the final post-operative exam was reduced for both SSC and SSD patients. A correlation between the final postoperative angle at distance and the visual acuity of the affected eye was not found for SSC (r=-0.5, p=0.24), but was found in SSD (r=0.52, p=0.02). This study showed relatively stable long term results following eye muscle surgery for secondary sensory strabismus.

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Superior oblique tucks for apparent inferior oblique overaction and V-pattern strabismus associated with craniosynostosis.

HOLMES JM, HATT SR, LESKE DA: *Strabismus* 2010; 18: 111-115.

Apparent inferior oblique (IO) overaction and apparent superior oblique (SO) underaction are common in strabismus associated with craniosynostosis. It is thought that this type of strabismus may be due to excyclorotation of the globes such that the rectus muscles act with oblique vectors. The authors

present a patient with craniosynostosis who underwent bilateral SO tucks to address the excyclorotation of the globes. A 16-year old male with Saethre-Chotzen syndrome presented with a left esotropia since birth and apparent bilateral IO overaction and SO underaction. He measured 30 prism diopters (PD) of esotropia and a 5PD of left hypertropia by simultaneous prism and cover test (SPCT) at distance and near in primary position. This built to 40PD esotropia at near and distance with a 10PD left hypertropia at distance and 5PD LHT at near) with prism and alternate cover test. The patient had a V-pattern esotropia and fundus examination showed excyclotorsion of both globes. A CT scan confirmed the presence of both SO muscles, and documented the excyclotorsion of each eye. The SO tendons were tucked 10mm bilaterally and the medial rectus muscles were recessed 5.5mm on an adjustable suture with a 10mm inferior displacement. Surgical results were reviewed at 6 weeks and 2 years. The IO overaction, SO underaction, and V-pattern esotropia were markedly improved. The esotropia was reduced to 8PD in primary position at distance, 4PD esotropia at near. There was also a small left dissociated vertical deviation. The authors suggest bilateral SO tucks may be very useful in treating patients with excyclotorsion of the globes due to craniosynostosis.

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Large-angle strabismus: can a single surgical procedure achieve a successful outcome?

THOMAS S, GUHA S: *Strabismus* 2010; 18: 129-136.

This retrospective study evaluates the outcome of concomitant large angle strabismus with different etiologies after a single surgical procedure. An analysis of all operated cases of concomitant large angle strabismus of 50 prism diopters (PD) or more during a 1.5 year period was performed. Patients were excluded if they had incomitant strabismus, previous strabismus surgery or adjustable suture surgery. A successful outcome was defined as a deviation within 10PD of orthophoria/orthotropia for both distance and near, and outcome was assessed at the last follow up visit which was at least 6 weeks postoperative (mean 4.7 months, range 6 weeks-24 months). 50 patients met these criteria (mean age 11.02, range 1-59 years). The overall success rate was 60% (30), with esotropia having a higher success rate of 68.75% than exotropia (44.45%). 33 patients had a 2 muscle surgery with a success rate of 57.58%, while 17 patients had a 3 muscle surgery with a success rate of 64.7%, the difference being statistically insignificant. There was no statistically significant difference between the various age groups analyzed and no statistically significant difference for the type of surgical procedure performed. 12 patients were amblyopic at the time of surgery and had a success rate of 33.33%, which was poorer than the success rate of the remaining 38 patients (68.42%, $p=0.0348$). A good surgical outcome can be obtained in large angle strabismus with a single surgical procedure, but the authors believe a randomized controlled study needs to be done to establish whether 3 muscle surgeries give better results than 2 muscle surgeries.

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Bupivacaine injection to treat exotropia and esotropia.

WUTTHIPHAN S, SRISUWANPORN S: *Strabismus* 2010; 18: 137-141.

Myotoxicity from injection of bupivacaine into an extraocular muscle can induce transient paresis followed by contracture of that muscle. This study reports the results of bupivacaine injection into virgin extraocular muscles of 20 patients with horizontal strabismus. Fifteen had comitant strabismus and five were incomitant secondary to chronic nerve palsies. Bupivacaine, 4.5ml of a 0.50% solution, was injected into the medial rectus muscle in 14 exotropic patients and into the lateral rectus muscle in 6 esotropic patients under electromyographic control. Strabismus measurements were taken before the procedure and 1, 3, 6, and 12 months after injection. The mean age of the 20 patients was 49.75 years (range 16 to 81 years). Fifteen of 20 patients had improved ocular alignment with an average change of 8.4 prism diopters (PD) at 1 month, 8.2PD at 3 months, 8.33PD at 6 months, and 9PD at 12 months. Two of 5 (40%) patients with incomitant strabismus and 13/15 (86.66%) patients with comitant strabismus showed improved ocular alignment. Alignment was improved in 78.57% (11/14) of exotropic patients and 66.66% (4/6) of esotropic patients. The mean deviation at 12 months was 10.5 PD for esodeviations and 6.0 PD for exodeviations. There was no statistical difference in the change in ocular alignment when using bupivacaine as a treatment for esotropic vs. exotropic patients. The authors concluded that bupivacaine injection improved alignment in patients with comitant horizontal strabismus, but denervated extraocular muscles do not respond well.

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Burton J. Kushner, MD. Vertical Rectus Surgery for Knapp Class II Superior Oblique Muscle Paresis. *Arch Ophthalmol.* 2010;128(5):585-588.

The purpose is to evaluate the efficacy of treating Knapp class II superior oblique muscle palsy with 7-mm nasal transposition of the ipsilateral inferior rectus muscle combined with recession of the contralateral inferior rectus muscle when the primary position hypertropia is 10 prism diopters (PD) or less. A retrospective review of 8 consecutive patients with superior oblique muscle paresis who had nasal transposition of the inferior rectus muscle in the paretic eye and recession of the inferior rectus muscle in the nonparetic eye. Ocular motility, including objective and subjective torsion, were evaluated before and after surgery. The mean (SD) preoperative hypertropia was 5 PD (1.5) and 13.1 (3.6) PD in the primary position and downgaze, respectively. After surgery the mean (SD) hypertropia was 1.25 (1.0) and 3.25 (1.3) PD in the primary position and downgaze, respectively. The mean (SD) subjective excyclotropia decreased from 6.6° (1.3°) preoperatively to 0.5° (0.9°) after surgery, and there was a mean (SD) objective decrease in the excyclotorsion of the paretic eye by 7.8° (1.4°). All patients were diplopic before surgery and asymptomatic after surgery. Treatment with 7-mm nasal transposition of the ipsilateral inferior rectus muscle combined with recession of the contralateral inferior rectus muscle can effectively treat Knapp class II superior oblique muscle palsy when the primary position hypertropia is 10 PD or less.

Guo, S et al. Cut and Paste: Sutureless Conjunctival Closure in Strabismus Surgery. JPOS July-August 2010; 47: 228-230.

Study of 12 patients undergoing horizontal strabismus surgery had closure of one eye with 6-0 plain suture and closure of the opposite eye with fibrin glue. Fibrin glue closure provides decreased postoperative inflammation and patient discomfort compared with suture closure. Improved cosmesis also begins sooner in the postoperative period. Another potential benefit of fibrin glue is decreased surgical time under general anesthesia.

Wang L et al. Outcome Study of Unilateral Lateral Rectus Muscle Recession for Small to Moderate Angle Intermittent Exotropia in Children. JPOS July-August 2010; 47: 242-247.

100 consecutive children underwent unilateral lateral rectus muscle recession for small angle exodeviation with a minimum follow-up of six months. All but two patients had deviations of 15-25 prism diopters. Successful alignment was defined as an exodeviation of 5 PD or less and absence of any esotropia in primary and lateral gaze. The amount of the initial post-operative exodeviation was found to be significantly correlated with success at the final examination. 11 of 16 patients undergoing a second surgery had a successful alignment with a mean follow-up of 22 months. The low rate of overcorrection in the unilateral procedure may lower the risk of developing amblyopia and monofixation syndrome (with loss of stereopsis) in visually immature patients. Clinically significant lateral incomitance and abduction limitation were not noted in this study group. This approach limits surgery to one eye, decreases anesthesia time, and leaves other muscles untouched for possible future intervention and should be considered an alternative approach in the treatment of small to moderate angle exotropia.

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IX Cataract

Assessment of Risk Factors for Infantile Cataracts Using a Case-Control Study National Birth Defects Prevention Study, 2000-2004

Prakalapakorn SG, Lambert SR
Ophthalmology 2010;117:1500-1505 (August)

Design: A case-control study of case infants ($n = 152$) and control infants ($n = 4205$) enrolled in the National Birth Defects Prevention Study for birth years 2000-2004.

Results: Maternal interviews were completed for 43 case infants with bilateral and 109 with unilateral infantile cataracts of unknown etiology. Very low birth weight (<1500 g) was associated with both unilateral and bilateral cataracts, whereas low birth weight (1500-2499 g) was only associated with bilateral cataracts. Infants with unilateral cataracts were more likely to be born to primigravid women than women with ≥ 2 previous pregnancies. Suggesting a possible association between unilateral cataracts and maternal substance abuse during pregnancy, and between bilateral cataracts and urinary tract infection during pregnancy and aspirin use during pregnancy.

Reviewers Comments: Genetic Risk

The optics of aphakic and pseudophakic eyes in childhood

McClatchey SK, Hofmeister EM. *Surv Ophthalmol* 2010; 55:174-82. (Mar-Apr 2010).

This article reviews literature involving refractive growth of the eye (e.g. myopic shift in aphakic children, models of refractive growth, impact of cataract surgery on refractive growth), the optical effects of IOL power on myopic shift, and practical issues involving IOL calculation during pediatric cataract surgery. The authors explain that the growth of the eye results in a myopic shift in aphakic and pseudophakic eyes during childhood. Cataract surgery after the age of 6 months, with or without lens implantation, appears to have little effect on the rate of refractive growth. Most children with pseudophakia have a large amount of myopic shift, and this myopic shift is greatest in children with surgery at younger ages. It is also greater in eyes with high-power intraocular lenses due to an optical phenomenon analogous to the effect of vertex distance. The amount of myopic shift and the variance in rate of refractive growth can be predicted using an empiric, logarithmic model. The authors describe a revision of this logarithmic model to extend it patients with surgery before 3 months of age. They also analyze the variance in the rate of refractive growth, based on data from pseudophakic children with the longest follow-up in proportion to age.

Comment: Overall, this is an excellent summary of both theoretical and practical issues involving IOL selection for pediatric cataract surgery.

Changes in central corneal thickness after congenital cataract surgery.

[Faramarzi A](#), [Javadi MA](#), [Bonyadi MH](#), [Yaseri M](#). *J Cataract Refract Surg*. 2010 Dec;36(12):2041-7.

This comparative case series evaluates the central corneal thickness (CCT) changes after congenital cataract surgery with or without intraocular lens (IOL) implantation.

An anterior lensectomy and anterior vitrectomy were performed in eyes with congenital cataract. Eyes had IOL implantation (pseudophakic group) or remained aphakic (aphakic group). The CCT and intraocular pressure were measured in all cases preoperatively and 1 and 6 months postoperatively. Age-matched normal eyes served as a control group.

RESULTS: The study evaluated 47 eyes (30 patients), 32 pseudophakic and 15 aphakic. The mean preoperative CCT was $540 \mu\text{m} \pm 34$ (SD) in the pseudophakic group, $548 \pm 61 \mu\text{m}$ in the aphakic group, and $558 \pm 36 \mu\text{m}$ in the control group ($P = .207$). The mean CCT in the aphakic group was significantly greater than in the pseudophakic group ($587 \pm 65 \mu\text{m}$ versus $539 \pm 37 \mu\text{m}$) 1 month postoperatively ($P = .018$) and at 6 months ($602 \pm 65 \mu\text{m}$ versus $540 \pm 36 \mu\text{m}$) ($P = .012$). Although the CCT values in the pseudophakic group at 1 month and 6 months were similar to preoperative values ($P = .463$ and $P = 1.00$, respectively), both postoperative CCT values in the aphakic group were significantly greater than preoperatively ($P < .001$).

CONCLUSIONS: The preoperative CCT in eyes with congenital cataract was similar to that in normal age-matched eyes. However, shortly after cataract removal, the CCT was significantly greater in aphakic eyes than in pseudophakic eyes. The authors feel that implanting an IOL may be protective. However, they note that although no case of glaucoma was identified postoperatively, the follow up time of six months is short.

X. CATARACT SURGERY

Binocular function in pseudophakic children.

Ing, MR. JPOS 2011;48:13-17. (January/February)

Purpose: Evaluation of binocular function of patients who had primary IOL insertion following removal of cataracts during childhood.

Methods: 21 patients were selected from a consecutive series and observed for a minimum of five years with baseline and serial evaluation of sensory and binocular function.

Results: Mean age of surgery on first eye was 6.3 years. Mean age at the date of the author's examination was 16.5 years with a mean follow-up of 10.3 years. All but two patients had motor alignment within 8 prism diopters of ortho at near. Fusion and stereopsis was found in 15 patients, but only four demonstrated fine (60 seconds of arc or better) stereoacuity. Patients with fine versus gross stereoacuity were similar in age at first surgery, follow-up, and refraction but different in the quality of best-corrected visual acuity.

Conclusions: Despite good motor alignment, fusion, and some stereopsis present in the majority of patients, fine stereoacuity is uncommon in pseudophakic children.

Comment: The monocular visual acuity scores in the patients who demonstrated fine stereoacuity were superior to the visual acuity scores in those patients with a lesser quality of binocularity. This may partially explain why fine stereoacuity was an uncommon finding in this population of pseudophakic children.

Simultaneous vs Sequential Bilateral Cataract Surgery for Infants With Congenital Cataracts

Visual Outcomes, Adverse Events, and Economic Costs

Hreem Dave, BA; Vidya Phoenix, MD; Edmund R. Becker, PhD; Scott R. Lambert, MD

Arch Ophthalmol. August 2010;128(8):1050-1054.

This purpose of this study is to compare the incidence of adverse events and visual outcomes and to compare the economic costs of sequential vs simultaneous bilateral cataract surgery for infants with congenital cataracts. This was a retrospective review of simultaneous vs sequential bilateral cataract surgery for infants with congenital cataracts who underwent cataract surgery when 6 months or younger at our institution. The authors reviewed records available for 10 children who underwent sequential surgery at a mean age of 49 days for the first eye and 17 children who underwent simultaneous surgery at a mean age of 68 days ($P = .25$). They found a similar incidence of adverse events between the 2 treatment groups. Intraoperative or postoperative complications occurred in 14 eyes. The most common postoperative complication was glaucoma. No eyes developed endophthalmitis. The mean (SD) absolute interocular difference in logMAR visual acuities between the 2 treatment groups was 0.47 (0.76) for the sequential group and 0.44

(0.40) for the simultaneous group ($P = .92$). Payments for the hospital, drugs, supplies, and professional services were on average 21.9% lower per patient in the simultaneous group. The authors conclude that simultaneous bilateral cataract surgery for infants with congenital cataracts is associated with a 21.9% reduction in medical payments and no discernible difference in the incidence of adverse events or visual outcomes. However, their small sample size limits our ability to make meaningful comparisons of the relative risks and visual benefits of the 2 procedures.

This paper is also followed by an editorial by Burton Kushner, MD. Dr. Kushner points out that a single devastating complication from procedures can change physicians' practices. He feels that the cost savings of simultaneous bilateral cataract surgery would not outweigh the consequences of bilateral endophthalmitis.

Outcomes of cataract surgery and intraocular lens implantation with and without intracameral triamcinolone in pediatric eyes.

[Dixit NV](#), [Shah SK](#), [Vasavada V](#), [Vasavada VA](#), [Praveen MR](#), [Vasavada AR](#), [Trivedi RH](#). *J Cataract Refract Surg*. 2010 Sep;36(9):1494-8.

This study evaluates whether intracameral triamcinolone has an effect on anterior segment inflammation and visual axis obscuration after pediatric cataract surgery with intraocular (IOL) implantation.

This is a retrospective age-matched case-control, consecutive study of 124 children's eyes having phacoaspiration, posterior capsulectomy, vitrectomy, and IOL implantation. In the study group, eyes received a standardized application of an intracameral preservative-free triamcinolone acetonide suspension intraoperatively. In the control group, age-matched consecutive eyes had surgery with a similar technique but without intracameral preservative-free triamcinolone acetonide. Cell deposits, posterior synechiae, visual axis obscuration, and intraocular pressure (IOP) were evaluated 1 month and 12 months postoperatively.

RESULTS: The mean patient age at surgery was 9.15 months \pm 5.04 (SD) in the study group (41 eyes) and 9.34 \pm 5.10 months in the control group (83 eyes) ($P = .91$). The visual axis was not obscured in any eye in the study group, while 9 eyes (10.8%) in the control group had an obscured axis; the difference between groups was statistically significant ($P < .029$). Six eyes (7.2%) in the control group required secondary membranectomy with pars plana vitrectomy. There was a statistically significant difference between the 2 groups in posterior synechiae and cell deposits (both $P < .033$), whereby the study eyes had less of each finding. There was no significant difference in preoperative or postoperative IOP ($P = .29$ and $P = .50$, respectively) in the two groups. No patient developed glaucoma post-operatively.

The authors conclude that pediatric eyes receiving intracameral triamcinolone intraoperatively had significantly less anterior segment inflammation and no visual axis obscuration after cataract surgery with IOL implantation.

Intracameral triamcinolone acetate after pediatric cataract surgery. [Cleary CA, Lanigan B, O'Keeffe M. *J Cataract Refract Surg.* 2010 Oct;36\(10\):1676-81.](#)

This retrospective case series from 2008 to 2009 assesses the use of preservative-free intracameral triamcinolone as an adjunct to topical steroidal agents after pediatric cataract surgery. Intracameral preservative-free triamcinolone 4 mg/0.1 mL (Triesence) was used immediately after cataract surgery. Clinical indices of anterior segment inflammation were assessed at 1, 7, 14, 21 days and at 6 weeks postoperatively. There were no complications secondary to triamcinolone use in 36 eyes of 26 children. In all but 1 case, intracameral triamcinolone was highly effective in controlling postoperative inflammation after pediatric cataract surgery, resulting in quiet eyes with few inflammatory signs (grade 0 to 1).

CONCLUSION: Intracameral triamcinolone provided a safe and useful adjunct to topical steroid drops after pediatric cataract surgery.

Multifocal IOL implantation in children: is the future clear?

[Rychwalski PJ. *J Cataract Refract Surg.* 2010 Dec;36\(12\):2019-21.](#)

This editorial discusses the study by Cristobal, et al (referenced immediately below this reference). This author discusses the theoretical pros and cons of implanting a multifocal IOL in a child instead of a monofocal IOL. The author notes that Cristobal reports good outcomes. He highlights that although the multifocal IOL may provide children with a greater potential range of focal points for good vision, the pediatric brain may actually be confused by the numerous focal points and incite confusion and produce amblyopia. The small number of patients in the study (5) is a weakness of the study. He recommends further study under the auspices of a strict protocol, consent, and data and safety monitoring.

Multifocal intraocular lenses for unilateral cataract in children.

[Cristóbal JA, Remón L, Del Buey MÁ, Montés-Micó R. *J Cataract Refract Surg.* 2010 Dec;36\(12\):2035-40.](#)

This is a prospective clinical study of five children between 4 and 6 years of age with unilateral cataract who had cataract extraction and implantation of an apodized diffractive multifocal IOL (AcrySof Restor SN60D3). Phacoaspiration was

accompanied by posterior capsulorhexis followed by an anterior vitrectomy. Uncorrected distance (UDVA), corrected distance (CDVA), and corrected near (CNVA) visual acuities; binocular function using the Worth 4-dot test and the TNO stereotest; and subjective symptoms such as glare and halos were evaluated over 21 months of follow-up.

RESULTS: At the final follow-up visit, the mean UDVA was 0.45 ± 0.149 logMAR and the mean CDVA was 0.30 ± 0.06 logMAR with 20/32 in 3 eyes, 20/50 in 1 eye, and 20/63 in 1 eye. The mean CNVA was 0.10 ± 0.05 logMAR (about 20/25) with J1 in 2 eyes, J2 in 1 eye, J3 in 1 eye, and J4 in 1 eye. The stereoacuity was 120 seconds of arc (arcsec) in 2 patients, 240 arcsec in 1 patient, 1980 arcsec in 1 patient, and nonexistent in 1 patient. The Worth 4-dot test showed that 4 patients had fusion. None of the 5 patients complained about halos or glare. No IOL decentration was observed in any patient. These authors conclude that implantation of an apodized multifocal IOL seems to be a satisfactory alternative to monofocal pseudophakia in children with unilateral cataract.

Interocular axial length difference as a predictor of postoperative visual acuity after unilateral pediatric cataract extraction with primary IOL implantation. Gochnauer, A.C. MD,MSCR, Trivedi, R.H. MD,MSCR, Hill, E.G. PhD, Wilson, M.E. MD. J AAPOS 2010;14:20-24. (Feb)

Unilateral infantile cataracts are often associated with interocular axial length difference. The affected eye may be shorter than the unaffected eye, as would be seen in the case of microphthalmia, or longer secondary to axial elongation from visual deprivation. The authors proposed that greater absolute interocular axial length difference in patients with unilateral cataract increases the likelihood of poor final acuity in the affected eye. Patients in this study underwent surgery between ages 7 months and 18 years of age. 64 subjects met inclusion criteria. There was an 83% increase in the odds of poor postoperative visual acuity for every millimeter increase in the absolute interocular axial length difference. Amblyopia therapy compliance was also found to be significantly associated with postoperative visual acuity. The authors postulate that knowing the patient has a higher risk for poor visual acuity postoperatively could change the choice in selection of proper IOL power. These patients might benefit from correction to immediate emmetropia to allow better acuity, rather than hypermetropia, which is usually chosen because of the expected myopic shift. This study was retrospective and a prospective study might be beneficial in validating these findings.

Long-term visual outcome after extraction of unilateral congenital cataracts.

[Allen RJ](#), [Speedwell L](#), [Russell-Eggitt I](#). *Eye* 2010 July 24(7),1263-1267

The aim of this study was to investigate whether useable visual acuity (VA) is a realistic goal in patients with unilateral congenital cataracts. The authors acknowledge that some children do achieve good vision post-operatively. However, given that there is a significant risk of aphakic glaucoma, there is significant cost to the quality of life from patching and there is risk of occlusion amblyopia to the fellow eye from patching they aim to gain new information so that parents and clinicians can have a meaningful discussion about whether to proceed with surgery.

METHODS: A retrospective case review from 1990 onwards from a tertiary referral center was performed. This study included children with unilateral congenital cataract who

underwent cataract surgery with posterior capsulectomy and anterior vitrectomy. All patients wore a contact lens for all or part of the follow-up. None of the patients had a secondary IOL. RESULTS: A total of 62 patients were identified. 32% of aphakic eyes had a final VA of 0.6 LogMAR or better (average 0.34+/-0.17). The average age at the time of surgery was 5.0+/-4.1 weeks. The remaining 68% had vision that was less than 0.6, with 27% having vision of <1.00. The group with vision less than 0.6 (68%) had an average age of 9.7+/-6.5 weeks at the time of surgery. One case (1.6%) achieved a VA of 0.0 and also had demonstrable stereoacuity (110 arc s). Manifest strabismus was present in 85% of cases. Glaucoma developed in 19% of patients: 50% in those children operated on at 4 weeks old or less. 31% discontinued the occlusion regime before the age of 4 years. In most of these cases, occlusion was ceased by the age of 2 years when testing revealed dense amblyopia in the aphakic eye, even if good compliance had previously been achieved. In many cases, this coincided with the child becoming noncompliant with occlusion. CONCLUSIONS: Younger age at time of surgery correlated with better visual outcome, as has been found in previous studies. More than two-thirds of children in our cohort did not develop acuity better than 0.6 LogMAR in their aphakic eye.

Hreem Dave, BA; Vidya Phoenix, MD; Edmund R. Becker, PhD; Scott R. Lambert, MD. Simultaneous vs Sequential Bilateral Cataract Surgery for Infants With Congenital Cataracts: Visual Outcomes, Adverse Events, and Economic Costs. *Arch Ophthalmol.* 2010;128(8):1050-1054. doi:10.1001/archophthalmol.2010.136

This purpose of this manuscript is to compare the incidence of adverse events and visual outcomes and to compare the economic costs of sequential vs simultaneous bilateral cataract surgery for infants with congenital cataracts. The study consisted of a retrospective review of simultaneous vs sequential bilateral cataract surgery for infants with congenital cataracts who underwent cataract surgery when 6 months or younger at our institution. Records were available for 10 children who underwent sequential surgery at a mean age of 49 days for the first eye and 17 children who underwent simultaneous surgery at a mean age of 68 days ($P = .25$). They found a similar incidence of adverse events between the 2 treatment groups. Intraoperative or postoperative complications occurred in 14 eyes. The most common postoperative complication was glaucoma. No eyes developed endophthalmitis. The mean (SD) absolute interocular difference in logMAR visual acuities between the 2 treatment groups was 0.47 (0.76) for the sequential group and 0.44 (0.40) for the simultaneous group ($P = .92$). Payments for the hospital, drugs, supplies, and professional services were on average 21.9% lower per patient in the simultaneous group. The authors conclude that simultaneous bilateral cataract surgery for infants with congenital cataracts is associated with a 21.9% reduction in medical payments and no discernible difference in the incidence of

adverse events or visual outcomes. However, their small sample size limits their ability to make meaningful comparisons of the relative risks and visual benefits of the 2 procedures.

The Infant Aphakia Treatment Study Group. A Randomized Clinical Trial Comparing Contact Lens With Intraocular Lens Correction of Monocular Aphakia During Infancy: Grating Acuity and Adverse Events at Age 1 Year. *Arch Ophthalmol.* 2010;128(7):810-818. Published online May 10, 2010.

This purpose of this manuscript is to compare the visual outcomes and adverse events of contact lens with primary intraocular lens (IOL) correction of monocular aphakia during infancy. In a randomized, multicenter (12 sites) clinical trial, 114 infants with a unilateral congenital cataract were assigned to undergo cataract surgery between 1 to 6 months of age either with or without primary IOL implantation. Contact lenses were used to correct aphakia in patients who did not receive IOLs. Grating visual acuity was tested at 1 year of age by a masked traveling examiner. The main outcome for the study was grating visual acuity at 1 year of age. Results demonstrated that the median logMAR visual acuity was not significantly different between the treated eyes in the 2 groups (contact lens group, 0.80; IOL group, 0.97; $P = .19$). More patients in the IOL group underwent 1 or more additional intraocular operations than patients in the contact lens group (63% vs 12%; $P < .001$). Most of these additional operations were performed to clear lens re proliferation and pupillary membranes from the visual axis. The authors conclude there was no statistically significant difference in grating visual acuity at age 1 year between the IOL and contact lens groups; however, additional intraocular operations were performed more frequently in the IOL group. They recommend that until longer-term follow-up data are available, caution should be exercised when performing IOL implantation in children aged 6 months or younger given the higher incidence of adverse events and the absence of an improved short-term visual outcome compared with contact lens use.

**Axial eye length growth and final refractive outcome after unilateral paediatric cataract surgery
Br J Ophthalmol 2010;94:547-550 (May)**

This paper compared the axial eye length growth of the two fellow eyes within one patient after unilateral paediatric cataract surgery and to assess changes in refraction and keratometry. This is a retrospective study of 90 eyes of 45 patients. The 45 patients were divided into two groups, group 1 (patients younger than 18 months at the time of surgery, $n=25$) and group 2 (patients 18 months or older at the time of surgery, $n=20$). The axial eye length, spherical equivalent refraction and keratometry were measured during surgery and at follow-up. All outcome data in the operated eyes were compared with the outcome data of the fellow non-operated eyes. In group 1 the absolute growth (mm) of the operated eyes was borderline statistically significantly less than in the fellow non-operated eyes ($p=0.049$). No statistically significant difference in the rate of axial growth between the two eyes was found ($p=0.25$). A larger myopic shift ($p=3.85 \times 10^{-5}$) and a larger change in keratometry ($p=0.02$) were found in the operated eyes. In group 2, no statistically significant differences were found between the two eyes. The authors did not find a statistically significant difference in axial length growth between the operated eyes and fellow non-operated eyes in unilateral paediatric cataract patients.

Partial coherence interferometry versus immersion ultrasonography for axial length measurement in children.[Lenhart PD](#), [Hutchinson AK](#), [Lynn MJ](#), [Lambert SR](#). *J Cataract Refract Surg*. 2010 Dec;36(12):2100-4.

The purpose of this study was to determine whether measurements obtained by partial coherence interferometry (PCI) correlate well with measurements obtained using immersion ultrasound (US) in children. Immersion US is the gold standard for measuring Axial Length (AL) in children. It is easy to perform while the child is under general anesthesia but difficult to perform while the child is awake. The advantages of performing PCI on the awake child in the clinic would be less OR time, less time under general anesthesia, and the ability to compare future measurements of growth without the need for general anesthesia.

The charts of 18 pediatric patients (27 eyes) who had cataract surgery from August 2008 to September 2009 were reviewed. Axial length measurements in the operative eye were obtained using PCI at the preoperative clinic visit and then using immersion US in the operating room before surgery. The data were compared to determine the degree of agreement. Preoperative AL measurements by PCI were obtained in 21 eyes (78%). On average, the PCI-measured ALs were 0.1 mm less than the immersion US values (95% confidence interval, -0.2 to -0.1; P = .002). All eyes with an AL of 23.5 mm or less had lower PCI values than immersion US values. There was no systematic pattern of 1 measurement being greater or less than the other in eyes with an AL longer than 23.5 mm.

Depending on the length of the eye, a 0.1 mm error in AL measurement could result in a 0.25 to 0.75 diopter difference in intraocular lens calculation that could be clinically significant in some patients.

Visual axis opacification after cataract surgery and hydrophobic acrylic intraocular lens implantation in the first year of life.[Trivedi RH](#), [Wilson ME](#), [Vasavada AR](#), [Shah SK](#), [Vasavada V](#), [Vasavada VA](#). *J Cataract Refract Surg*. 2011 Jan;37(1):83-7.

This study reports the incidence of visual axis opacification (VAO) requiring surgery after primary posterior capsulectomy, vitrectomy, and in-the-bag hydrophobic acrylic IOL cataract extraction during the first year of life. In bilateral cases, 1 eye was randomly chosen. The need for surgery for visually significant VAO was evaluated 12 months after cataract surgery.

Seventy-two eyes were included. The mean age at cataract surgery was 6.0 months. Seventeen eyes (23.6%) required surgery for VAO a mean of 6.2 ± 2.9 months postoperatively. The odds for VAO surgery were 3.5 times greater in eyes of female children than in eyes of male children. For AcrySof MA60AC, SA60AT, SN60AT, or SN60WF IOLs, surgery for VAO was required in 25%, 23%, 23%, and 23% of eyes, respectively. The earliest time between cataract and secondary VAO surgery was relatively later (9.0 months) with the SN60WF IOL than with the MA60AC, SA60AT, or SN60AT IOL (4.4, 2.2, and 2.0 months, respectively).

CONCLUSIONS: Nearly 25% of operated eyes of infants required a secondary surgical procedure for VAO; the rate was higher in eyes of female infants but did not differ between IOL models. The data indicate that surgery for VAO is required later in eyes with an SN60WF IOL than in eyes in which other AcrySof IOLs were used.

Short-term outcomes of dry pars plana posterior capsulotomy and anterior vitrectomy in paediatric cataract surgery using 25-gauge instruments (Aug)

Br J Ophthalmol 2010;94:1024-1027

This paper evaluated the safety and efficacy of dry pars plana posterior capsulotomy and anterior vitrectomy in paediatric cataract surgery using 25-gauge instruments. This is a retrospective consecutive series of 57 paediatric patients (80 eyes) who underwent dry pars plana posterior capsulotomy and anterior vitrectomy with 25-gauge devices after in-the-bag intraocular lens (IOL) implantation. The mean follow-up period was 13.7 (SD 8.3) months. All IOLs were well centred in the capsular bags. No intraoperative complications were noted to be attributable to the small-gauge instruments. Postoperative hypotony (intraocular pressure <8 mm Hg) was observed in two eyes (2.5%), which spontaneously recovered within 3 days. Eight eyes (10%) had light fibrin reactions and two eyes (2.5%) had mild posterior synechiae. No reopacification of the visual axis, IOL capture, vitreous prolapse, choroidal detachment or retinal detachment was found during the follow-up. The authors concluded that dry pars plana posterior capsulotomy with anterior vitrectomy using 25-gauge instruments after in-the-bag IOL implantation is safe and effective for the management of the posterior lens capsule and anterior vitreous in surgery for paediatric cataract.

XI. REFRACTIVE SURGERY

Laser-assisted subepithelial keratectomy for bilateral hyperopia and hyperopic anisometropic amblyopia in children: one-year outcomes. [Astle WF](#), [Huang PT](#), [Ereifej I](#), [Paszuk A.J](#) *Cataract Refract Surg.* 2010 Feb;36(2):260-7.

PURPOSE: To assess the refractive, visual acuity, and binocular results of laser-assisted subepithelial keratectomy (LASEK) in children with bilateral hyperopia or hyperopic anisometropic amblyopia.

METHODS: This retrospective review comprised children with bilateral hyperopia or hyperopic anisometropic amblyopia who had LASEK. Refractive status, visual acuity, and binocular vision were assessed and recorded 2 months and 1 year postoperatively.

RESULTS: The mean spherical equivalent (SE) in all 72 hyperopic eyes (47 patients) was +3.42 diopters (D) (range 0.00 to +12.50 D) preoperatively and +0.59 D (range -1.25 to +2.00 D) 1 year postoperatively. After LASIK, 41.7% of eyes had improved corrected distance visual acuity (CDVA). No patient had reduced CDVA or loss of fusional ability; there was a 25.0% improvement in stereopsis at 1 year. The mean anisometropic difference in the hyperopic anisometropic amblyopia subgroup (18 eyes, 10 patients) was 4.39 D (range +1.75 to +7.75 D) preoperatively and +0.51 D (range 0 to +0.875 D) at 1 year. One year postoperatively, 83% of anisometropic eyes were within +/-1.00 D of the fellow eye and 94.0% were within +/-3.00 D. Postoperatively, 64.7% of eyes had improved CDVA with no reduced CDVA or loss of fusional ability; there was a 22% improvement in stereopsis at 1 year.

CONCLUSION: Laser-assisted subepithelial keratectomy improved visual acuity in pediatric hyperopia with or without associated hyperopic anisometropic amblyopia.

Comparison of Intraocular Lens Power Calculation Formulae in Pediatric Eyes

Nihalani BR, VanderVeen DK
Ophthalmology 2010;117:1493-1499 (August)

Purpose: To evaluate accuracy of intraocular lens (IOL) power calculation formulae (SRK II, SRK/T, Holladay 1, Hoffer Q) in pediatric eyes. A retrospective case series of 135 eyes of 96 children with congenital, developmental, or acquired cataracts who underwent uncomplicated cataract surgery with IOL implantation by a single surgeon over a 10-year period at Children's Hospital in Boston.

Results: The mean age at surgery was 6.4 years. There was a trend toward greater prediction error (PE) in eyes of younger children (≤ 2 years), shorter AL (AL ≤ 22 mm) and steeper corneas (mean K > 43.5 diopters [D]).

Conclusion: The PE was insignificant in 43% eyes, and similar for all formulae. However, the Hoffer Q was predictable for the highest number of eyes. When the PE was > 0.5 D, most formulae gave an undercorrection, except for the Hoffer Q,

Reviewer's Comments: Excluded all sulcus IOL's and traumatic cataracts

Photorefractive keratectomy for the treatment of purely refractive accommodative esotropia: 6 years' experience **Br J Ophthalmol 2010;94:236-240 (Feb)**

This paper reported the long term outcomes of photorefractive keratectomy (PRK) for the treatment of hyperopia associated with purely refractive accommodative esotropia. This was a retrospective chart review of 40 patients aged 17–39 years who underwent PRK to eliminate their dependence on glasses. Pre- and postoperative best spectacle corrected visual acuity, uncorrected visual acuity, refractive spherical equivalent, ocular alignment and stereoacuity were recorded. Preoperative spherical equivalent was $+3.06$ D hyperopia. The mean final postoperative spherical equivalent was $+0.06$ D. The mean pre-operative esotropia at distance and near was 18.6 prism D. All patients were orthophoric without correction at the 1 month, 1 year and at final postoperative evaluations. Visual acuity, refractive error and alignment remained stable after the 1 year postoperative examination. Stereoacuity was unchanged in 80% of patients postoperatively. There were no complications. The authors concluded that PRK can be used to treat low to moderate hyperopia associated with purely refractive accommodative esotropia in young adults.

Refractive surgery in patients with accommodative and non-accommodative strabismus: 1-year prospective follow-up **Br J Ophthalmol 2010;94:898-902 (Jul)**

This paper wanted to determine the efficacy and safety of keratorefractive surgery in patients with accommodative and non-accommodative strabismus in a prospective study. The preoperative assessment included uncorrected and best-corrected visual acuity, manifest and cycloplegic refraction and orthoptic examination. Laser in situ keratomileusis, laser epithelial keratomileusis and Artisan phakic intraocular lens implantation were performed. All treated eyes had a best corrected visual acuity of at least 6/18 preoperatively. One year postoperatively, visual acuity, refractive error and ocular alignment were reassessed. 28 patients (nine male, 19 female) of mean age 33.0 ± 10.0 years (range 20–59) were included in

the study. Esotropia was present in 16 patients; nine fully accommodative, three partially accommodative and four non-accommodative. Twelve patients had exodeviations; 10 exotropia and two exophoria and a history of strabismus surgery. Excellent visual and refractive outcomes were obtained postoperatively. There was no loss of vision, and one eye gained a line of vision. Fully accommodative esotropes attained orthophoria or microtropia. Improved ocular alignment occurred in partially accommodative esotropes and myopic exotropes. No patient experienced decompensation of strabismus or diplopia. The authors concluded that refractive surgery may be performed successfully in patients with accommodative and non-accommodative strabismus. However, great care must be taken when determining patient suitability.

XII. GENETICS

A Chinese family with progressive childhood cataracts and IVS3+1G>A CRYBA3/A1 mutations

Zhu Y, Shentu X, Wang W, Li J, [Jin C](#), Yao K. *Mol Vis*. 2010 Nov 9;16:2347-53.

Purpose: To characterize disease-causing mutations in a Chinese family with progressive childhood cataracts.

Methods: Clinical characterization and candidate gene sequencing

Results: Affected family members had cataracts in childhood that involved the Y sutures and progressive cortical opacities. Inheritance was autosomal dominant. Sequencing of the CRYBA3/A1 gene revealed mutation IVS3+1 G>A in affected members.

Conclusion: There are many genes that can cause autosomal dominant congenital or early onset cataracts. The crystalline genes, of which CRYBA3/A1 is one, are among the most common. The mutation reported here has been found in other families, but with different types of cataract. This shows that dominant congenital cataract, like other dominant diseases, has variable expressivity—the same mutation can cause a different clinical appearance in different people. It also confirms that crystallin gene mutations are a common cause of congenital cataracts and should be given high priority in screening paradigms.

A family with Townes-Brocks syndrome with congenital hypothyroidism and a novel mutation of the SALL1 gene.

Choi WI, Kim JH, Yoo HW, Oh SH. *Korean J Pediatr*. 2010 Dec;53(12):1018-21. Epub 2010 Dec 31.

Purpose: to describe an unusual presentation of Townes-Brock syndrome (TBS) caused by mutation in the SALL 1 gene.

Methods: Case report.

Results: TBS is an autosomal dominant disorder with features that overlap several other syndromes. In this family congenital hypothyroidism was also present, and a novel mutation in SALL1.

Conclusion: TBS may include coloboma, Duane syndrome, or Arnold Chiari malformation. Other features include dysplastic ears and decreased hearing, abnormal thumbs, congenital heart and kidney problems and in some cases mental retardation. The clinical diagnosis of TBS can be difficult; mutation analysis of SALL1 can help confirm the diagnosis.

Identification of Disease-Causing Mutations in Autosomal Dominant Retinitis Pigmentosa (adRP) Using Next-Generation DNA Sequencing Sara J. Bowne, Lori S. Sullivan, Daniel C. Koboldt, Li Ding, Robert Fulton, Rachel M. Abbott, Erica J. Sodergren, David G. Birch, Dianna H. Wheaton, John R. Heckenlively, Qin Liu, Eric A. Pierce, George M. Weinstock, and Stephen P. Daiger. *IOVS* January 2011 52:494-503; published ahead of print September 22, 2010, doi:10.1167/iovs.10-618

Purpose: To determine whether this new type of sequencing is useful in detecting mutations in patients with retinitis pigmentosa (RP), a monogenic disease in individuals but highly heterogeneous in populations with many different genes, mutations, and inheritance types represented.

Methods: 21 Pairs of affected individuals with apparently dominantly inherited RP had their DNA tested by massively parallel next generation sequencing. One thousand amplicons of of 249,267 unique bases of 46 candidate genes were sequenced with the Roche 454GS FLX Titanium (Roche Diagnostics, Indianapolis, IN) and the Illumina/Solexa GAllx (San Diego) platforms. Bioinformatic analysis of data was performed and segregation of possible disease causing variations within families was investigated.

Results: With the 454 platform, more than 9000 DNA variants were found in the 21 pairs of individuals studied. Variations that were also found in normal controls were removed from analysis, as were variations reported in the literature as benign. This removed about 8000 which were deemed non-disease-causing. Of the remaining variations, duplicate variants in the same family were sought and removed, leaving 420. These were each analyzed as to their location in the gene (e.g. exon vs intron) and whether the variation changed an amino acid. This brought the number of possible disease-causing variations to 112. Traditional Sanger sequencing was then used to sequence the variations identified by the 454 in the samples, to see if they were really there or were artifacts of the 454GS FLX sequencing, which are known to occur. In fact, sequencing of the original samples showed that only 55/112 were actually present in the patient samples. Segregation analysis was then used to see how many of these 55 variations segregated correctly with disease in each family. 43/55 real variations did not segregate with disease in the family, proving they could not be disease causing. 5/10 segregating variants were found to be either known pathogenic mutations, or novel mutations in known RP genes that appeared disease-causing. Of the other 5 segregating variants, 3/5 were subsequently found in normal controls. In the other two, when more affected family members were ascertained the variation no longer segregated with the disease.

Of the 5 true disease-causing mutations found, 3 were in known AD RP or cone-rod dystrophy genes (KLHL7, PRPF31, GUCY2D), however 2 were in RPGR. RPGR is on the X chromosome and causes X-linked RP, but in these two families there were numerous manifesting females, making the pedigrees appear AD (however there was no male to male transmission, so X-linked was still a possibility).

The Illumina platform was used to confirm the validity of the 112 variations that were further analyzed and did confirm their existence in the original DNA.

Conclusions: Next generation, or massively parallel sequencing, is a new technique in which many patients' DNA is sheared into small overlapping pieces, then the pieces are sequenced in a high throughput, inexpensive fashion. Very large amounts of DNA sequence data can be generated much more rapidly than with traditional Sanger sequencing, which is the gold standard. The promise and potential of this technique is that it could be used to identify disease-causing mutations in monogenic diseases such as RP. This study shows that it is possible to use this technique to discover the disease causing mutations in a wide variety of genes in patients with RP. However the bioinformatic analysis of the data from Next Generation sequencing is necessary to make sense of the data, and is very complex. This type of sequencing generates a huge number of "false positives" that must be analyzed and removed. It also has many "false negatives" or misses, that are not as easy to identify. In this study, if the authors had not had numerous family members in each pedigree to check for segregation of variations, they would not have been able to accurately detect the disease-causing mutations, which means it is less useful for singleton patients. The utility of Next Generation sequencing for clinical and research use in ophthalmic genetic eye diseases is still being explored.

Two interesting findings in this study are that in 2 families there were so many manifesting females with RP that the transmission was consistent with autosomal dominant inheritance. X-linked inheritance could be suspected because there was no male to male transmission, but was confirmed by finding mutations in a known X chromosome gene, RPGR. In addition, a family with ADRP had a mutation of GUCY2D as their disease-causing mutation. This gene causes Leber Congenital Amaurosis as well as many other retinal degeneration phenotypes.

Therapeutic potential of valproic acid for retinitis pigmentosa.

Clemson CM, Tzekov R, Krebs M, Checchi JM, Bigelow C, Kaushal S.

Br J Ophthalmol. 2011 Jan;95(1):89-93. Epub 2010 Jul 20

Purpose: To investigate whether valproic acid is a safe and effective treatment for retinitis pigmentosa (RP).

Methods: 13 eyes were examined before and after treatment with systemic valproic acid. The average follow up was 4 months. Endpoints were visual field (VF) area measured from digitized

Goldmann Kinetic Perimetry, and Snellen visual acuity.

Results: 9 eyes demonstrated improved VF, 2 eyes demonstrated no change in VF. This was statistically significant when compared to an expected loss of visual field over time in untreated RP. There was an increase in visual acuity from 20/32 to 20/47 which was also found to be statistically significant based on no expected decrease in visual acuity over this time period.

Conclusion: This study looked at valproic acid as a treatment for RP in 13 eyes over 4 months. RP is a slowly progressive disorder for which 4 month follow up is not adequate. This results of this study are inconclusive and much more data is necessary to evaluate whether there is a role for valproic acid in the treatment of RP.

Deducing the pathogenic contribution of recessive ABCA4 alleles in an outbred population.

Schindler EI, Nylen EL, Ko AC, Affatigato LM, Heggen AC, Wang K, Sheffield VC, Stone EM. Hum Mol Genet. 2010 Oct 1;19(19):3693-701. Epub 2010 Jul 20

Purpose: To determine whether certain mutations in the ABCA4 gene cause a more severe retinal degeneration than others.

Methods: Multiple regression analysis of genotypes and phenotypes in patients with ABCA4 mutations and retinal degeneration.

Results: This analysis revealed quantitative allelic effects on two aspects of the visual phenotype, visual acuity ($P < 10^{-3}$) and visual field ($P < 10^{-7}$). Discordance between visual acuity and visual field in individual patients suggests the existence of at least two non-ABCA4 modifying factors.

Conclusion: This study demonstrates that in recessive diseases, the severity of the phenotype may be determined by relative pathogenicity of the 2 alleles. In Stargardt disease individual patients may be counseled that their disease is likely to be mild vs severe based on which alleles they carry in their mutated ABCA4 genes. The severity of ABCA4 allele combination ranges from patients with 2 mild mutations having almost no symptoms or signs, to patients who have typical "macular dystrophy" Stargardt disease, to patients who progress to a retinitis pigmentosa like phenotype. The findings of this study will facilitate the discovery of factors that modify ABCA4 disease and will also aid in the optimal selection of subjects for clinical trials of new therapies. In clinical trials of Stargardt, it will be important to have mild and severe cases stratified to different interventions to avoid false positives and negatives. This study will also help in prognostication for individual patients who are genotyped.

Genotype-phenotype analysis of the branchio-oculo-facial syndrome.

Milunsky JM, Maher TM, Zhao G, Wang Z, Mulliken JB, Chitayat D, Clemens M, Stalker HJ, Bauer M, Burch M, Chénier S, Cunningham ML, Drack AV, Janssens S, Karlea A, Klatt R, Kini U, Klein O,

Lachmeijer AM, Megarbane A, Mendelsohn NJ, Meschino WS, Mortier GR, Parkash S, Ray CR, Roberts A, Roberts A, Reardon W, Schnur RE, Smith R, Splitt M, Tezcan K, Whiteford ML, Wong DA, Zori R, Lin AE. *Am J Med Genet A*. 2011 Jan;155A(1):22-32. doi: 10.1002/ajmg.a.33783

Purpose: To describe the phenotypic range of Branchio-Oculo-Facial (BOFS) syndrome caused by variations in the TFAP2A gene. Branchio-oculo-facial syndrome (BOFS; OMIM#113620) is a rare autosomal dominant craniofacial disorder with variable expression. Major features include cutaneous and ocular abnormalities, specifically colobomata, characteristic facies, renal, ectodermal, and temporal bone anomalies.

Methods: Case series.

Results: 30 families with clinical and genetic BOFS were included in the study. 26/30 fulfilled the clinical diagnostic criteria. Four of the 30 families lacked one of the cardinal features (cleft lip/palate, cervical cutaneous defect, ectopic thymus) but had definite disease-causing mutations in the TFAP2A gene along with other known features, thus broadening the clinical criteria. A hotspot for mutations in exons 4 and 5 of the TFAP2A gene was found. No strict genotype-phenotype correlation could be found, however the one family without cleft lip/palate is the only one with a deletion, and a family with primarily ocular features of coloboma, congenital cataract, and/or anophthalmos has a novel mutation.

Conclusion: Coloboma, especially associated with cleft lip/palate, premature grey hair, erythematous cutaneous defects near the ear, renal anomalies and/or ectopic thymus or abnormal temporal bone should raise the suspicion for BOFS. Clinical genetic testing is now available, and so far this syndrome has only been associated with mutations in one gene, TFAP2A.

Whirlin Replacement Restores the Formation of the USH2 Protein Complex in Whirlin Knockout Photoreceptors.

Zou J, Luo L, Shen Z, Chiodo VA, Ambati BK, Hauswirth WW, Yang J. *Invest Ophthalmol Vis Sci*. 2011 Jan 6. [Epub ahead of print]

Purpose: Ush2D is an autosomal recessive disorder which includes congenital deafness and retinitis pigmentosa. It is caused by mutations in the Whirlin gene. This study evaluated whether adeno-associated virus (AAV)-mediated whirlin replacement is a treatment option using a mouse model.

Methods: Murine whirlin cDNA driven by the human rhodopsin kinase promoter (hRK) was packaged as an AAV2/5 vector and delivered into the whirlin knockout retina through subretinal injection. The efficiency, efficacy and safety of this treatment were examined using immunofluorescent staining, confocal imaging, immunoelectron microscopy, western analysis, histological analysis and electroretinogram.

Results: The AAV-mediated whirlin expression started at 2 weeks, reached its maximum level at 10 weeks, and lasted up to 6 months post injection. The transgenic whirlin product had a molecular size

and an expression level comparable to the wild-type. It was distributed at the PMC in both rod and cone photoreceptors from the central to peripheral retina. Importantly, the transgenic whirlin restored the cellular localization and expression level of both USH2A and VLGR1 and did not cause defects in the retinal histology and function in the whirlin knockout mouse.

Conclusion: Mutations in Whirlin appear to cause disease by disrupting a protein complex called the Ush2 complex. This complex serves a vital function in photoreceptor cells, so in order for gene therapy to work for this disease the gene replaced under the retina must make its product, then this product must correctly help form the Ush2 protein complex. In this mouse model it was demonstrated that subretinal gene replacement of Whirlin appears to do that, making this disease a very promising candidate for gene therapy.

Gene therapy rescues cone structure and function in the 3-month-old rd12 mouse: a model for midcourse RPE65 leber congenital amaurosis.

Li X, Li W, Dai X, Kong F, Zheng Q, Zhou X, Lü F, Chang B, Rohrer B, Hauswirth WW, Qu J, Pang JJ. Invest Ophthalmol Vis Sci. 2011 Jan 5;52(1):7-15. Print 2011

Purpose: RPE65 function is necessary in the retinal pigment epithelium (RPE) to generate chromophore for all opsins. Its absence results in vision loss and rapid cone degeneration. Recent Leber congenital amaurosis type 2 (LCA with RPE65 mutations) phase I clinical trials demonstrated restoration of vision on RPE65 gene transfer into RPE cells overlying cones. In the rd12 mouse, a naturally occurring model of RPE65-LCA, early cone degeneration was observed; however, some peripheral M-cones remained. A prior study showed that AAV-mediated RPE65 expression can prevent early cone degeneration. The present study was conducted to test whether the remaining cones in older rd12 mice can be rescued.

METHODS: Subretinal treatment with the scAAV5-smCBA-hRPE65 vector was initiated at postnatal day (P)14 and P90. After 2 months, electroretinograms were recorded, and cone morphology was analyzed by using cone-specific peanut agglutinin and cone opsin-specific antibodies.

Results: Gene therapy starting at P14 (age 14 days) resulted in almost wild-type M- and S-cone function and morphology. Delaying gene-replacement rescued the remaining M-cones, and more M-cone opsin-positive cells were identified than were present at the onset of gene therapy, suggesting that opsin expression could be reinitiated in cells with cone sheaths.

CONCLUSIONS: A major question about gene therapy is whether it will be useful in older patients, and in those in whom widespread retinal degeneration has already occurred, or whether it will only be useful very early in disease. For RPE65 this would mean only the youngest patients would benefit

since these mutations in this gene cause Leber Congenital Amaurosis. The results of this study support the concept that gene therapy can stop early cone degeneration, and that delayed treatment can restore the function and morphology of the remaining cones. These results have important implications for the ongoing LCA2 clinical trials.

Novel Properties of Tyrosine-mutant AAV2 Vectors in the Mouse Retina.

Petrus-Silva H, Dinculescu A, Li Q, Deng WT, Pang JJ, Min SH, Chiodo V, Neeley AW, Govindasamy L, Bennett A, Agbandje-McKenna M, Zhong L, Li B, Jayandharan GR, Srivastava A, Lewin AS, Hauswirth WW. *Mol Ther.* 2011 Feb;19(2):293-301. Epub 2010 Nov 2

Purpose: To evaluate whether modifications of the adeno-associated virus (AAV) 2 capsid will lead to better transduction of retinal cells in mouse. This is the most common viral vector being used for subretinal gene therapy.

Methods: The authors evaluated the transduction characteristics of AAV2 vectors containing combinations of multiple tyrosine to phenylalanine mutations in seven highly conserved surface-exposed capsid tyrosine residues following subretinal or intravitreal delivery in adult mice.

Results: Vectors containing single-point mutations of capsid surface tyrosines in serotypes displayed significantly increased transduction efficiency in the retina compared with their wild-type counterparts.

Conclusion: This technique of modifying the capsid of AAV2 to improve its ability to get the gene of interest into retinal cells more efficiently is very important to the future of gene therapy. The authors have shown that it is possible to customize the capsid to make entry into certain cell types of the retina easier than others, with some enabling the transgene to be expressed in all retinal layers.

Leber hereditary optic neuropathy gene therapy clinical trial recruitment: year 1. Lam BL, Feuer WJ, Abukhalil F, Porciatti V, Hauswirth WW, Guy J. *Arch Ophthalmol.* 2010 Sep;128(9):1129-35.

Purpose: To describe the patient profiles of the Leber hereditary optic neuropathy (LHON) Gene Therapy Clinical Trial, year 1. This study aims to identify and characterize affected patients and carriers with the G11778A mutation in mitochondrial DNA for planned gene therapy that will use "allotopic expression" by delivering a normal nuclear-encoded ND4 gene into the nuclei of retinal ganglion cells via an adeno-associated virus vector injected into the vitreous.

Methods: Affected patients and unaffected maternal relatives were screened for the ND1, ND4 and ND6 mitochondrial mutations known to cause LHON. All participants underwent complete neuro-ophthalmic examination, automated visual field testing, pattern ERG, and OCT.

Results: Twenty-five subjects with LHON and 21 carriers positive for the G11778A mitochondrial DNA mutation were recruited. Mean retinal nerve fiber thickness and PERG amplitudes were reduced in the affected patients. Some unaffected carriers had low PERG amplitudes and normal nerve fiber layers. Mean retinal nerve fiber layer thickness was 78.3 micron up to 32 months after vision loss.

Conclusion: Potential candidates for future gene therapy may include affected patients, as late as 32

months after loss of vision, with mildly reduced RNFL thickness or carriers with low PERG amplitudes and normal RNFL thickness, if the PERG amplitude is a predictor of conversion to LHON in these carriers. Patients with LHON can be told that a gene therapy trial is starting for their disorder.

Induction of rapid and highly efficient expression of the human ND4 complex I subunit in the mouse visual system by self-complementary adeno-associated virus.

Koilkonda RD, Chou TH, Porciatti V, Hauswirth WW, Guy J. Arch Ophthalmol. 2010 Jul;128(7):876-83

Purpose: To demonstrate that the ND4 subunit of complex 1, the most common cause of Leber Hereditary Optic Neuropathy (LHON) can be expressed in mouse retina using gene therapy.

Methods: The human ND4 subunit was packaged in self-complementary adeno-associated virus (scAAV2) capsids or single-stranded (ss) AAV2 capsids. These constructs were injected into the vitreous cavities of mice. One week later pattern erg and gene expression of ND4 were evaluated.

Results: Pattern ERG remained normal. Expression of ND4 in retinal ganglion cells was 91% for the scAAV vector and was 51% for the single stranded.

Conclusion: It is possible to deliver the ND4 gene to the retinal ganglion cell layer using AAV mediated gene therapy. This may provide a treatment for the vision loss in LHON!

Gene therapy rescues cone function in congenital achromatopsia.

Komáromy AM, Alexander JJ, Rowlan JS, Garcia MM, Chiodo VA, Kaya A, Tanaka JC, Acland GM, Hauswirth WW, Aguirre GD. Hum Mol Genet. 2010 Jul 1;19(13):2581-93. Epub 2010 Apr 8

Purpose: To determine whether gene therapy can rescue cone function in dogs with achromatopsia.

Methods: Subretinal AAV vector injection of WT human red cone opsin promoter in two canine models of CNGB3 achromatopsia. Vision is daylight was evaluated before and after treatment.

Results: Daylight vision was restored in both dog models. Subretinal administration of rAAV5-hCNGB3 with a long version of the red cone opsin promoter in younger animals led to a stable therapeutic effect for at least 33 months.

Conclusion: It is possible to restore cone function in dogs with mutations in the same gene that commonly causes achromatopsia in humans! The cones were able to be targeted for this therapy. This increases the number of retinal disorders likely to be amenable to gene therapy in humans!

Variations in NPHP5 in patients with nonsyndromic leber congenital amaurosis and Senior-

Loken syndrome.

Stone EM, Cideciyan AV, Aleman TS, Scheetz TE, Sumaroka A, Ehlinger MA, Schwartz SB, Fishman GA, Traboulsi EI, Lam BL, Fulton AB, Mullins RF, Sheffield VC, Jacobson SG. Arch Ophthalmol. 2011 Jan;129(1):81-7

Purpose: To investigate whether mutations in NPHP5 can cause Leber congenital amaurosis (LCA) without early-onset renal disease.

Methods: DNA samples from 276 patients with isolated LCA were screened for variations in the NPHP5 gene after mutations in other known LCA genes had been ruled out.

Results: 9/276 LCA patients (3.2%) had 2 disease-causing mutations in the NPHP5 gene. Six of these mutations have been reported in Senior Loken patients and 3 were novel. All of these 9 patients had severely reduced vision since birth. None of them had renal disease in the first decade of life. 2 patients developed nephronophthisis in the second decade of life.

Conclusion: NPHP5, also called IQCB1, is a gene which has been reported to cause Senior Loken syndrome when mutated. Senior Loken syndrome is Leber Congenital Amaurosis plus renal failure due to nephronophthisis. This study shows that some children with seemingly isolated LCA may have mutations in this same gene. Over time genetic testing has demonstrated over and over that the same mutation can cause different phenotypes in different people, and that different mutations can cause diseases that look clinically similar. With this study we learn that genes whose mutation can cause complex, multiorgan phenotypes are capable of causing individual parts of the syndrome in isolation, and/or of causing the different parts of the phenotype at different times. Thus patients with LCA should have the NPHP5 gene screened whether or not they have known renal disease at the time of diagnosis. LCA patients who have a mutation found in NPHP5 should be followed by a nephrologist because although not all patients will develop nephronophthisis, they are certainly at increased risk.

Invest Ophthalmol Vis Sci. 2011 Feb 11;52(2):834-9. Print 2011.

IQCB1 Mutations in Patients with Leber Congenital Amaurosis.

Estrada-Cuzcano A, Koenekoop RK, Coppieters F, Kohl S, Lopez I, Collin RW, De Baere EB, Roeleveld D, Marek J, Bernd A, Rohrschneider K, van den Born LI, Meire F, Maumenee IH, Jacobson SG, Hoyng CB, Zrenner E, Cremers FP, den Hollander AI.

Invest Ophthalmol Vis Sci. 2011 Feb 11;52(2):834-9. Print 2011.

Purpose. Leber congenital amaurosis (LCA) is genetically heterogeneous, with 15 genes identified thus far, accounting for ~70% of LCA patients. The aim of the present study was to identify new genetic causes of LCA.

Methods. Homozygosity mapping in >150 LCA patients of worldwide origin was performed with high-density SNP microarrays to identify new disease-causing genes.

Results. In three isolated LCA patients, the authors identified large homozygous regions on chromosome 3 encompassing the IQCB1 gene, which has been associated with Senior-Loken syndrome (SLSN), characterized by nephronophthisis and retinal degeneration. Mutation analysis of IQCB1 in these three patients and a subsequent cohort of 222 additional LCA patients identified frameshift and nonsense mutations in 11 patients diagnosed with LCA. On re-inspection of the patient's disease status, seven were found to have developed SLSN, but four maintained the diagnosis of LCA as the kidney function remained normal.

Conclusions. Results show that the onset of renal failure in patients with IQCB1 mutations is highly variable, and that mutations are also found in LCA patients without nephronophthisis, rendering IQCB1 a new gene for LCA. However, these patients are at high risk for developing renal failure, which in early stages is often not recognized and can cause sudden death from fluid and electrolyte imbalance. It is therefore recommended that all LCA patients be screened for IQCB1 mutations.

This study used homozygosity mapping to identify LCA patients who shared homozygous regions of the genome, then investigated the genes that are in the shared region. This is a novel and innovative approach to finding causative genes.

Autosomal recessive best vitelliform macular dystrophy: report of a family and management of early-onset neovascular complications.

Arch Ophthalmol. Iannaccone A, Kerr NC, Kinnick TR, Calzada JI, Stone EM. 2011 Feb;129(2):211-7.

OBJECTIVES: To report a child with early-onset autosomal recessive Best vitelliform macular dystrophy and compound heterozygous BEST1 mutations, the management of a choroidal neovascular membrane with intravitreal bevacizumab in the proband, the benefits of amblyopia therapy in the fellow eye, and the findings in the parents, carriers of heterozygous BEST1 mutations.

METHODS: A 5-year-old white girl presented with monocular visual acuity loss and bilateral vitelliform macular lesions. Her parents were also examined. Examinations included electro-oculograms (EOGs), electroretinograms, imaging studies, and BEST1 gene testing. Interventions included off-label treatment with intravitreal bevacizumab in the left eye and amblyopia therapy in the right eye.

RESULTS: The proband presented with visual acuity of 20/200 OD with an atypical subfoveal vitelliform scar and 20/16 OS with asymptomatic vitelliform deposits. Subfoveal choroidal neovascularization developed at age 6 years, causing marked vision loss (20/200 OS). Visual acuity recovered to 20/20 OS after serial intravitreal bevacizumab injections. Amblyopia therapy improved visual acuity to 20/50 OD. The proband showed subnormal EOG Arden ratios and mild electroretinogram changes. Molecular testing showed missense BEST1 mutations (R141S and R141H) in the proband. Unlike dominant Best vitelliform macular dystrophy, in the heterozygous

parents EOGs were normal and minimal autofluorescence changes were seen.

CONCLUSIONS: Choroidal neovascularization treatment with bevacizumab was associated with vision restoration. Amblyopia treatment also yielded significant benefit. Patients presenting with vitelliform lesions should be screened for BEST1 mutations, even when parents have normal EOG and imaging results.

Comment: Best Disease has an autosomal recessive form, which is more rare than the autosomal dominant form. The recessive form may be more aggressive and vision-threatening, and may be associated with CNV even in childhood.

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

Kumar A, Gottlob I, [McLean RJ](#), Thomas S, Thomas M, Proudlock FA. Invest Ophthalmol Vis Sci. 2011 Jan 10. [Epub ahead of print]

Purpose: Previous studies have found no difference between nystagmus associated with idiopathic infantile nystagmus (IIN) and that associated with albinism. Our 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: We compared oculomotor characteristics and related clinical features between albinism (n=52) and the idiopathic nystagmus associated with FRMD7 mutations (FRMD7-IIN, n=83). 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 to the albinism group ($p < 0.0001$). Nystagmus frequency was significantly lower in albinos (mean=3.3Hz, SD=0.13Hz) compared to the FRMD7-IIN group (mean=4.3Hz, SD=0.18Hz) ($F=14.5$, $p < 0.0001$). Strabismus and anomalous head posture was seen in higher proportions in the albinism group and stereopsis was worse compared to the FRMD7-IIN group ($p < 0.0001$).

Conclusion: We describe for the first time differences in nystagmus characteristics associated with albinism and those associated with FRMD7 mutations leading to IIN. 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 a great paper which demonstrates that nystagmus can look very similar in patients who have very different etiologies. Since all patients were genotyped it is an excellent study. The take-home message is that FRMD7 mutations, which cause X-linked motor nystagmus, are not uncommon. Patients with this type of nystagmus have better vision and stereopsis than children with albinism, and the frequency of nystagmus is on average higher, but it is not possible to diagnose based on just observing the eye movements. Molecular genetic testing is very useful to determine etiology in these patients.

A novel mutation in MIP associated with congenital nuclear cataract in a Chinese family.

Wang KJ, Li SS, Yun B, Ma WX, Jiang TG, Zhu SQ. [Mol Vis](#). 2011 Jan 8;17:70-7.

PURPOSE: To identify the underlying genetic defect in a Chinese family affected with autosomal dominant congenital nuclear cataract.

METHODS: A four-generation Chinese family with inherited nuclear cataract phenotype was recruited. Detailed family history and clinical data were recorded. All reported nuclear cataract-related candidate genes were screened for causative mutations by direct DNA sequencing. Effects of amino acid changes on the structure and function of protein were predicted by bioinformatics analysis.

RESULTS: All affected individuals in this family showed nuclear cataracts. Sequencing of the candidate genes revealed a heterozygous c.559C>T change in the coding region of the major intrinsic protein (MIP), which caused a substitution of highly conserved arginine by cysteine at codon 187 (p.R187C). This mutation co-segregated with all affected individuals and was not observed in unaffected family members or 110 ethnically matched controls. Bioinformatics analysis showed that the mutation was predicted to affect the function and secondary structure of MIP protein.

CONCLUSIONS: This study identified a novel disease-causing mutation p.R187C in MIP in a Chinese cataract family, expanding the mutation spectrum of MIP causing congenital cataract.

Comment: Congenital cataracts are genetically heterogeneous. Many genes must be screened to find the causative gene, and although some mutations are recurrent, many patients and/or families will be found to have a novel mutation, which must then be studied to determine if it is disease-causing or a benign polymorphism. For this reason, giving individual cataract patients and their families a molecular diagnosis is very challenging.

A Novel Mutation of LAMB2 in a Multigenerational Mennonite Family Reveals a New Phenotypic Variant of Pierson Syndrome.

Mohney BG, Pulido JS, Lindor NM, Hogan MC, Consugar MB, Peters J, Pankratz VS, Nasr SH, Smith SJ, Gloor J, Kubly V, Spencer D, Nielson R, Puffenberger EG, Strauss KA, Morton DH, Eldahdah L, [Harris PC](#).

Ophthalmology. 2011 Jan 12. [Epub ahead of print]

PURPOSE: To describe a novel laminin β -2 (LAMB2) mutation associated with nephrotic syndrome and severe retinal disease without microcoria in a large, multigenerational family with Pierson syndrome.

DESIGN: Retrospective chart review and prospective family examination.

PARTICIPANTS: An extended consanguineous family of 52 members.

METHODS: The eyes, urine, and serum DNA were evaluated in all family members after discovering 2 patients, both younger than 10 years, with bilateral retinal detachments and concurrent renal dysfunction. Linkage analysis was performed in the 9 living affected individuals, 7 using the Illumina Human Hap370 Duo Bead Array (Illumina, San Diego, CA) and 2 using GeneChip 10K (Affymetrix, Santa Clara, CA) mapping arrays.

MAIN OUTCOME MEASURES: The prevalence and severity of ocular and kidney involvement and genetic findings.

RESULTS: Eleven affected family members were identified (9 living), all manifesting chronic kidney disease and bilateral chorioretinal pigmentary changes, with or without retinal detachments, but without microcoria or neurodevelopmental deficits, segregating in an autosomal recessive pattern. The causative gene was localized to a 9-Mb region on chromosome 3. Comprehensive gene sequencing revealed a novel LAMB2 variant (c.440A→G; His147R) that was homozygous in the 9 living, affected family members, observed at a frequency of 2.1% in the Old Order Mennonite population, and absent in 91 non-Mennonite controls. The mutation is located in a highly conserved site in the N-terminal domain VI of LAMB2.

CONCLUSIONS: This study describes a novel mutation of LAMB2 and further expands the spectrum of eye and renal manifestations associated with defects in the laminin β -2 chain.

Comment: Mapping arrays such as the Illumina and Affymetrix can make possible “linkage analysis” in relatively small families, especially if the disease is autosomal recessive. In this very nice study they characterize a family with Pierson syndrome a rare disorder characterized by microcoria and nephritic syndrome at birth. They are able to confirm the LAMB2 gene as causative, and show that this novel mutation presents in a novel way—without microcoria and with retinal detachment.

Anti- γ -enolase autoimmune retinopathy manifesting in early childhood.

Ko AC, Hernández J, Brinton JP, Faidley EA, Mugge SA, Mets MB, Kardon RH, Folk JC, Mullins RF, Stone EM. *Arch Ophthalmol*. 2010 Dec;128(12):1590-5.

OBJECTIVE: To describe the clinical, molecular, and serologic findings of a case in which autoimmune retinopathy and early-onset heritable retinal degeneration were both considered in the differential diagnosis.

METHODS: A 3-year-old girl had clinical findings suggestive of a childhood-onset retinal degeneration. Samples of DNA and serum were collected. The coding regions of 11 genes associated with Leber congenital amaurosis were sequenced. The patient's serum reactivity to soluble and insoluble fractions of human retinal protein was compared with that of healthy control subjects (n = 32), patients with inflammatory eye disease (n = 80), and patients with molecularly confirmed retinal degenerations (n = 11). Two-dimensional gel electrophoresis and mass spectrometry were used to

identify a protein that corresponded to a reactive band on Western blot.

RESULTS: No plausible disease-causing mutations were identified in any of the retinal disease genes tested. However, the patient's serum showed reactivity to a single retinal antigen of approximately 47 kDa. Two-dimensional gel electrophoresis and mass spectrometry revealed the major reactive species to be neuron-specific enolase (NSE). Autoantibodies targeting NSE were not observed in any healthy control subjects or patients with inflammatory eye disease. However, anti-NSE activity was found in 1 child with molecularly confirmed Leber congenital amaurosis.

CONCLUSION: This patient's clinical and laboratory findings coupled with the recently discovered role of anti-NSE antibodies in canine autoimmune retinopathy suggest that autoantibodies targeting NSE are involved in the pathogenesis of her disease.

Comment: Patients with many types of retinal degeneration exhibit cells in the vitreous and/or CME and posterior polar cataract. This study points out that autoantibodies and immune mediated inflammation likely play a role in some retinal degenerations, and may offer a means of treatment for some of these disorders. Antiretinal antibodies should be considered in atypical retinal dystrophies in both adults and children.

Preimplantation Genetic Diagnosis for Stargardt Disease.

[Sohrab MA](#), [Allikmets R](#), [Guarnaccia MM](#), [Smith RT](#).

[Am J Ophthalmol](#). 2010 Feb 9. [Epub ahead of print]

PURPOSE: To report the first use of in vitro fertilization (IVF) and preimplantation genetic diagnosis to achieve an unaffected pregnancy in an autosomal-recessive retinal dystrophy.

METHODS: An affected male with Stargardt disease and his carrier wife underwent IVF. Embryos obtained by intracytoplasmic sperm injection underwent single-cell DNA testing via polymerase chain reaction and restriction enzyme analysis to detect the presence of ABCA4 mutant alleles. Embryos were diagnosed as being either affected by or carriers for Stargardt disease. A single carrier embryo was implanted.

RESULTS: Chorionic villus sampling performed during the first trimester verified that the fetus possessed only 1 mutant paternal allele and 1 normal maternal allele, thus making her an unaffected carrier of the disease. A healthy, live-born female was delivered.

Br J Ophthalmol 2010;**94**:121-127 doi:10.1136/bjo.2008.154187

Ophthalmological findings in children and young adults with genetically verified mitochondrial disease

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Abstract

Aim: To describe ophthalmological phenotypes in patients with mitochondrial disease and known genotypes.

Methods: A retrospective study was performed on 59 patients (29 male, 30 female) with a mean age of 11.8 years who had mitochondrial disease with known DNA mutations. Fifty-seven of the 59 subjects underwent a detailed ophthalmological examination including visual acuity (VA), eye motility, refraction, slit-lamp examination, ophthalmoscopy and, in almost one-half of the cases, a full-field electroretinogram (ERG).

Results: Forty-six (81%) of the patients had one or more ophthalmological findings such as ptosis (n=16), reduced eye motility (n=22) including severe external ophthalmoplegia (n=9), strabismus (n=4), nystagmus (n=9), low VA (n=21), refractive errors (n=26), photophobia (n=4), and partial or total optic atrophy (n=25). Pigmentation in the macula and/or periphery was noted in 16 patients. In 10/27 investigated individuals with full field ERG, retinal dystrophy was recorded in six different genotypes representing Kearns–Sayre syndrome (n=5), Leigh syndrome (n=1), Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (n=1), Myoclonus epilepsy with red ragged fibres (MERRF) (n=1), Leber hereditary optic neuropathy (n=1) and mitochondrial myopathy (n=1).

Conclusion: The results show that a majority of patients with mitochondrial disorders have ophthalmological abnormalities. We recommend that an ophthalmological examination, including ERG, be performed on all children and adolescents who are suspected of having a mitochondrial disease.

Comment: weakness: it is a retrospective article, strength: largest cohort of these types of patients to date. Recommend ERG be performed on all pts that we suspect having mitochondrial disease.

Gene therapy for Leber's congenital Amaurosis is safe and effective through 1.5 years after vector administration.

Simonelli F, Maguire AM, Testa F, Pierce EA et al.

Molec Ther 2010 Mar; 18(3):643-650.

The groups' results showed improvement in both subjective and objective measurements of visual/retinal function observed as early as 1 month after subretinal administration of a low dose of AAV@-hrRPE65v2 in 3 patients persisting through the 1.5 year post injection period. They noted improvement in both velocity and amplitude of papillary light reflex testing (PLR) and felt it was particularly relevant, considering the objectivity of the test which is used to probe transmission of retinal signals to higher nervous centers. The test also revealed a sustained improvement in light sensitivity in each of the subjects. Additionally they noted a significant reduction in nystagmus in all subjects continuing thru 1.5 post injection. Even though the subjects received unocular treatment, the nystagmus showed binocular dampening. Two patients had at least 50% reduction in both monocular and binocular nystagmus amplitude in primary gaze. Visual acuity significantly improved in the injected eye in all 3 patients as early as 1 month post injection and continued to improve. An analysis of the mobility tests performed at various time points post injection showed a gradual and more confident behavior of the subjects when navigating the obstacle course. A better perception of the course and its obstacles was evident.

The authors drew several conclusions for the 1.5 year follow-up data in the LCA2 patients treated in this study; 1) transgene expression resulting from AAV delivery is stable over time, thus ruling out the possibility that the improvement in visual function observed is the result of a transient neurotrophic effect induced by the surgical procedure, 2) the kinetics of the improvement with early amelioration which stabilizes over time are consistent with AAV-hrRPE65v2 mediated correction of a visual cycle

enzymatic defect, 3) although longer term follow-up is required, efficacy of gene transfer seems not be affected by the progressive degenerative nature of LCA2 and 4) AAV2 mediated gene transfer to the human retina, similarly to what was observed in muscle and CNS does not elicit the cytotoxic T lymphocyte responses to AAV capsid observed in human liver. The safety and efficacy results reported suggest that the retina is an amenable target for stable AAV2-mediated gene transfer in humans.

Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome.

Zentner GE, Layman WS, Martin DM Scacheri PC.

***Am J Med Genet A* 2010 Mar; 52A(3):674-86.**

This is a compilation of 379 published cases of CHARGE syndrome patients, having undergone molecular testing. CHARGE syndrome (no longer just an association) includes Coloboma of eye, Heart malformations, Atresia of choanae, Retardation of growth, Genital hypoplasia, and Ear anomalies. Of the 379 individuals tested, 254 (67%) were CHD7 mutation-positive, with 125 (33%) mutation negative. Methods of mutation testing varied across sites, but all included full sequencing of coding exons. Of the CHD7 mutations reported thus far, about 72% were nonsense or frameshift, 13% splice site, and 10% were missense. Almost all cases of CHARGE syndrome patients were sporadic, a small number of cases of familial and parent-to-child transmission of CHD7 mutations have been reported. From the 254 CHD7 mutation-positive individuals reported since 2004, the most common clinical findings were temporal bone anomalies (98%) and hearing loss (89%). Ocular colobomas were more common in mutation-positive (75%) than in mutation-negative (65%) individuals. The ocular colobomas were typically bilateral and more frequently involved the optic nerve and/or chorioretina with less frequent involvement of iris and eyelids. The mutation positive individuals were more likely to have inner ear malformations, including semicircular canal aplasia/dysplasia, facial nerve palsy and ocular colobomas and less likely to have delayed growth and development. The authors highly recommend the use of temporal bone CT as a diagnostic tool for evaluation of CHARGE patients. The paper also highlights the recent genetic and genomic studies that have provided functional insights in CHD7 and the pathogenesis of CHARGE syndrome.

Disease Association of the CD103 Polymorphisms in Taiwan Chinese Graves' Ophthalmopathy Patients

Liu YH, et al.

Ophthalmology 2010;117:1645-1651 (August)

Methods: A case-control study of a total of 484 Chinese patients with Graves' disease in Taiwan, including 203 patients with GO and 281 patients without GO. Five single nucleotide polymorphisms (SNPs) in CD103 were genotyped.

Results: The CD103 region on chromosome 17p13 was associated with GO, which may decrease the risk of GO by 1.57-fold.

Conclusions: This study provides evidence for the association of multiple genetic and nongenetic factors toward the development of GO. The results suggest that the presence of the *G* allele in CD103, may protect against the development of GO.

Gene therapy in the second eye of RPE65 deficient dogs improves retinal function.

Annear MD, Bartoe JT, Barker SE, Smith AJ et al.
Gene Ther 2010 Aug. [Epub ahead of print]

The purpose of this study was to evaluate whether immune responses interfered with gene therapy rescue using subretinally delivered recombinant adeno-associated viral vector serotype 2 carrying the RPE65 cDNA gene driven by the human RPE65 promoter (rAAV2.hRPE65p.hRPE65) in the second eye of RPE65^{-/-} dogs that had previously been treated in a similar manner in the other eye. Bilateral subretinal injection was performed in nine dogs with the second eye treated 85-180 days after the first. Electroretinography (ERG) and vision testing showed rescue in 16 of 18 treated eyes, with no significant difference between first and second treated eyes. A serum neutralizing antibody (NAb) response to rAAV2 was detected in all treated animals, but this did not prevent or reduce the effectiveness of rescue in the second treated eye. We conclude that successful rescue using subretinal rAAV2.hRPE65p.hRPE65 gene therapy in the second eye is not precluded by prior gene therapy in the contralateral eye of the RPE65^{-/-} dog. This finding has important implications for the treatment of human LCA type II patients.

Visual acuity in patients with Leber's congenital amaurosis and early childhood-onset retinitis pigmentosa.

Walia S, Fishman GA, Jacobson SG, Aleman TS et al.
Ophthalmology 2010 Jun; 117(6):1190-1198

Purpose: To correlate visual acuity of patients with Leber's congenital amaurosis (LCA) and early childhood onset retinitis pigmentosa (RP) with mutations in underlying LCA genes.

Design: Multicentered retrospective observational study.

Participants: After exclusion of 28 subjects, 169 patients with the diagnosis of LCA and 27 patients with

early childhood-onset RP were included in the study because the underlying mutations in *AiPL1*, *GUCY2D*, *RDH12*, *RPE65*, *CRX*, *CRB1*, *RPGRIP1*, *CEP290*, *LCA5*, and *TULP1* genes could be identified in this cohort of patients.

Methods: We collected data on best-corrected visual acuity as recorded at the time of the patient's most recent visit to one of the participating ophthalmology departments. The median and range of visual acuities for each genetic subtype were calculated separately for the LCA and early childhood-onset RP groups.

Main Outcome Measures: The range and median best-corrected visual acuities for each genetic subtype and age-related mean visual acuities for each genetic subtype.

Results: A wide variation in visual acuity was observed in patients with LCA and *RPE65*, *RDH12*, and *CRB1* mutations, whereas *AiPL1*, *GUCY2D*, *CRX*, and *RPGRIP1* gene mutations were associated with severely decreased visual acuities beginning within the first year of life. It was also noted that patients with either an *RPE65* or *CRB1* mutation have progressive visual loss with advancing age. Onset of visual symptoms after infancy was associated with a relatively better visual prognosis.

Conclusions: The data obtained from this study will help clinicians provide counseling on visual prognosis to patients with known mutations in LCA genes and be of value in future studies aimed at the treatment of LCA and early childhood-onset RP.

Leber congenital amaurosis due to RPE65 mutations and its treatment with gene therapy.

Cideciyan AV.

Prog Retin Eye Res 2010 Sep; 29(5):398-427

Leber congenital amaurosis (LCA) is a rare hereditary retinal degeneration caused by mutations in more than a dozen genes. RPE65, one of these mutated genes, is highly expressed in the retinal pigment epithelium where it encodes the retinoid isomerase enzyme essential for the production of chromophore which forms the visual pigment in rod and cone photoreceptors of the retina. Congenital loss of chromophore production due to RPE65-deficiency together with progressive photoreceptor degeneration cause severe and progressive loss of vision. RPE65-associated LCA recently gained recognition outside of specialty ophthalmic circles due to early success achieved by three clinical trials of gene therapy using recombinant adeno-associated virus (AAV) vectors. The trials were built on multitude of basic, preclinical and clinical research defining the pathophysiology of the disease in human subjects and animal models, and demonstrating the proof-of-concept of gene (augmentation) therapy. Substantial gains in visual function of clinical trial participants provided evidence for physiologically relevant biological activity resulting from a newly introduced gene. This article reviews the current knowledge on retinal degeneration and visual dysfunction in animal models and human patients with RPE65 disease, and examines the consequences of gene therapy in terms of improvement of vision reported.

The revised Ghent nosology for the Marfan syndrome.

Loeys BL, Dietz HC, Braverman AC, Callewaert BL et al.
J Med Genet 2010 Jul; 47(7):476-485

The diagnosis of Marfan syndrome (MFS) relies on defined clinical criteria (Ghent nosology), outlined by international expert opinion to facilitate accurate recognition of this genetic aneurysm syndrome and to improve patient management and counselling. These Ghent criteria, comprising a set of major and minor manifestations in different body systems, have proven to work well since with improving molecular techniques, confirmation of the diagnosis is possible in over 95% of patients. However, concerns with the current nosology are that some of the diagnostic criteria have not been sufficiently validated, are not applicable in children or necessitate expensive and specialised investigations. The recognition of variable clinical expression and the recently extended differential diagnosis further confound accurate diagnostic decision making. Moreover, the diagnosis of MFS whether or not established correctly can be stigmatising, hamper career aspirations, restrict life insurance opportunities, and cause psychosocial burden. An international expert panel has established a revised Ghent nosology, which puts more weight on the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features. In the absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS. In absence of either of these two, the presence of a bonafide FBN1 mutation or a combination of systemic manifestations is required. For the latter a new scoring system has been designed. In this revised nosology, FBN1 testing, although not mandatory, has greater weight in the diagnostic assessment. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults. We anticipate that these new guidelines may delay a definitive diagnosis of MFS but will decrease the risk of premature or misdiagnosis and facilitate worldwide discussion of risk and follow-up/management guidelines.

Clinical and genetic analysis of Korean patients with Marfan syndrome: Possible ethnic differences in clinical manifestations.

Woo YEH, Ki CS, Lee HJ, Kim DK et al.
Clin Genet 2010 Feb; 77(2):177-82

Marfan syndrome (MFS) is an autosomal dominant disorder of the fibrous connective tissue caused by mutations in the fibrillin-1 (*FBN1*) gene. Although clinical and genetic analyses have been performed in various populations, there have been few studies in Korea. The aim of this study was to investigate the clinical characteristics and genetic background of Korean patients with MFS. In 39

Korean patients with MFS who met the Ghent criteria, the most common clinical finding was aortic dilatation and/or dissection (94.9%), whereas only 35.9% of patients had ectopia lentis. The majority of MFS patients had fewer than four of the skeletal findings required to fulfill the major skeletal Ghent criterion for MFS. Only 21% of Korean patients had major skeletal abnormalities and most cases showed only minor skeletal involvement. *FBN1* gene mutations were detected in 35 out of 39 patients (89.7%), which is similar to rates presented in the previous reports. These results suggest that some clinical features in Korean patients with MFS differed from those reported in Western MFS patients.

Cardiovascular manifestations in men and women carrying a *FBN1* Mutation.

Detaint D, Faivre L, Collod-Beroud G, Child AH et al.

Eur Heart J 2010 Aug. [Epub ahead of print]

Aims: In patients with Marfan syndrome and other type-1 fibrillinopathies, genetic testing is becoming more easily available, leading to the identification of mutations early in the course of the disease. This study evaluates the cardiovascular (CV) risk associated with the discovery of a fibrillin-1 (*FBN1*) mutation.

Methods and Results: A total of 1013 probands with pathogenic *FBN1* mutations were included, among whom 965 patients [median age: 22 years (11–34), male gender 53%] had data suitable for analysis. The percentage of patients with an ascending aortic (AA) dilatation increased steadily with increasing age and reached 96% (95% CI: 94–97%) by 60 years. The presence of aortic events (dissection or prophylactic surgery) was rare before 20 years and then increased progressively, reaching 74% (95% CI: 67–81%) by 60 years. Compared with women, men were at higher risk for AA dilatation [≤ 30 years: 57% (95% CI: 52–63) vs. 50% (95% CI: 45–55), $P = 0.0076$] and aortic events [≤ 30 years: 21% (95% CI: 17–26) vs. 11% (95% CI: 8–16), $P < 0.0001$; adjusted HR: 1.4 (1.1–1.8), $P = 0.005$]. The prevalence of mitral valve (MV) prolapsed [≤ 60 years: 77% (95% CI: 72–82)] and MV regurgitation [≤ 60 years: 61% (95% CI: 53–69)] also increased steadily with age, but surgery limited to the MV remained rare [≤ 60 years: 13% (95% CI: 8–21)]. No difference between genders was observed (for all $P > 0.20$). From 1985 to 2005 the prevalence of AA dilatation remained stable (P for trend = 0.88), whereas the percentage of patients with AA dissection significantly decreased (P for trend = 0.01).

Conclusion: The CV risk remains important in patients with an *FBN1* gene mutation and is present throughout life, justifying regular aortic monitoring. Aortic dilatation or dissection should always trigger suspicion of a genetic background leading to thorough examination for extra-aortic features and comprehensive pedigree investigation.

Paucity of skeletal manifestations in Hispanic families with *FBN1* mutations.

Villamizar C, Regalado ES, Fadulu VT, Hasham SN et al.

[javascript:AL_get\(this, 'jour', 'Eur J Med Genet.'\):Eur J Med Genet](#) 2010 Mar-Apr; 53(2):80-4

Marfan syndrome (MFS) is an autosomal dominant condition with pleiotropic manifestations involving the skeletal, ocular, and cardiovascular systems. The diagnosis is based primarily on clinical involvement of these and other systems, referred to as the Ghent criteria. We have identified three Hispanic families from Mexico with cardiovascular and ocular manifestations due to novel *FBN1* mutations but with paucity of skeletal features. The largest family, hMFS001, had a frameshift mutation in exon 24 (3075delC) identified as the cause of aortic disease in the family. Assessment of eight affected adults revealed no major skeletal manifestation of MFS. Family hMFS002 had a missense mutation (R1530C) in exon 37. Four members fulfilled the criteria for ocular and cardiovascular phenotype but lacked skeletal manifestations. Family hMFS003 had two consecutive missense *FBN1* mutations (C515W and R516G) in exon 12. Eight members fulfilled the ocular criteria for MFS and two members had major cardiovascular manifestations, however none of them met criteria for skeletal system. These data suggest that individuals of Hispanic descent with *FBN1* mutations may not manifest skeletal features of the MFS to the same extent as Caucasians. We recommend that echocardiogram, ocular examination and *FBN1* molecular testing be considered for any patients with possible MFS even in the absence of skeletal features, including Hispanic patients

KMeyeDB: A graphical database of mutations in genes that cause eye disease.

Kawamura T, Ohtsubo M, Mitsuyama S, Ohno-Nakamura S et al.

Hum Mutat 2010 Jun; 31(6):667-674.

KMeyeDB (<http://mutview.dmb.med.keio.ac.jp/>) is a database of human gene mutations that cause eye diseases. We have substantially enriched the amount of data in the database, which now contains information about the mutations of 167 human genes causing eye related diseases including retinitis pigmentosa, cone-rod dystrophy, night blindness, Oguchi disease, Stargardt disease, macular degeneration, Leber congenital amaurosis, corneal dystrophy, cataract, glaucoma, retinoblastoma, Bardet–Biedl syndrome, and Usher syndrome. KMeyeDB is operated using the database software MutationView, which deals with various characters of mutations, gene structure, protein functional domains, and polymerase chain reaction (PCR) primers, as well as clinical data for each case. Users can access the database using an ordinary Internet browser with smooth user interface, without user registration. The results are displayed on the graphical windows together with statistical calculations. All mutations and associated data have been collected from published articles. Careful data analysis with KMeyeDB revealed many interesting features regarding the mutations in 167 genes that cause 326 different types of eye diseases. Some genes are involved in multiple types of eye diseases, whereas several eye diseases are caused by different mutations in one gene.

Frequency of Usher Syndrome in two pediatric populations: Implications for genetic screening of deaf and hard of hearing children

Kimberling WJ, Hildebrand MS, Shearer AE, Jensen ML et al.

Genet Med 2010 Aug; 12(8):512-516

Purpose: Usher syndrome is a major cause of genetic deafness and blindness. The hearing loss is usually congenital and the retinitis pigmentosa is progressive and first noticed in early childhood to the middle teenage years. Its frequency may be underestimated. Newly developed molecular technologies can detect the underlying gene mutation of this disorder early in life providing estimation of its prevalence in at risk pediatric populations and laying a foundation for its incorporation as an adjunct to newborn hearing screening programs.

Methods: A total of 133 children from two deaf and hard of hearing pediatric populations were genotyped first for *GJB2/6* and, if negative, then for Usher syndrome. Children were scored as positive if the test revealed ≥ 1 pathogenic mutations in any Usher gene.

Results: Fifteen children carried pathogenic mutations in one of the Usher genes; the number of deaf and hard of hearing children carrying Usher syndrome mutations was 15/133 (11.3%). The population prevalence was estimated to be 1/6000.

Conclusion: Usher syndrome is more prevalent than has been reported before the genome project era. Early diagnosis of Usher syndrome has important positive implications for childhood safety, educational planning, genetic counseling, and treatment. The results demonstrate that DNA testing for Usher syndrome is feasible and may be a useful addition to newborn hearing screening programs.

Imaging of head and neck neoplasms in children

Robson CD.

Pediatr Radiol 2010 Apr; 40(4):499-509

The characteristic imaging appearance for a variety of common and/or important pediatric head and neck tumors will be described in this review. These include benign masses such as hemangioma, teratoma, nerve sheath tumors, juvenile nasopharyngeal angiofibroma and malignant masses such as rhabdomyosarcoma, lymphoma, carcinoma and retinoblastoma. This review focuses primarily on soft tissue tumors.

Next generation sequencing in research and diagnostics of ocular birth defects

Raca G, Jackson C, Warman B, Bair T. et al.

Mol Genet Metab 2010 Jun; 100(2):184-92

Sequence capture enrichment (SCE) strategies and massively parallel next generation sequencing (NGS) are expected to increase the rate of gene discovery for genetically heterogeneous hereditary

diseases, but at present, there are very few examples of successful application of these technologic advances in translational research and clinical testing. Our study assessed whether array based target enrichment followed by re-sequencing on the Roche Genome Sequencer FLX (GS FLX) system could be used for novel mutation identification in more than 1000 exons representing 100 candidate genes for ocular birth defects, and as a control, whether these methods could detect two known mutations in the PAX2 gene. We assayed two samples with heterozygous sequence changes in PAX2 that were previously identified by conventional Sanger sequencing. These changes were a c.527G > C (S176T) substitution and a single base pair deletion c.77delG. The nucleotide substitution c.527G > C was easily identified by NGS. A deletion of one base in a long polyG stretch (c.77delG) was not registered initially by the GS Reference Mapper, but was detected in repeated analysis using two different software packages. Different approaches were evaluated for distinguishing false positives (sequencing errors) and benign polymorphisms from potentially pathogenic sequence changes that require further follow-up. Although improvements will be necessary in accuracy, speed, ease of data analysis and cost, our study confirms that NGS can be used in research and diagnostic settings to screen for mutations in hundreds of loci in genetically heterogeneous human diseases.

Clinical and genetic aspects of neurofibromatosis 1.

Jett K, Friedman JM.

Genet Med 2010 Jan; 12(1):1-11.

Neurofibromatosis 1 is an autosomal dominant disorder characterized by multiple cafe´-au-lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules. Learning disabilities are present in at least 50% of individuals with neurofibromatosis 1. Less common but potentially more serious manifestations include plexiform neurofibromas, optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, scoliosis, tibial dysplasia, and vasculopathy. The diagnosis of neurofibromatosis 1 is usually based on clinical findings.

Neurofibromatosis 1, one of the most common Mendelian disorders, is caused by heterozygous mutations of the *NF1* gene. Almost one half of all affected individuals have de novo mutations. Molecular genetic testing is available clinically but is infrequently needed for diagnosis. Disease management includes referral to specialists for treatment of complications involving the eye, central or peripheral nervous system, cardiovascular system, spine, or long bones. Surgery to remove both benign and malignant tumors or to correct skeletal manifestations is sometimes warranted. Annual physical examination by a physician familiar with the disorder is recommended. Other recommendations include ophthalmologic examinations annually in children and less frequently in adults, regular developmental assessment in children, regular blood pressure monitoring, and magnetic resonance imaging for follow-up of clinically suspected intracranial and other internal tumors.

Epiretinal membranes indicate a severe phenotype of neurofibromatosis type 2.

Sisk RA, Berrocal AM, Scheffler AC, Dubovy SR et al.

Retina 2010 Apr; 30(4 Suppl):S51-S58

Purpose: The purpose of this study was to describe a subset of severely affected patients with neurofibromatosis type 2 (NF2), multiple central nervous system tumors, and characteristic retinal lesions.

Methods: This is a retrospective observational case series of 4 patients with NF2. The time domain-optical coherence tomography findings of three patients have previously been described in another series.

Results: Ophthalmic signs were identified at a mean age of 6 years, and NF2 was diagnosed at a mean age of 11 years. Patients presented with diminished visual acuity in one or both eyes and epiretinal membranes in the absence of posterior vitreous detachment. The biomicroscopic and optical coherence tomography features were distinct from secondary epiretinal membranes or combined hamartomas of the retina and retinal pigment epithelium and pathognomonic for NF2. The

ophthalmic manifestations were recognized before neurologic signs and led to the diagnosis of NF2 in 3 of the 4 patients. Each patient had 2 central nervous system tumors at the time of diagnosis, and 3 of 4 eventually required neurosurgical interventions for symptomatic, compressive lesions at a mean age of 12 years.

Conclusion: Recognition of epiretinal membranes with a characteristic optical coherence tomography appearance may permit early diagnosis in neurologically asymptomatic children with a severe phenotype of NF2.

Utility of optic pathway glioma screening in young children with neurofibromatosis type 1: questions generated by clinical audit

Pilling RF, Lloyd IC, Huson S

Eye (Lond) 2010 Aug. [Epub ahead of print]

Aim: Neurofibromatosis type I (NFI) is a phakomatosis that affects approximately 1 per 3000 live births. About 15% children with NFI develop optic pathway glioma (OPG). The Neurofibromatosis UK society recommend annual ophthalmic screening to identify those children who may have OPG affecting vision and refer for investigation and treatment as necessary.

Methods: We undertook a retrospective audit with three aims: (1) to elicit if departmental screening practice of children with NFI for OPG meets current guidelines, (2) to document the age at which tests of visual function are useful in the diagnosis and screening of OPG, and (3) to document the contribution eye screening has made to the diagnosis of OPG.

Results: A total of 37 children were identified from the clinic register. Overall 43% children met the criterion for an appropriate number of screening episodes. All the children met the visual acuity and optic disc assessment criteria; 84% met the pupil-testing criterion. No child was mature enough to perform visual fields or colour vision testing.

Conclusion: Further education is required to encourage patients to attend eye clinic for screening as the majority of patients failing to reach the standard were due to nonattendances.

No OPGs were detected during 128 screening episodes over approximately 7 years of screening. The authors question the usefulness of including visual field and colour vision assessment in the protocol for this age group.

Therapeutic potential of valproic acid for retinitis pigmentosa.

Clemson CM, Tzekov R, Krebs M, Checchi JM et al.

Br J Ophthalmol 2010 Jul. [Epub ahead of print]

Background/aim: To examine the efficacy and safety of valproic acid (VPA) in patients with retinitis pigmentosa (RP).

Methods: Thirteen eyes were examined before and after brief treatment (average 4 months) with VPA. Visual fields (VF) for each eye were defined using digitized Goldmann Kinetic Perimetry tracings. VF areas were log transformed and VF loss/gain relative to baseline was calculated. Visual acuity was measured using a Snellen chart at a distance of 20 feet (6.1 m). Values were converted to the logarithm of the minimum angle of resolution (logMAR) score.

Results: Nine eyes had improved VF with treatment, two eyes had decreased VF and two eyes experienced no change, with an overall average increase of 11%. Assuming typical loss in VF area without treatment, this increase in VF was statistically significant ($p < 0.02$). An average decrease (0.172) in the logMAR scores was seen in these 13 eyes, which translates to a positive change in Snellen score of approximately 20/47 to 20/32, which was significant ($p < 0.02$) assuming no loss in acuity without treatment. Side effects were mild and well tolerated.

Conclusion: Treatment with VPA is suggestive of a therapeutic benefit to patients with RP. A placebo controlled clinical trial will be necessary to assess the efficacy and safety of VPA for RP rigorously.

XIII. RETINOBLASTOMA

Ultrasound biomicroscopy in the management of retinoblastoma LM Vasquez,, GP Giuliari,, W Halliday, CJ Pavlin, BL Gallie and E He'onEye (2011) 25, 141–147

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.

Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators S Canturk, I Qaddoumi, V Khetan, et al.

Br J Ophthalmol 2010 94: 1432-1436

Background The survival of retinoblastoma in less developed countries (LDCs) and the impact of socioeconomic variables on survival are not widely available in the literature.

Methods A systematic review of publications from LDCs was performed. Articles were from multiple databases and written in seven languages. Results were correlated with socioeconomic indicators.

Lower-income countries (LICs) and middle-income countries (MICs) were included in our analyses.

Results An analysis of 164 publications including 14 800 patients from 48 LDCs was performed.

Twenty-six per cent of the papers were written in languages other than

English. Estimated survival in LICs was 40% (range, 23e70%); in lower MICs, 77% (range, 60e92%)

and in upper MICs, 79% (range, 54e93%; p1/40.001). Significant Differences were also found in the occurrence of metastasis: in LICs, 32% (range, 12e45); in lower MICs, 12% (range, 3e31) and in upper MICs, 9.5% (range, 3e24; p1/40.04). On multivariate analysis, physician density and human development index were significantly associated with survival and metastasis. Maternal Mortality rate and per capita health expenditure were significantly associated with treatment refusal. Conclusions Important information from LDCs is not always available in English or in major databases. Indicators of socioeconomic development and maternal And infant health were related with outcome.

Review: Article gives rough estimate about the trend of survival in RB patients. Talks about the possible lacunae. There are major disparities in the data collection in different countries. This information needs to be kept in mind when extrapolating these results.

Eye movement recordings to investigate a supranuclear component in chronic progressive external ophthalmoplegia: a cross-sectional study

A E Ritchie, P G Griffiths, P F Chinnery, et al. *Br J Ophthalmol* 2010 94: 1165-1168

Background It has been postulated that eye movement disorders in chronic progressive external ophthalmoplegia (CPEO) have a neurological as well as a myopathic component to them.

Aim To investigate whether there is a supranuclear component to eye movement disorders in CPEO using eye movement recordings.

Methods Saccade and smooth pursuit (SP) characteristics together with vestibulo-ocular reflex (VOR) gain and VOR suppression (VORS) gain in 18 patients with CPEO and 34 normal patients were measured using Eyelink II video-oculography.

Results The asymptotic values of the peak velocity main sequence curves were reduced in the CPEO group compared to those of normal patients, with a mean of 1618/s (95% CI 1268/s to 1978/s) compared with 4538/s (95% CI 430 to 4758/s), respectively. Saccadic latency was longer in CPEO (263 ms; 95% CI 250 to 278), compared to controls (185 ms; 95% CI 181 to 189). Smooth pursuit and VOR gains were impaired in CPEO, although this could be explained by non-supranuclear causes. VORS gain was identical in the two groups.

Conclusions This study does not support a supranuclear component to the ophthalmoplegia of CPEO, although the increased latencies observed may warrant further investigation.

Review: This study is interesting in the sense that it showing some new concept behind the CPEO. Inaccuracies associated with eye movements should be taken into consideration when interpreting the results.

Irradiation Toxic Effects During Intra-arterial Chemotherapy for Retinoblastoma : Should We Be Concerned?

Rajakrishnan Vijayakrishnan, MD; Carol L. Shields, MD; Aparna Ramasubramanian, MD; Jacqueline Emrich, PhD; Robert Rosenwasser, MD; Jerry A. Shields, MD

Arch Ophthalmol. November 2010;128(11):1427-1431.

The goal of this paper is to evaluate irradiation toxic effects from fluoroscopy during intra-arterial chemotherapy for retinoblastoma. This is a prospective trial involving eight patients treated with intra-arterial chemotherapy. The main outcome measure was irradiation toxic effects in vital organs. The mean patient age was 29 months (range, 10-74 months) and 63% were male. The mean irradiation dose to the skin of the affected eye was 0.19173 Gy, to the contralateral eye was 0.03533 Gy, to the chest wall was 0.00296 Gy, and to the abdominal wall was 0.00104 Gy. The estimated irradiation dose to the lens in the treatment eye was 0.16 Gy, which, in accumulated doses, could be cataractogenic. The estimated irradiation dose from a single fluoroscopy session to other organs, including the brain (0.05560 Gy), thyroid (0.00192 Gy), bone marrow (0.00059 Gy), and gonads (0.00015 Gy), was far lower than the minimal toxic level. The authors conclude that careful use of fluoroscopy during intra-arterial chemotherapy with limited irradiation exposure is advised. Accumulated irradiation toxic effects following multiple sessions of intra-arterial chemotherapy could be cataractogenic and possibly carcinogenic, especially in irradiation-sensitive patients with retinoblastoma.

Trilateral retinoblastoma: Potentially curable with intensive chemotherapy.

Dunkel IJ, Jubran RF, Gururangan S, Chantada GL et al.

Pediatr Blood Cancer 2010 Mar; 54(3):384-7.

This is a retrospective multicenter review of 13 patients with trilateral Rb treated with intensive chemotherapy, defined as the intention to include high dose chemotherapy with autologous hematopoietic stem cell rescue. Twelve patients had bilateral intra-ocular Rb and one had unilateral disease. Median age at diagnosis of intra-ocular Rb was 8 months. Five patients had trilateral Rb at original diagnosis of intra-ocular Rb; 8 had later onset at median age of 35 months (range 3-60 months). Trilateral sites were pineal (11) and suprasellar (2). Seven patients had localized (M-O) disease while 6 presented with leptomeningeal dissemination (M-1+). One patient died due to toxicity (septicemia and multi-organ failure) while undergoing induction chemotherapy. Three patients developed tumor recurrence prior to receiving high dose chemotherapy with autologous hematopoietic stem cell rescue. Nine patients received high dose chemotherapy at a median of 5 months (range 4-9) post diagnosis of trilateral disease. Five patients survive event-free at a median of 77 months (range 36-104 months) and never received external beam radiation therapy. Four of seven patients with M-O disease survive event-free versus only 1 of 6 patients with M-1+ disease.

Whereas patients with intra-ocular Rb have an excellent prognosis for survival, trilateral disease is rare (6% of bilateral RB) and accounts for a significant proportion of the mortality. These results demonstrate that intensive chemotherapy is potentially curative for patients with trilateral Rb, including those who present symptomatically and with large tumors. There is now an ongoing prospective multi-center trial to better determine the role of intensive chemotherapy in the treatment of patients with trilateral Rb.

Changing causes of enucleation over the past 60 years.

Setlur VJ, Parikh JG, Rao NA.

Graefes Arch Clin Exp Ophthalmol 2010 Apr; 248(4):593-7.

This is a retrospective clinicopathologic study of enucleated globes over the past 60 (1950-2006) years at Doheny Eye Institute. Over time, the total number of enucleated globes per decade decreased from a peak of 1,014 in the 60's to 275 in the 2000's. Glaucoma was the most common cause of enucleation early in the study, comprising 23% and 31% for the 50's and 1960's respectively. The next 3 decades showed a drop in enucleation due to glaucoma. Conversely, neovascular glaucoma increased from 21% to 57% of glaucoma in the same time period. The 1990 and 2000's

each showed a higher proportion of neovascular glaucoma which was significantly different from the lower amounts seen in either 1950's or 60's. However, as the total number of enucleations for all causes steadily decreased, neoplasms represented an increasingly larger proportion. Within the category of neoplasms, a trend between melanoma and Rb was also seen. In the 1950's, 77% of enucleations secondary to neoplasm were due to melanoma. Rb was responsible for 17% of enucleations in the 1950's. In each subsequent decade, Rb made up an increasingly larger share of neoplasms, while melanoma consistently decreased. Trauma did not show a consistent trend over time as glaucoma and tumor did. They did not see a decrease in trauma-related enucleations until after the 1980's. Trauma has then subsequently decreased in each of the last 3 decades, suggesting improved repair starting in the 1980's. Improved medical and surgical treatment of conditions that lead to end-stage eye disease have led to a decrease in total enucleated globes.

Superselective Ophthalmic Artery Chemotherapy as Primary Treatment for Retinoblastoma (Chemosurgery)

Abramson DA, Dunkel IJ, Brodie SE, Marr B, Gobin P
Ophthalmology 2010;117:1623-1629 (August)

Participants: A 3-year prospective, institutional review board-approval clinical trial at Sloan-Kettering Hospital. Twenty-eight eyes of 23 newly diagnosed retinoblastoma patients ages 3-88 months followed for 3-37 months.

Methods: Cannulation of 1 or both ophthalmic arteries in young children with retinoblastoma was performed via the femoral artery under general anesthesia on an outpatient basis and chemotherapy.

Results: Treated 23 newly diagnosed retinoblastoma patients initially with 75 separate intra-arterial chemotherapy infusions over a 3-year period. All children survived. Only 1 of the 28 eyes came to enucleation. No eye was enucleated for ocular complications of the procedure and the only adverse ophthalmic findings were occasional transient lid edema, forehead hyperemia, and loss of nasal lashes. There were no deaths, or transfusions of any blood products. Conclusions: The ophthalmic artery(s) of children can safely be repeatedly cannulated in very young children and high concentrations (but low doses) of chemotherapy infused on an outpatient basis. When used as initial therapy superselective chemotherapy delivered through the ophthalmic artery prevented enucleation, primary radiation or the use of systemic chemotherapy in 27 of 28 eyes.

Reviewers Comments: The technique was minimally toxic to the eye in previously untreated cases, has minimal systemic toxicity, can restore vision in some eyes, can be done repeatedly and will likely replace the use of systemic chemotherapy, external beam radiation, and enucleation for the majority of retinoblastoma cases.

Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy.

Shield CL, Shield JA.

Curr Opin Ophthalmol 2010 May; 21(3):203-12.

PURPOSE OF REVIEW: To provide an update on current management of retinoblastoma

RECENT FINDINGS: The current major treatment strategies for retinoblastoma involve enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. Enucleation is reserved for eyes with extensive retinoblastoma, in which there is no hope for useful vision. Newer implants following enucleation allow excellent cosmetic and motility outcome. Intravenous chemoreduction has been popular for nearly two decades and continues to

provide favorable tumor control for most eyes classified as groups A, B, or C and some D eyes, using the International Classification of Retinoblastoma. Using chemoreduction, there has been an apparent reduction in the incidence of pinealoblastoma in children with germline mutation retinoblastoma. Intra-arterial chemotherapy involves single-agent injection into the ophthalmic artery under careful neurointerventional guidance. This recently popularized therapy can be useful for eyes that fail standard treatments or for some eyes as a primary treatment. Short-term results are favorable but longer follow-up is warranted.

SUMMARY: Progress has been made in the past few years in the management of retinoblastoma with better enucleation implants, chemoreduction-prevention of pinealoblastoma and excellent tumor control, and we face the recently popularized modality of intra-arterial chemotherapy with caution and hope.

Intra-arterial chemotherapy for retinoblastoma: the beginning of a long journey.

Shields CL, Shields JA.

Clin Experiment Ophthalmol 2010 Aug; 38(6):638-43.

Conservative management of retinoblastoma has evolved from external beam radiotherapy to systemic chemotherapy by intravenous route and now to localized chemotherapy by intra-arterial route in some cases. With 16-year experience, systemic chemotherapy has been found effective for minimal to moderately advanced retinoblastoma with tumour control of 90% or better, few side effects and even hope for return of some vision. Localized intra-arterial chemotherapy with delivery under fluoroscopy and catheterization of the ophthalmic artery is now undergoing evaluation and appears to provide striking control for retinoblastoma, particularly recurrent tumour seeds following other therapies. The limitations and complications of this approach have yet to be defined. Toxicity of the chemotherapy to the delicate retinal vessels is unknown. Despite its allure, intra-arterial chemotherapy should be used with caution, as in other fields of paediatric oncology it has been found to provide no advantage over intravenous chemotherapy. Time will tell.

Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery).

Abramson DH, Dunkel IJ, Brodie SE, Marr B, Bogin YP.

Ophthalmology 2010 Aug; 117(8):1623-9.

PURPOSE: To report on our 3-year experience with the use of superselective ophthalmic artery infusion of chemotherapy as initial, primary treatment for intraocular retinoblastoma.

DESIGN: Prospective, institutional review board-approved clinical trial.

PARTICIPANTS: Twenty-eight eyes of 23 newly diagnosed retinoblastoma patients (Reese-Ellsworth [RE] group V, 25 eyes; RE IV, 1 eye; RE III, 1 eye; RE II, 1 eye), ages 3-88 months (mean, 22; median, 11) followed for 3-37 months (mean, 15; median, 14).

METHODS: Cannulation of 1 or both ophthalmic arteries in young children with retinoblastoma was performed via the femoral artery under general anesthesia on an outpatient basis and chemotherapy (melphalan [n = 12], melphalan plus topotecan [n = 7], melphalan plus topotecan and carboplatin [n = 3], or melphalan plus carboplatin [n = 1]) infused.

MAIN OUTCOME MEASURES: Patient survival, eye survival, systemic toxicity, complete blood counts, ophthalmic examination, retinal photography, and electroretinograms.

RESULTS: We treated 23 newly diagnosed retinoblastoma patients initially with 75 separate intra-arterial chemotherapy infusions (range, 1-6 treatments; mean, 3.2) over a 3-year period. All children survived. Only 1 of the 28 eyes came to enucleation (for progressive disease). No eye was enucleated for ocular complications of the procedure and the only adverse

ophthalmic findings were occasional transient lid edema, forehead hyperemia, and loss of nasal lashes. Kaplan-Meier enucleation free was 100% at 12 months and 89% at 2 years (95% confidence interval, 43%-98%). There were no deaths, strokes, or transfusions of any blood products; no effect on red cell count; 9 cycles of grade 3 and 1 cycle of grade 4 neutropenia; and no hospitalizations, episodes of fever/neutropenia, or complications at the site of femoral artery puncture.

CONCLUSIONS: The ophthalmic artery(s) of children can safely be repeatedly cannulated in very young children and high concentrations (but low doses) of chemotherapy infused on an outpatient basis. When used as initial therapy superselective chemotherapy delivered through the ophthalmic artery prevented enucleation, primary radiation or the use of systemic chemotherapy in 27 of 28 eyes.

Differential gene expression profile of retinoblastoma compared to normal retina.

Ganguly A, Shields CL.

Mol Vis 2010 Jul; 16:1292-303

PURPOSE: The retinoblastoma gene (RB1) is a tumor suppressor gene that was first discovered in a rare ocular pediatric tumor called retinoblastoma (RB). The RB1 gene is essential for normal progression through the cell cycle and exerts part of its function through the family of transcription factors (E2F) and many other intermediaries. In the absence of normal RB1, genomic instability and chromosomal aberrations accumulate, leading to tumor initiation, progression, and ultimately metastasis. The purpose of this report was to identify the molecular pathways that are deregulated in retinoblastoma.

METHODS: We compared gene expression signatures of matched normal retinal tissue and retinoblastoma (RB) tumor tissue from six individuals, using microarray analysis followed by statistical and bioinformatic analyses.

RESULTS: We identified 1,116 genes with increased expression and 837 with decreased expression in RB tumor tissue compared to matched normal retinal tissue. Functional categories of the cognate genes with the greatest statistical support were cell cycle (309 genes), cell death (437 genes), DNA replication, recombination and repair (270 genes), cellular growth and proliferation (464 genes), and cellular assembly and organization (110 genes). The list included differentially expressed retinal cone-cell-specific markers. These data indicated the predominance of cone cells in RB and support the idea that the latter group of cells may be the cells of origin for RB.

CONCLUSIONS: The genes differentially expressed in RB as compared to normal retina belong mainly to DNA damage-response pathways, including, but not limited to, breast cancer associated genes (BRCA1, BRCA2), ataxia telangiectasia mutated gene (ATM), ataxia telangiectasia and Rad3 related gene (ATR), E2F, checkpoint kinase 1 (CHK1) genes. In addition, novel pathways, such as aryl hydrocarbon receptor (AHR) signaling, polo-like kinase and mitosis, purine metabolism pathways were involved. The molecules AHR, CHK1, and polo-like kinases are of particular interest because there are several currently available drugs that target these molecules. Further studies are needed to determine if targeting these pathways in RB will have therapeutic value. It is also important to evaluate the relative importance of these pathways in different cells that make up the normal retina.

Pediatric solid tumors and second malignancies: characteristics and survival outcomes.

Vasudevan V, Cheung MD, Yang R, Zhuge Y et al.

J Surg Res 2010 May; 160(2):184-9.

BACKGROUND: To examine the incidence, characteristics, and outcomes for second malignancies following the diagnosis of a primary solid tumor in pediatric patients.

METHODS: The Surveillance, Epidemiology, and End Results (SEER) database was queried from 1973 to 2005, excluding recurrences, in patients <20 y.

RESULTS: A total of 31,685 cases of pediatric solid malignancies were identified. Overall, 177 patients were diagnosed with a unique second malignancy before the age 20 (0.56%). The mean follow-up was for 8.5 y (2 mo-30.8 y). Mean age at diagnosis of the primary tumor was 7.7 y. The most common primary malignancies were CNS tumors (22.5%), followed by soft tissue sarcoma (15.8%), retinoblastoma (14.1%), and bone tumors (13%). Hematologic malignancies (35.5%) were the most common second malignancies noted in the cohort, followed by bone tumors (18%) and soft tissue sarcomas (15%). Hematologic malignancies had a shorter latency (3.1 y) compared with solid second tumors (11.6 y). The overall 10-y survival for the entire cohort was 41.5%. For most tumor categories, development of a secondary malignancy was associated with lower 5- and 10-y survival than expected.

CONCLUSIONS: CNS tumors, retinoblastoma, and soft tissue sarcomas in children are the most common solid primary tumors, with an increased risk of a second malignancy. Leukemia is the most common second malignancy seen in pediatric solid tumors. Second malignancies are associated with significantly reduced survival rates compared with the general childhood cancer population.

What's so special about RB?

Burd CE, Sharpless NE

Cancel Cell 2010 Apr; 17(4):313-4

Comment on: Cancel Cell 2010 Apr; 17(4):376-87

RB, p107, and p130 are highly related proteins, each capable of regulating cellular proliferation. However, only RB is frequently mutated in cancer. In this issue of *Cancer Cell*, Chicas et al. shed new light on this conundrum, defining a "special," nonredundant role for RB in promoting cellular senescence.

Role of genetic testing in retinoblastoma management at a tertiary referral centre.

Pradhan MA, Ng Y, Strickland A, George PM Raizis A et al.

Clin Experiment Ophthalmol 2010 Apr; 38(3):231-6.

BACKGROUND: Retinoblastoma (MIM +180 200) is a malignant neoplasm affecting embryonal retina, associated with mutations in the RB1 gene. This paper investigates the results of RB1 testing in retinoblastoma management in a tertiary referral centre.

METHODS: A retrospective audit of genetic testing for retinoblastoma from 2003 to 2008, to determine epidemiology, rate of mutation detection and spectrum was undertaken. Eligible probands were identified from the department database and hospital records examined. DNA extracted from tumour tissue and/or peripheral blood was analysed. All patients and families underwent genetic counselling.

RESULTS: Twenty patients, including one family, were identified. Eight had bilateral tumours, of whom seven presented before 2 years of age, whereas 10 of 12 unilateral cases presented after 2 years of age. Ten patients (50%) were European, four Maori (20%), three Pacific (15%), two Asian (10%), and one of mixed ancestry (5%). Genetic analysis achieved mutation detection on all affected alleles of all the patients, with tumour tissue available for testing in 19 cases. Ten (40%) had germline mutations (eight bilateral and two unilateral), including one mosaic. 75% of affected Maori had germline mutations compared with 40% Europeans. A wide range of mutations was detected with one novel mutation identified in a familial case.

CONCLUSION: Advances in gene testing have enabled a high rate of mutation detection, particularly when tumour tissue is genotyped. Genetic analysis is integral to the management of retinoblastoma patients allowing enhanced follow-up care, avoidance of unnecessary examinations, family screening, counselling and reproductive planning, with early tumour detection in predisposed individuals.

Trilateral retinoblastoma: Potentially curable with intensive chemotherapy.

Dunkel IJ, Jubran RF, Gurugangan S, Guillermo L et al.

Pediatr Blood Cancer 2010 Mar; 54(3):384-387

Background. Trilateral retinoblastoma has been lethal in virtually all cases previously reported. We describe a series of 13 patients treated with intensive chemotherapy, defined as the intention to include high-dose chemotherapy with autologous hematopoietic stem cell rescue. **Procedure.**

Induction chemotherapy generally included vincristine, cisplatin or carboplatin, cyclophosphamide, and etoposide. Hematopoietic stem cells typically were harvested after the first or second cycle of induction chemotherapy, usually from peripheral blood. High-dose chemotherapy regimens were thiotepa-based (n¼7) or melphalan and cyclophosphamide (n¼3).

Results. Trilateral sites were pineal (n¼11) and suprasellar (n¼2); 7 patients had localized (M-0) disease and six had leptomeningeal dissemination (M-1p). Five patients had trilateral retinoblastoma at original diagnosis of intra-ocular retinoblastoma; eight later developed trilateral disease at a median of 35 months (range 3–60 months) following diagnosis of intra-ocular retinoblastoma. One patient died of toxicity (septicemia and multi-organ system failure) during induction and three developed disease progression prior to high dose chemotherapy. Nine patients received high-dose chemotherapy at a median of 5 months (range 4–9) post-diagnosis of trilateral disease. Five patients survive event-free at a median of 77 months (range 36–104 months) and never received external beam radiation therapy. Four of seven patients with M-0 disease survive event-free versus only one of six patients with M-1p disease. **Conclusions.** Intensive chemotherapy is potentially curative for some patients with trilateral retinoblastoma, especially those with M-0 disease.

Medical radiation exposure and risk of retinoblastoma resulting from new germline *RB1* mutation.

Bunin GR, Felice MA, Davidson W, Friedman DL

Int J Cancer 2010 Jul. [Epub ahead of print]

Although ionizing radiation induces germline mutations in animals, human studies of radiation-exposed populations have not detected an effect. We conducted a case-control study of sporadic bilateral retinoblastoma, which results from a new germline *RB1* mutation, to investigate gonadal radiation exposure of parents from medical sources before their child's conception. Parents of 206 cases from 9 North American institutions and 269 controls participated; fathers of 184 cases and 223 friend and relative controls and mothers of 204 cases and 260 controls provided information in telephone interviews on their medical radiation exposure. Cases provided DNA for *RB1* mutation testing. Of common procedures, lower GI series conferred the highest estimated dose to testes and ovaries. Paternal history of lower GI series was associated with increased risk of retinoblastoma in the child (matched odds ratio (OR)=3.6, 95% confidence interval (CI) 1.2, 11.2, 2-sided *P*=0.02), as was estimated total testicular dose from all procedures combined (OR for highest dose=3.9, 95% CI 1.2, 14.4, *P*=0.02). Maternal history of lower GI series was also associated with increased risk (OR=7.6, 95% CI 2.8, 20.7, *P*<0.001) as was estimated total dose (OR for highest dose=3.0, 95% CI 1.4, 7.0, *P*=0.005). The *RB1* mutation spectrum in cases of exposed parents did not differ from that of other cases. Some animal and human data support our findings of an association of gonadal radiation exposure in men and women with new germline *RB1* mutation detectable in their children, although bias, confounding, and/or chance may also explain the results.

The detection of simulated retinoblastoma by using red-reflex testing.

Li J, Coats DK, Fung D, O'Brien Smith E, Paysse E.

Pediatrics 2010 Jul; 126(1):e202-e207

OBJECTIVE: To determine the ability to detect simulated retinoblastoma by using the red-reflex test.
METHODS: Discs that simulated retinoblastoma lesions were affixed to the retina of model eyes with an 8- or 3-mm pupil. The diameter, height, and location of the discs varied. Five examiners evaluated the red reflex with direct ophthalmoscopy by using straight-on and oblique viewing. The generalized estimating equation was used to assess the effects of pupil dilation and observer viewing orientation on tumor detection.

RESULTS: Significant 3-way interactions between pupil dilation, observer orientation, and tumor diameter ($P = .004$) or height ($P = .02$) were detected; these relationships depended on tumor diameter and height. A similar 3-way interaction was found between pupil dilation, observer orientation, and tumor location in degrees from the fovea ($P = .001$). Oblique viewing and pupillary dilation improved the tumor detection rate. With straight-on viewing, the degree of detection was 48% (95% confidence interval [CI]: 39%–57%) for even the largest lesions, compared with 96% (95% CI: 93%–98%) for oblique viewing. For peripheral lesions, the percentage detection for straight-on viewing was 35% (95% CI: 21%–50%) for 30° from the fovea and 16% (95% CI: 2%–31%) for 60° from the fovea; these detection rates significantly improved with oblique viewing to 70% or higher ($P = .001$).

CONCLUSIONS: Detection of simulated retinoblastoma was better when lesions were large and when oblique viewing and dilation were used. Peripheral location was negatively associated with detection. Red-reflex testing to detect leukocoria may be improved with oblique viewing and pharmacologic dilation.

Diffuse anterior retinoblastoma without retinal involvement.

Longmuir SQ, Syed NA, Boldt HC.

Ophthalmology 2010 Jul. [Epub ahead of print]

Purpose: To present a unique case of an 8.5-year-old child with unilateral, anterior, pseudouveitis. He was found to have unilateral, invasive, small blue cell tumor of the anterior segment that was diagnosed as diffuse infiltrating retinoblastoma despite lack of retinal involvement on fundus examination or histopathologic analysis.

Design: Interventional case report.

Participants: One patient.

Intervention: The patient was treated with topical prednisolone acetate 1% and oral prednisone with no improvement in anterior chamber reaction. The patient underwent fine-needle aspiration biopsy (FNAB) of anterior chamber fluid, the results of which were consistent with a primitive neuroectodermal neoplasm, either retinoblastoma or medulloepithelioma. Retinoblastoma was favored strongly, and the patient underwent enucleation followed by chemotherapy with vincristine, carboplatin, and etoposide, and radiation to the eye socket of 4140 cGy total was performed.

Main Outcome Measures: The patient is alive and tumor free with follow-up of 5 years.

Results: Microscopic examination demonstrated cells similar to those seen on the FNAB infiltrating the iris stroma, trabecular meshwork, Schlemm's canal, and the inner portion of sclera in the region of the angle. No calcifications were identified. Serial sections of the entire globe were performed to determine the origin of the tumor. No retinal involvement was identified, and tumor was not seen to arise from the ciliary epithelium. Immunohistochemistry demonstrated positive staining with synaptophysin and negative staining with leukocyte common antigen and CD34.

Conclusions: This patient represents a case of diffuse anterior retinoblastoma with lack of obvious retinal involvement. Morphologic features typical of medulloepithelioma were not found on pathologic analysis. Although the patient lacked a retinal focus, he is alive at 5 years without evidence of recurrence of tumor.

Review of 676 second primary tumors in patients with retinoblastoma. Association between age at onset and tumor type.

Woo KI, Harbour W.

Arch Ophthalmol 2010 Jul; 128(7):865-870

Objective: To obtain a more accurate understanding of second primary tumors (SPTs) by analyzing a large number of SPTs from the published literature.

Methods: A literature search was performed to identify published cases of SPTs in patients with retinoblastoma. Patient age, radiation field, tumor location, and tumor type were analyzed for statistical association.

Results: The study included 676 SPTs in 602 patients. Median age at diagnosis of SPT was 13.0 years (range, 0.3-60.4 years) for all SPTs, 2.7 years for midline intracranial primitive neuroectodermal tumors, 13.0 years for sarcomas, 27.0 years for melanomas, and 29.0 years for carcinomas. The median age at which SPTs occurred inside the radiation field was younger than that for SPTs occurring outside the radiation field or in patients who did not undergo irradiation ($P_{.001}$). Sarcomas occurred more commonly inside the radiation field ($P_{.001}$). Melanomas, lipomas, leukemias, and lymphomas occurred more commonly outside the radiation field or in patients who did not undergo irradiation ($P_{.001}$).

Conclusions: Retinoblastoma patients pass through multiple windows of susceptibility to specific SPTs. This information will aid health care providers in monitoring this high-risk group, and it provides new insights for studying the underlying genetic predisposition to SPTs.

Differential gene expression profile of retinoblastoma compared to normal retina.

Ganguly A, Shields CL.

Mol Vis 2010 Jul; 16:1292-1303

Purpose: The retinoblastoma gene (*RB1*) is a tumor suppressor gene that was first discovered in a rare ocular pediatric tumor called retinoblastoma (RB). The *RB1* gene is essential for normal progression through the cell cycle and exerts part of its function through the family of transcription factors (E2F) and many other intermediaries. In the absence of normal *RB1*, genomic instability and chromosomal aberrations accumulate, leading to tumor initiation, progression, and ultimately metastasis. The purpose of this report was to identify the molecular pathways that are deregulated in retinoblastoma.

Methods: We compared gene expression signatures of matched normal retinal tissue and retinoblastoma (RB) tumor tissue from six individuals, using microarray analysis followed by statistical and bioinformatic analyses.

Results: We identified 1,116 genes with increased expression and 837 with decreased expression in RB tumor tissue compared to matched normal retinal tissue. Functional categories of the cognate genes with the greatest statistical support were cell cycle (309 genes), cell death (437 genes), DNA replication, recombination and repair (270 genes), cellular growth and proliferation (464 genes), and cellular assembly and organization (110 genes). The list included differentially expressed retinal cone-cell-specific markers. These data indicated the predominance of cone cells in RB and support the idea that the latter group of cells may be the cells of origin for RB.

Conclusions: The genes differentially expressed in RB as compared to normal retina belong mainly to DNA damage response pathways, including, but not limited to, breast cancer associated genes (*BRCA1*, *BRCA2*), ataxia telangiectasia mutated gene (*ATM*), ataxia telangiectasia and *Rad3* related gene (*ATR*), *E2F*, checkpoint kinase 1 (*CHK1*) genes. In addition, novel pathways, such as aryl hydrocarbon receptor (AHR) signaling, polo-like kinase and mitosis, purine metabolism pathways were involved. The molecules AHR, *CHK1*, and polo-like kinases are of particular interest because there are several currently available drugs that target these molecules. Further studies are needed to determine if targeting these pathways in RB will have therapeutic value. It is also important to evaluate the relative importance of these pathways in different cells that make up the normal retina.

A clinicopathological correlation of 67 eyes primarily enucleated for advanced intraocular retinoblastoma.

Wilson MW, Quaddoumi I, Billups C et al.

Br J Ophthalmol Aug. [Epub ahead of print]

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.

Bilateral retinoblastoma presenting at retinopathy of prematurity screening.

Self J, Bush K, Baral VR et al.

Arch Dis Child Fetal Neonatal Ed 2010 Jul; 95(4):F288-F292

Diamniotic, dichorionic, male in vitro fertilisation (IVF) twins were born at 26+6 weeks. Retinopathy of prematurity screening revealed bilateral posterior pole retinoblastoma in twin A at 34 weeks' gestation. Aggressive chemoreduction therapy regressed the tumours significantly, which await definitive treatment (figure 1). Genetic analyses identified a heterozygous mutation in the RB1 gene in the affected twin that was absent in either parent or twin B.

Retinoblastoma is a rare disease caused by an anomaly in the RB1 gene (chromosome 13).

Mechanisms of mutation are varied. Few bilateral cases picked up at retinopathy of prematurity screening have been described previously with even fewer cases in IVF twins.

Several links between infertility and genetic mutations are the focus of much study. Various groups have shown an increased incidence of epigenetic phenomena such as methylation and imprinting defects in the sperm of men with infertility. However, some groups have also linked the techniques of assisted fertility with similar defects. Initial worries that the RB1 anomaly could be due to such epigenetic processes were allayed by the discovery of the RB1 mutation in twin A.

Significant questions regarding the zygosity of the twins were initially raised. Monozygotic twins can arise from division of a developing embryo from day 1 to 15 after fertilisation. Division occurring early enough (days 1–3) can lead to dichorionic and diamniotic, but still monozygotic, pregnancy. This occurs at an increased rate with IVF. Before genetic analysis, there was concern that twin B may share identical DNA, thus having a 100% chance of developing retinoblastoma.

XIV TRAUMA

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* 2011 95: 99-104

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 κ /40.219) 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 κ 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.

An interrater reliability study of a new 'zonal' classification for reporting the location of retinal haemorrhages in childhood for clinical, legal and research purposes
Br J Ophthalmol 2010;94:886-890 (Jul)

This paper reports the development and assessment a new zonal classification of the retina to facilitate the description of the location of retinal haemorrhages in children.

They used a novel zonal classification of the retina based on the anatomical landmarks of the optic disc and vascular arcades. They reviewed a large number of wide field digital retinal images drawn from their database of children with accidental and non-accidental head injury and other encephalopathies. Four expert examiners then independently 'located' 142 retinal haemorrhages by zone, from 31 high quality photographs. The calculated Cohen's unweighted κ scores for all possible pairs of the four raters (ie, six pairs) ranged from 0.86 to 0.92, that is 'almost perfect' agreement. Fleiss' κ for agreement between multiple raters (four) and for multiple categories (three) was 0.8841, that is 'almost perfect' agreement. Cohen's unweighted κ statistic for intrarater reliability gave an overall concordance that ranged from 'substantial' to 'perfect' agreement. The authors concluded that this new retinal zone classification and the use of photographs and templates is a very reliable tool for reporting the location of retinal haemorrhages from multiple aetiologies in children, and may be useful for research and medico-legal reports.

Odds of abuse associated with retinal hemorrhages in children suspected of child abuse.

Binbenbaum G, Mirza-George N, Christian C, Forbes B.

J AAPOS 2009 Jun; 13(3):268-272.

Retrospective study from CHOP of 110 children 15 months or younger suspected of abusive head trauma (AHT) who had an ophthalmological examination. The majority of the children (74%) were younger than 6 months old. Retinal hemorrhage was scored by type, size, location, and extent. The higher the score, the greater the severity.

Forty-five were known abuse and 37% were known accidental. Retinal hemorrhages were found in 32%. The presence of retinal hemorrhages was highly correlated with abuse and the severity was greater. Retinal hemorrhages were more commonly found the younger the child with AHT.

XV Anterior Segment

Mavrakanas, N et al. Pediatric Ocular Rosacea. JPOS March-April 2010; 47: 117-120.

Pediatric ocular rosacea may be misdiagnosed because of a paucity or absence of skin changes in children. A common disease in adults, ocular rosacea is possibly underreported in the pediatric population. An 8 year-old girl presented to the emergency department with decreased vision, photophobia and redness of both eyes of 2.5 years duration. Various treatment modalities had been unsuccessful in resolving her symptoms. Ocular rosacea was diagnosed despite the absence of skin findings. Treatment with ofloxacin 0.3%, fluoromethalone 0.1%, autologous serum eye drops, and oral clarithromycin 250 mg daily was initiated. Corneal findings improved over three weeks of treatment. To the authors knowledge this represents the first successful use of both topical autologous serum and oral clarithromycin for pediatric ocular rosacea.

Augmentin Duo in the treatment of childhood blepharokeratoconjunctivitis

Cehajic-Kapetanovic J, Kwartz J. JPOS 2010;47:356-360. (November/December)

Purpose: To report the use of Augmentin Duo 400/57 (GlaxoSmithKline, UK) in the treatment of childhood blepharokeratoconjunctivitis (BKC).

Methods: Retrospective interventional case series of 7 consecutive patients treated with Augmentin Duo 400/57 for BKC during 18 months were reviewed. Diagnostic criteria for BKC included recurrent chalazia, facial rosacea, recurrent red eye, superficial punctuate keratopathy, corneal neovascularization, and corneal ulcers.

Results: Seven children (age range 6-14 years) were diagnosed with BKC. All received systemic Augmentin Duo 400/57 and showed improvement within the first month of therapy. Six children had no recurrence within 6 months follow-up. No patients experienced side effects from treatment.

Conclusions: Augmentin Duo 400/57 proved to be as effective as current treatments with systemic erythromycin or doxycycline with the advantage of a twice-daily dosage and a superior side-effect profile.

Comment: Introduces yet another potential therapeutic agent for the treatment of BKC in children. Efficacy may be related to either improved compliance with bid dosing or superior sensitivity to Augmentin Duo 400/57 of micro-organisms implicated in BKC.

Relapse Rate of Uveitis Post-Methotrexate Treatment in Juvenile Idiopathic Arthritis

Viera Kalinina Ayuso, Evelyne Leonce van de Winkel, Aniki Rothova, Joke Helena de Boer

American Journal of Ophthalmology

Volume 151, Issue 2, Pages 217-222 (February 2011)

Purpose: To evaluate the efficacy of methotrexate (MTX) and the effect of its withdrawal on relapse rate of uveitis associated with juvenile idiopathic arthritis (JIA).

Design: Retrospective case series.

Methods: Data of 22 pediatric JIA patients who were being treated with MTX for active uveitis were studied retrospectively. Relapse rate after the withdrawal of MTX was established. Anterior chamber (AC) inflammation, topical steroid use during the first year of MTX treatment, and associations of relapses after the withdrawal were evaluated statistically. Duration of MTX treatment and its withdrawal was determined individually in collaboration with a rheumatologist with an intention to continue the treatment for at least 1 year and to withdraw in case of inactivity of uveitis and arthritis. Inactivity of uveitis was defined as the presence of $\leq 0.5+$ cells in the AC.

Results: Eighteen patients (18/22; 82%) showed improvement of their uveitis with a significant decrease in activity of AC inflammation after a minimal period of 3 months of MTX treatment. A topical steroid-sparing effect was observed when MTX was administered for a period of 3 to 9 months. MTX was discontinued because of inactive uveitis in 13 patients. In 9 patients (8/13; 69%) a relapse of uveitis was observed after a mean time of 7.5 months (\pm SD 7.3). Six patients (6/13; 46%) had a relapse within the first year after the withdrawal. Relapse-free survival after withdrawal of MTX was significantly longer in patients who had been treated with MTX for more than 3 years ($P = .009$), children who were older than 8 years at the moment of withdrawal ($P = .003$), and patients who had an inactivity of uveitis of longer than 2 years before withdrawal of MTX ($P = .033$). Longer inactivity under MTX therapy was independently protective for relapses after the withdrawal (hazard ratio = 0.07; 95% confidence interval 0.01-0.86; $P = .038$), which means that 1-year increase of duration of inactive uveitis before the withdrawal of MTX results in a decrease of hazard for new relapse of 93%.

Conclusions: A high number of patients with inactive uveitis relapse quickly after the withdrawal of MTX. Our results suggest that a longer period of inactivity prior to withdrawal and a longer treatment period with MTX reduce the chance of relapse after withdrawal.

Comment: Steroid-sparing agents are being used more often now for patients with uveitis. Although we wish to taper and stop medication as soon as possible, these findings should make us pause when considering stopping methotrexate, particularly if inactivity has been present for less than one year.

Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis J C
Goebel, M Roesel, C Heinz, et al. 2010 *Br J Ophthalmol* 2011 95: 209-213

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

Long-term ocular complications in aphakic versus pseudophakic eyes of children with juvenile idiopathic arthritis-associated uveitis. K M Sijssens, L I Los, A Rothova, et al. *Br J Ophthalmol* 2010 94: 1145-1149

Aim To evaluate the long-term follow-up of aphakic and pseudophakic eyes of children with juvenile idiopathic arthritis (JIA)-associated uveitis with a special interest in whether intraocular lens implantation increases the risk of developing ocular complications.

Methods Data were obtained from the medical records of 29 children (48 eyes) with JIA-associated uveitis operated on for cataract before the age of 16 years from January 1990 up to and including March 2007. Main outcome measures were long-term postsurgical complications and visual acuity in aphakic and pseudophakic eyes of children with JIA-associated uveitis.

Results The number of complications after cataract extraction including new onset of ocular hypertension and secondary glaucoma, cystoid macular oedema and optic disc swelling did not differ between aphakic and pseudophakic eyes. Moreover, no hypotony, perilenticular membranes and phthisis were encountered in the pseudophakic group. Better visual acuity was observed in the pseudophakic eyes up to and including 7 years of follow-up (p1/40.012 at 7 years of follow-up). No differences in the preoperative or adjuvant perioperative treatment with periocular or systemic corticosteroids were found between the two groups; however, significantly more children were treated with methotrexate in the pseudophakic group (p1/40.006).

Conclusion With maximum control of perioperative inflammation and intensive follow-up, the implantation of an intraocular lens in well-selected eyes of children with JIA-associated uveitis is not associated with an increased risk of ocular hypertension, secondary glaucoma, cystoid macular oedema and optic disc swelling and showed better visual results up to and including 7 years after cataract extraction.

Review: The numbers of pseudophakic were more than aphakic. The sample size was very small, especially who had longer follow up.

XVI Retina

Congenital vascular malformations of the retina and choroid.

[Heimann H](#), [Damato B](#). *Eye* 2010 March 24(3), 459-467

This article is a review of the current literature on retinal hemangioblastoma, racemose hemangiomas, retinal cavernous hemangioblastoma, circumscribed choroidal hemangioma, and diffuse choroidal hemangioma. The management of patients with congenital vascular lesions of the retina and choroid is advancing rapidly through recent developments in genetic testing, ocular imaging, and treatment. Ocular imaging devices can aid in the measurement of the tumors and OCT can aid in the detection of maculopathy. Most are associated with systemic disease, which may be life-threatening. New therapeutic methods such as Verteporfin photodynamic therapy and anti-angiogenic therapy have significantly improved the treatment of retinal and choroidal angiomas and vascular malformations. Ophthalmologists have a major role in detecting and diagnosing these tumors and in providing long-term care in collaboration with a specialist in the field. This article defines the differences between the different types of vascular tumors, and is worth reading in its entirety by ophthalmologists.

Therapeutic potential of valproic acid for retinitis pigmentosa C M Clemson, R Tzekov, M Krebs, et al 2010 *Br J Ophthalmol* 2011 95: 89-93

Background/aim To examine the efficacy and safety of valproic acid (VPA) in patients with retinitis pigmentosa (RP).

Methods Thirteen eyes were examined before and after brief treatment (average 4 months) with VPA. Visual fields (VF) for each eye were defined using digitised

Goldmann Kinetic Perimetry tracings. VF areas were log transformed and VF loss/gain relative to baseline was calculated. Visual acuity was measured using a Snellen chart at a distance of 20 feet (6.1 m). Values were converted to the logarithm of the minimum angle of resolution (logMAR) score.

Results Nine eyes had improved VF with treatment, two eyes had decreased VF and two eyes experienced no change, with an overall average increase of 11%. Assuming typical loss in VF area without treatment, this increase in VF was statistically significant ($p < 0.02$). An average decrease (0.172) in the logMAR scores was seen in these 13 eyes, which translates to a positive change in Snellen score of approximately 20/47 to 20/32, which was significant ($p < 0.02$) assuming no loss in acuity without treatment. Side effects were mild and well tolerated.

Conclusion Treatment with VPA is suggestive of a therapeutic benefit to patients with RP. A placebo controlled clinical trial will be necessary to assess the efficacy and safety of VPA for RP rigorously.

Review: Novel treatment option, but small sample size. It is just a pilot study showing marginal improvement in Visual function in Retinitis pigmentosa patients.

Petros E. Carvounis, MD, FRCSC; Jed Poll, MD; Mitch P. Weikert, MD; Kirk Wilhelmus, MD; Rohit R. Lakhnani, MD; Eric R. Holz, MD. Refractive Outcomes of Lens-Sparing Vitrectomy for Retinopathy of Prematurity. *Arch Ophthalmol.* 2010;128(7):843-846.

The purpose of this paper is to evaluate the refractive outcomes of 3-port lens-sparing vitrectomy (LSV) for subtotal retinal detachments owing to retinopathy of prematurity. The study included 9 infants who had undergone complete ablative laser treatment for threshold retinopathy of prematurity in both eyes, subsequently developed stage 4A retinal detachment in 1 eye for which they underwent LSV, and maintained complete retinal attachment bilaterally. Eyes that underwent LSV were compared with fellow eyes. Cycloplegic refraction was performed, and corneal curvature, axial length, lens thickness, lens position, and anterior chamber depth were measured. There was significantly less myopia was present in eyes that had undergone LSV compared with control eyes (mean spherical equivalent, -6.78 vs -10.33 diopter [D]; $P < .001$). The reduced myopia in LSV eyes was predominantly owing to increased anterior chamber depth (mean, 3.81 vs 2.96 mm; $P < .001$) and a more posterior position of the lens (mean, 5.58 vs 4.63 mm; $P < .001$). There was a minor contribution from reduced corneal power in LSV eyes (mean, 43.90 vs 44.20 D; $P = .02$). There was no significant difference in axial length, lens thickness, or lens power between LSV and control eyes. Infant eyes undergoing 3-port LSV for stage 4A retinopathy of prematurity develop less myopia than fellow eyes treated with ablative laser alone. The difference is owing to posterior displacement of the lens, with a smaller contribution from reduced corneal power. The reduction in myopia may explain the excellent functional outcomes following 3-port LSV for stage 4A retinopathy of prematurity.

Mark K. Walsh, MD, PhD; Kimberly A. Drenser, MD, PhD; Antonio Capone Jr, MD; Michael T. Trese, MD. Early Vitrectomy Effective for Norrie Disease. *Arch Ophthalmol.* 2010;128(4):456-460.

The purpose is to review our experience with Norrie disease to determine if early vitrectomy abrogates the natural history of this rare disease; namely, bilateral no light perception visual acuity and phthisis bulbi. We retrospectively reviewed the medical records of all patients seen in our tertiary care pediatric retinal clinical practice from 1988 through 2008 with a potential diagnosis of Norrie disease. Inclusion required not only clinical findings consistent with Norrie disease but also genetics and/or a family history consistent with Norrie disease. Medical record review revealed 14 boys with clinically diagnosed Norrie disease and either Norrie disease gene (*NDP*) mutations noted on genetic testing (13 patients) and/or a clear family history consistent with Norrie disease (4 patients). All 14 boys with definite Norrie disease had vitrectomy with or without lensectomy in at least 1 eye prior to 12 months of age. Of the 14 boys with definite Norrie disease, 7 maintained at least light perception visual acuity in 1 eye and 3 had no light perception visual acuity bilaterally; visual acuity data were not available for 4 patients. Only 2 of 24 (8%) eyes became phthisical. Historically, no treatment has been offered to mitigate the dismal natural history of Norrie disease. We recommend consideration of early vitrectomy in Norrie disease.

A population-based study of Coats disease in the United Kingdom I: epidemiology and clinical features at diagnosis.

[Morris B](#), [Foot B](#), [Mulvihill A](#). *Eye*. 2010 Dec;24(12):1797-801.

This is the first of a set of two prospective, population-based papers on Coats disease in the United Kingdom. This paper describes the features at presentation; gender, mode of presentation, visual acuity, anterior and posterior segment findings, amount of retinal exudation, and disease staging. A total of 55 eligible cases of Coats disease were identified giving an estimated population incidence of 0.09 per 100.000 of the population. All cases were unilateral and 85% were male. Mean age at presentation was 146 months (median 96 months). The mean age of diagnosis was markedly different with differing mechanisms of presentation. Cases presenting with leucocoria or strabismus presented early whereas subjective visual loss presented much later. A large proportion of eyes (44%) were blind at diagnosis. The great majority of eyes (71%) had 6 or fewer clock hours of retinal exudation. More severe forms/stages of Coats disease were more common in the youngest patients.

A population-based study of Coats disease in the United Kingdom II: investigation, treatment, and outcomes.

[Mulvihill A](#), [Morris B](#). *Eye*. 2010 Dec;24(12):1802-7.

This is the second of a series of two population-based papers on Coats disease in the UK. This paper reports the diagnostic methods, treatments and the anatomic and visual outcomes of this disease. 55 baseline and 42 follow-up questionnaires were returned. Ultrasound was performed in 26% of cases, fluorescein angiography in 35%, and examination under anesthesia in 42% of the cases. Laser photocoagulation was by far the primary treatment modality, used in 92%, with cryotherapy used mainly as a second-line or adjunctive treatment. In more advanced cases with significant retinal detachment, laser photocoagulation combined with pars plana vitrectomy and drainage of sub-retinal fluid can produce anatomic stability and prevent progress to end-stage disease. Intravitreal injections of steroids or VEGF inhibitors were performed in 4 eyes. Overall, treatment resulted in stabilization of visual acuity with improvement in 32%, worsening in 27% and stabilization in 41%. Anatomic stabilization or improvement was achieved in 98% of eyes. Intravitreal injections of VEGF inhibitors were only used as an adjunctive therapy in a small number of eyes and they did not have a marked effect on outcome.

Susan Huang, MD; Tina Rutar, MD; Michele Bloomer, MD; J. Brooks Crawford, MD.
Analysis of Clinical Misdiagnoses in Children Treated With Enucleation. *Arch Ophthalmol.* 2010;128(8):1009-1013.

The purpose of this manuscript is to evaluate discordant clinical and pathological diagnoses leading to pediatric enucleations over time. Authors reviewed all pathology reports of pediatric enucleation specimens (subjects aged 0 to 18 years) from 1960 to 2008 were reviewed. Specimens with discordant clinical and pathologic diagnoses were further analyzed. Formalin-fixed, paraffin-embedded sections of enucleated eyes of any misdiagnosed cases were reevaluated. They found that, of 729 pediatric patients (746 eyes) who had enucleation from 1960 to 2008, 29 patients (4.0%) and 30 eyes (4.0%) had discordant clinical and pathological diagnoses. The misdiagnosis enucleation rate decreased with each respective decade studied, with the highest rate of 6.5% (18 of 276 eyes) in the 1960s and no misdiagnoses from 1990 to 2008. Of the 369 eyes enucleated for the clinical indication of malignancy, 22 eyes (6.0%) were misdiagnosed in that no evidence of malignancy was found on histopathological examination. Of the 377 eyes enucleated for benign clinical indications, 7 cases (1.9%) were found to be malignant by histopathology. The authors concluded that misdiagnoses leading to pediatric enucleation have decreased during the past 5 decades, likely owing to improved diagnostic techniques. Benign and malignant intraocular conditions can simulate each other, especially retinoblastoma, Coats disease, nematode and bacterial endophthalmitis, panuveitis, and persistent hyperplastic primary vitreous.

Analysis of Clinical Misdiagnoses in Children Treated With Enucleation

Susan Huang, MD; Tina Rutar, MD; Michele Bloomer, MD; J. Brooks Crawford, MD

Arch Ophthalmol. August 2010;128(8):1009-1013.

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that misdiagnoses leading to pediatric enucleation have decreased during the past 5 decades, likely owing to improved diagnostic techniques. Benign and malignant intraocular conditions can simulate each other, especially retinoblastoma, Coats disease, nematode and bacterial endophthalmitis, panuveitis, and persistent hyperplastic primary vitreous.

Rizzardi, E et al. D-Dimer Evaluation of Hemorrhagic Orbital Lymphangioma. JPOS May-June 2010; 47: 174-177.

An 8 year-old boy with recurrent acute bleeding from lymphangioma of the left orbit is described. The therapeutic approach to hemorrhagic complications of these lesions remains controversial. D-dimer levels are often used in the diagnosis of venous thromboembolism to exclude thrombosis (when the result is negative) and is often helpful in the diagnosis of disseminated intravascular coagulation. As these conditions were absent in this patient, D-dimer levels were useful in following the evolution of intramass hemorrhage. This allowed conservative treatment with corticosteroids which led to rapid resolution of pain, ocular hypertension and proptosis. It also prevented the need for surgical intervention and damage to orbital structures. This experience could represent a starting point for wider clinical study of the usefulness of D-dimer levels in hemorrhagic orbital lymphangioma in children.

XVIII PLASTICS

Relationship of infantile periocular hemangioma depth to growth and regression pattern. Tambe K, Munshi V, Dewsbery C, et al. J AAPOS 2009;13:567-570.Dec

This retrospective case review evaluated all patients with periocular hemangiomas who fulfilled inclusion criteria and were seen at a tertiary eye care center over seven years. Forty-two patients met inclusion criteria. Thirty-four of the 42 patients were female. Fourteen patients presented with superficial hemangiomas. They presented earlier and reached peak growth by 3 months of age. This was followed by an involutinal phase and 5/14 (38%) completely resolved by 24 months of age. Thirteen patients presented with deep (subcutaneous) hemangiomas. These were noticed later and only 2/13 (15%) completely resolved by 24 months of age. The behavior of the 8 hemangiomas that were mixed (deep and superficial components) was based on the dominant component. Seven patients had hemangiomas with orbital extension. Only one of these 7 (14%) completely resolved by 24 months of age. This data is clinically useful for physicians counseling families on the natural course of periocular hemangiomas.

Fay A, Nguyen J, Jakobiec FA, Meyer-Junghaenel L, Waner M. Topical treatment for capillary hemangioma of the eyelid using Beta Blocker solution Arch Ophthalmol. 2010 Feb;128(2):255.

This is a case report describing the use of topical Timolol in the treatment of a large capillary hemangioma on a child's left upper eyelid. The patient was 4 months old at presentation and had a large hemangioma of the left upper eyelid with associated ptosis and evidence of poor fixation in the involved eye as well as astigmatic anisometropia. The Timolol 0.5% was used twice daily on the surface of the hemangioma and within 5 weeks of treatment, the hemangioma was significantly reduced in size, thickness, and color with decrease of astigmatism in that eye. The patient did not suffer any adverse effects.

This report suggests that topical Beta blockers should be considered in the treatment of capillary hemangiomas.

[Fay A, Nguyen J, Jakobiec FA, Meyer-Junghaenel L, Waner M.](#) Propranolol for isolated orbital infantile hemangioma. [Arch Ophthalmol](#). 2010 Feb;128(2):256-8.

The authors describe the use of systemic propranolol in an infant who had an isolated and extensive, deep orbital infantile hemangioma. The child presented at 4 months of age with painless protrusion of the eye. Propranolol treatment was initiated at 2mg/kg/day IV for 5 days and then continued at home orally. By 6 weeks after initiating treatment, the proptosis had resolved and the patient was treated with the propranolol until 1 year of age without adverse effects or regrowth. This report suggests that propranolol is a promising alternative agent for treatment of deep orbital or other inaccessible infantile hemangiomas.

Reduction in Astigmatism Using Propranolol as First-Line Therapy for Periocular Capillary Hemangioma Ido Didi Fabian, Itay Ben-Zion, Claude Samuel, Abraham Spierer *American Journal of Ophthalmology*

Volume 151, Issue 1, Pages 53-58 (January 2011)

Purpose: To examine the shift in astigmatic error following the use of oral propranolol as first-line treatment for periocular capillary hemangioma.

Design: Retrospective observational study.

Methods: STUDY POPULATION: Three healthy infants (1 male) clinically diagnosed with periocular capillary hemangioma. Cycloplegic refraction measurements were obtained at presentation. After a comprehensive clinical evaluation, oral propranolol therapy was starting with a loading dose and titrated up to 2 mg/kg/day under monitoring of heart rate, blood pressure, and blood glucose alterations. Clinical follow-up and repeating cycloplegic refraction measurements were undertaken at the 1-week and 1- and 3-month follow-up visits. INTERVENTION: Oral propranolol therapy for infants diagnosed with periocular capillary hemangioma. MAIN OUTCOME MEASURES: Astigmatic refractive errors before and after propranolol treatment.

Results: The infants' mean age at the initiation of propranolol therapy was 6.3 months (range: 3.0–8.0 months). A rapid therapeutic effect was noticed in all cases, including a major change in lesion size

and color. No complications were recorded during or following treatment. The mean astigmatic error decreased from 2.83 diopters before propranolol treatment to 1.33 diopters after 1 month of treatment. The drug was well tolerated by all 3 patients and no side effects were noted.

Conclusions: Infants can benefit from a rapid, meaningful reduction in periocular capillary hemangioma–induced astigmatism following oral propranolol treatment. Propranolol seems to be an effective and safe drug, which can be used as a steroid-sparing first-line treatment modality in this patient population.

Comment: Although there were only 3 patients in this small case series, the mean reduction in astigmatic error by 1.5 D after only 1 month of treatment is striking. This is important because anisometropia may be more of a threat to visual development than occlusion in some of these cases.

Outpatient treatment of periocular infantile hemangiomas with oral propranolol. Haider, K.M. MD, Plager, D.A. MD, Neely, D.E. MD, et al. J AAPOS 2010;14:251-256 (Jun)

The authors present their experience with propranolol treatment for periocular hemangiomas in an outpatient setting. This was a retrospective, observational case series. Seventeen patients were treated. Of the eight patients with anisotropic astigmatism, seven had resolution of the anisometropia with treatment. Side effects were mild and did not require altered dosing schedules, or discontinuation of propranolol. Reported side effects include mild lethargy and transient gastrointestinal upset. Overall, 10 of the 17 patients had excellent results and another 6 had good results. The authors discuss outpatient management suggestions to avoid side effects.

Puvanachandra, N et al. A National Survey of the Management of Congenital Nasolacrimal Duct Obstruction in the United Kingdom. JPOS March-April 2010; 47:76-80.

A telephone survey was conducted of 100 ophthalmologists in the United Kingdom involved in the management of congenital nasolacrimal duct obstruction. 49% use the dye disappearance test for diagnosis. 74% perform initial probing between 12 and 15 months of age with 25% using nasal endoscopy routinely at the time of the initial probing. No surveyed ophthalmologists performed in-office probing or balloon dacryoplasty dilation. By the third intervention three-fourths of the surveyed ophthalmologists were performing nasal endoscopy and lacrimal intubation. All opted for dacryocystorhinostomy as the fourth intervention. This study reflects differing approaches to the management of congenital nasolacrimal duct obstruction both within the United Kingdom and from that practiced in the United States and also shows the popularity of nasal endoscopy in the United Kingdom.

Hakim, OM et al. Nasal Endoscopic Visualization and Management of the Leading Causes of Probing Failure. JPOS July-August 2010; 47: 214-219.

A prospective study of 169 eyes in 130 children (4 to 48 months old) with primary congenital nasolacrimal duct obstruction (NLDO) underwent probing under direct nasal endoscopic visualization. 164 ducts became patent after the first probing and 5 became patent after the second probing for a total success rate of 100%. Suspected causes included thick membranous obstruction with false passage, membranous obstruction with trap-door or elastic valve re-closure, and narrow terminal end of the duct

with false passage. Inferior turbinate infraction was performed routinely as a prelude to nasal endoscopy. The sickle knife was also used in many cases to complete membranotomy and increase the size of the formed opening. During this study, the authors found that probing success was not related to the child's age, but rather was related to the nature of the obstruction at the time of the procedure. Interventional endoscopic probing facilitates exploration and management of prospective causes of probing failure and is recommended as a primary treatment for children with congenital NLDO.

XIX. GLAUCOMA

Dilation and probing of Schlemm's canal and viscocanalostomy in pediatric glaucoma.

Kay J, Mitchell R, and Miller J. JPOS 2011;48: 30-37. (January/February)

Purpose: To describe a novel surgical technique for the treatment of pediatric glaucoma.

Methods: 24 consecutive patients and 39 eyes that underwent dilation and probing of Schlemm's canal and viscocanalostomy between September 2002 and June 2008 were reviewed. Success defined as IOP less than 23mm Hg with or without glaucoma medication and without further surgery.

Results: Mean age 66 months (range 1 – 206 months) with mean pre-operative IOP of 40.4 +/- 10.2 mm Hg. Success achieved in 27 of 39 eyes (69%) with an average follow-up of 22 months. In patients without previous surgery and the diagnosis of primary congenital glaucoma, success was achieved in 17 of 19 eyes (89%) with an average follow-up of 20 months.

Conclusions: Goniosurgery with dilation and probing of Schlemm's canal in combination with viscocanalostomy appears to be safe and effective in lowering IOP, especially in surgically naïve primary congenital glaucoma.

Comment: Provides an alternative surgical approach in patients undergoing goniosurgery in whom goniotomy or trabeculotomy cannot be completed. Mechanism of action is unclear. Widely variable age at surgery and disparate etiology of glaucoma in this patient population limits further conclusions.

Heterochromia iridis and pertinent clinical findings in patients with glaucoma associated with Sturge-Weber Syndrome.

Aggarwal N, Gandham S, Weinstein R, et al. JPOS 2010;47:361-365. (November/December)

Purpose: To examine the clinical and gonioscopic findings in patients with glaucoma associated with Sturge-Weber syndrome.

Methods: Retrospective review of all patients with Sturge-Weber syndrome who presented between January 1978 and December 2003. Koeppe gonioscopy performed under general anesthesia and findings documented by drawing or photo.

Results: 55 patients were identified of whom 44 (80%) had glaucoma. Unilateral glaucoma was diagnosed in 30 eyes and bilateral glaucoma in 14 eyes, yielding 58 eyes with glaucoma and 52 eyes without. Gonioscopic examination revealed distinct anatomic abnormalities in the anterior chamber angle in 32 (55%) of the glaucomatous eyes in contrast to the eyes without glaucoma. Heterochromia

iris with darker iris on the glaucomatous side was present in 11 of 30 patients with unilateral glaucoma but in none of the patients without glaucoma.

Conclusions: The anterior chamber angle abnormalities observed in this series may support a role for neural crest derived anomalies in the pathogenesis of glaucoma in these infant eyes. .

Comment: In Sturge-Weber syndrome the presence of heterochromia iridis is important to note and may lead the examiner to consider the diagnosis of unilateral glaucoma.

Combined trabeculotomy and trabeculectomy: outcome for primary congenital glaucoma in a West African population VA Essuman, IZ Braimah, TA Ndanu and CT Ntim-Amponsah Eye (2011) 25, 77–83

Purpose To evaluate the surgical outcome of combined trabeculotomy–trabeculectomy in Ghanaian children with primary congenital glaucoma.

Materials and methods A retrospective case series involving 19 eyes of 12 consecutive children with primary congenital glaucoma who had primary trabeculotomy–trabeculectomy from 12 August 2004 to 30 June 2008, at the Korle-Bu Teaching Hospital, Ghana. Main outcome measures were preoperative and postoperative intraocular pressures, corneal diameter, corneal clarity, bleb characteristics, duration of follow-up, surgical success, and complications.

Results A total of 19 eyes of 12 patients met the inclusion criteria. Six of the patients were males. Mean age at diagnosis was 4.4 (range 2–8) months. Mean age at surgery was 5.9 months (range 3–16). Eight (67%) infants had bilateral disease. Mean duration of follow-up was 13.1 (range 5–38) months. The preoperative mean horizontal corneal diameter was 13.4 ± 1.1 (range 12–16) mm. Complete success (intraocular pressure ≤ 21 mmHg) was obtained in 15 (79%) eyes. The probability of success was 94.4, 83.3, 66.7, 44.4, 38.9, 33.3, and 13.3% at 3, 6, 9, 12, 15, 18, and 21 months, respectively (Kaplan–Meier analysis). All eyes had corneal oedema preoperatively. Seventeen eyes (90%) had clear cornea at their last follow-up. Mean preoperative and postoperative intraocular pressures were 30.3 ± 8.8 and 18.1 ± 6.8 mmHg respectively (Po0.001, t-test). Twelve (63%) eyes had well-functioning blebs at the last follow-up. One eye (5%) developed seclusio pupillae and cataract postoperatively.

Conclusion The overall success for combined trabeculotomy–trabeculectomy in Ghanaian children with primary congenital glaucoma was 79%. The probability of success reduced from more than 66% in the first 9 months postoperatively to below 45% after that.

Intraocular pressures after ketamine and sevoflurane in children with glaucoma undergoing examination under anaesthesia

1. L Jones¹,
2. V Sung¹,
3. G Lascaratos¹,
4. H Nagi²,
5. R Holder³

Abstract

Aim: For accurate intraocular pressure (IOP) measurement in very young children examination under anaesthesia (EUA) may be necessary. Most anaesthetic agents used for EUA have some effect on IOP. We compared IOPs in children after ketamine and sevoflurane anaesthesia.

Methods: Consecutive patients with definite or suspected glaucoma, uncooperative for reliable IOP measurement in clinic and requiring EUA, were included in this study. IOPs were measured after intramuscular injection (5 mg/kg) or intravenous injection (2 mg/kg) of ketamine using a Perkins applanation tonometer. Three measurements were taken from each eye. The IOPs were rechecked after sevoflurane, given for maintenance anaesthesia. Mean IOPs were used for analysis. Paired t test was used to assess the differences in IOPs for the whole group and one-way ANOVA for the three subgroups (ketamine IOP <20, 20–30, >30 mmHg).

Results: The records of eight patients (16 eyes) were available for review. The mean age was 55.42 (SD 25, range 26–89) months. Seventy data-points from both eyes (35 EUAs) were used for the analysis. The mean IOP after sevoflurane (17 (SD 10) mmHg) was statistically lower than after ketamine (24.4 (SD 12.7) mmHg, $p < 0.001$). The percentage difference was 28.5 (SD 20.8; 95% CI 23.5 to 33.4). The difference between the subgroups was not statistically significant ($p = 0.192$).

Conclusion: Sevoflurane lowers the IOP significantly compared with the IOP measured after ketamine. This difference is independent of the IOP level. It may be important to use ketamine as the induction anaesthetic agent when accurate IOP measurement is necessary during EUA for children.

Comment: many weaknesses to this paper: retrospective study, small number of pts ($n=8$). Sevoflurane IOP was measured after ketamine was given, so there could be an additive effect confounding the results. Ketamine can raise IOP; another confounding factor. Same person did the IOP measurements so there is a possible reproducibility bias confounding factor.

Outcome of angle surgery in children with aphakic glaucoma. Bothun, E.D. MD, Guo, Y MD, PhD, Christiansen, S.P. MD, et al. J AAPOS 2010;14:235-239. (Jun)

This paper is a retrospective review of trabeculotomy and/or goniotomy as treatment for pediatric aphakic glaucoma over a 16-year period at a tertiary-care center. 14 eyes of 11 patients met inclusion criteria. 8/14 eyes were considered treatment successes at their last follow-up visit. Treatment success was defined as an IOP of ≤ 24 mm Hg with or without topical medications, a lack of sight-threatening complications, and avoidance of trabeculectomy or tube shunt. Follow-up duration was adequate in this study, but the sample size is small.

Violation of the ISNT rule in nonglaucomatous pediatric optic disc cupping.

Pogrebniak AE, et al. Invest Ophthalmol Vis Sci 2010; 51:890-5. (Feb 2010)

Purpose: To determine whether nonglaucomatous optic disc cupping in children violates the ISNT rule (which states that for normal optic discs the neuroretinal rim width is greatest in the order inferior \geq superior \geq nasal \geq temporal).

Methods: Digital ocular fundus photographs from a random cohort of children with large optic disc cups of nonglaucomatous origin were analyzed in masked fashion by using computer graphic software. The diameter and perimeter of each optic disc and optic cup and the width of the neuroretinal rim were drawn and measured. Measurements were compared to a random cohort of normal pediatric optic discs.

Results: The ISNT rule was intact in 9 (16%) of 55 eyes of nonpremature children with nonglaucomatous cupping, in 6 (21%) of 28 eyes of children with a history of prematurity and nonglaucomatous cupping, and in 35 (73%) of 48 eyes with normal discs.

Conclusions: Violation of the ISNT rule occurs with greater frequency in the pediatric population with large optic disc cups of nonglaucomatous origin, compared with the pediatric population with normal optic discs. In discs with small cups, neuroretinal rim width conforms to the overall oval shape of the

disc, which is usually greatest in vertical dimension, whereas discs with large cups possess greater variability of relative neuroretinal rim width around the disc, greater relative vertical cup/disc ratio versus horizontal cup/disc ratio, and lower predictability of the ISNT rule.

Comment: This study is interesting because the authors conclude that violation of the ISNT rule occurs in a majority of eyes in children with large optic disc cups of nonglaucomatous origin. The normal optic disc usually demonstrates a configuration in which the inferior neuroretinal rim is the widest portion of the rim, followed by the superior rim, and then the nasal rim, with the temporal rim being the narrowest portion. Violation of this “ISNT rule” may be used to identify adult glaucoma, which frequently damages superior and inferior optic nerve fibers before temporal and nasal fibers (i.e. leading to thinning of the superior and inferior rims and violation of the rule).

Helen H. Yeung, MD; David S. Walton, MD. Clinical Classification of Childhood Glaucomas. *Arch Ophthalmol.* 2010;128(6):680-684.

This manuscript provides an updated classification of the primary and secondary childhood glaucomas is offered for clinical use, and associated systemic diseases are included to enable their early recognition in children with known glaucoma. Approximately 650 clinical records of patients with pediatric glaucoma were reviewed for type of glaucoma and associated systemic disease. A literature search was done for additional reported causes of childhood glaucoma. Previous classifications of pediatric glaucomas were also reviewed. Pertinent references to support inclusion of each clinical entity in the updated classification are included. A comprehensive and referenced classification of the pediatric glaucomas was enabled by this review. A comprehensive, etiologically based classification of the pediatric glaucomas is now available to assist with the recognition of the many causes of primary and secondary glaucoma in childhood and to support the selection of specific treatment choices.

XX. PEDIATRICS

Linear scleroderma ‘en coup de sabre’ with ptosis and oculomotility disorders: case report and review of the literature. Taylor C, Riley M, Bowyer J. *Br Ir Orthopt J* 2010; (June) 7: 72-76.

This uncommon autoimmune disorder is a form of scleroderma that begins with contraction and firmness of the skin over the affected area. A depression develops in the frontoparietal section of the face and scalp that looks like a saber cut. The linear depressed groove is associated with a linear zone of alopecia, often preceded by loss of hair color. There may be facial asymmetry affecting the face and cheek. It has been reported with ptosis or other lid abnormalities, but oculomotor disorders are rare.

In this case report, the authors describe a 9-year-old girl with an 18-year follow-up. She had progressive unilateral ptosis with mild periorbital swelling and discoloration. A neurological examination, CT scan of the brain and orbits and a chest X-ray did not identify a specific

etiology. She underwent several ptosis procedures before the subcutaneous cleft appeared over the unaffected eyebrow. At age 21, she presented as an emergency with a corneal ulcer and decreased corneal sensation. At this time significant ipsilateral duction deficits were recorded. She suppressed the affected eye. A CT scan showed enlarged medial and inferior recti and her deviation and ocular limitations were attributed to a restrictive mechanism. A review of other cases highlights the need for clinicians to identify this disorder in the differential diagnosis of patients with progressive ptosis, and that surgical repair of the ptosis can lead to corneal exposure if eyelid closure is compromised and muscle restrictions subsequently develop. [17 refs.]

Incidence, Ocular Manifestations, and Survival in Children with Neuroblastoma: A Population-Based Study.

[Smith SJ](#), [Diehl NN](#), [Smith BD](#), [Mohney BG](#).

[Am J Ophthalmol](#). 2010 Feb 9. [Epub ahead of print]

PURPOSE: To determine the incidence, ophthalmic manifestations, and survival among children with neuroblastoma in a defined population.

METHODS: The medical records of all pediatric (<19 years) residents of Olmsted County, Minnesota, diagnosed with neuroblastoma from January 1, 1969, through December 31, 2008, were retrospectively reviewed.

RESULTS: Fourteen children were diagnosed with neuroblastoma as residents of Olmstead County, Minnesota, during the 40-year period, yielding an age- and gender-adjusted incidence of 11.8 (95% confidence interval [CI]: 5.6-18.0) per million patients <15 years of age. The calculated incidence for patients presenting before the age of 5 in this cohort was 1 in 5970 children (95% CI: 3920-12 580 children). The mean age at diagnosis for the 14 study patients was 22.5 months (range, 10.4-42.6 months). Six of the 14 (43%; 95% CI: 18%-71%) had ocular manifestations, including orbital metastasis in 6 (100%), proptosis and ecchymosis in 4 (67%), ptosis in 2 (33%), and strabismus in 1 (17%). The Kaplan-Meier rate of survival for all 14 children was 57% at 1 year (95% CI: 36%-90%) and 50% at 5 years (95% CI: 30%-84%), while the 6 with eye findings had a survival rate of 17% at 9 months (95% CI: 3%-100%).

CONCLUSIONS: The incidence of neuroblastoma in this population was 11.8 per million patients <15 years, with ophthalmic involvement observed in 6 of the 14 study patients (43%). Orbital metastasis in the 6 children in this cohort was associated with poor prognosis.

Ophthalmic Abnormalities in Children with Down Syndrome.

Creavin AL, Brown RD.

JPOS 2009 Mar-Apr;46:76-82.

A comprehensive review of the available literature was performed to determine the common ophthalmic disorders in children aged 0-16 years with Down syndrome. Refractive error (esp. hyperopia) and strabismus (esp. esotropia) were common findings. Other frequent findings included poor visual acuity, nystagmus, blepharitis, and less frequently, cataract, and glaucoma. The high prevalence of ophthalmic disorders in children with Down syndrome demonstrated by all studies highlights the need for these children to undergo an ophthalmic assessment. One study showed that non-specialist examination of children with Down syndrome may miss up to 20% of ophthalmic

disorders. These results support pediatric ophthalmic monitoring in combination with an ophthalmologic screening program, rather than in place of one.

A Systematic Review of the Diagnostic Accuracy of Ocular Signs in Pediatric Abusive Head Trauma (AHT)

Bhardwaj G, et al.

Ophthalmology 2010;117:983-992 (May)

Clinical Relevance: Intraocular hemorrhages (IOH), perimacular retinal folds, traumatic retinoschisis and optic nerve sheath hemorrhages have been reported as cardinal signs of AHT. The evidence supporting this has not been systematically reviewed.

Methods: A review of original studies reporting ocular findings in AHT.

Results: Twenty studies met inclusion criteria and were included in the review. The overall sensitivity of IOH for AHT was 75% and their specificity was 94%. Intraretinal hemorrhage at the posterior pole was the most common finding, although extensive, bilateral, and multilayered IOH were the most specific for AHT. Optic nerve sheath hemorrhages had a sensitivity and specificity for AHT of 72% and 71% respectively. Traumatic retinoschisis and perimacular retinal folds were reported in 8% and 14% of AHT, respectively, but were not reported in other conditions.

Conclusions: Prospective, consecutive studies confirm that IOH in infants – particularly bilateral extensive, and multilayered – are highly specific for AHT. Optic nerve sheath hemorrhages are significantly more common in AHT than in other conditions, in autopsy studies. Traumatic retinoschisis and perimacular folds are present in a minority of AHT, but rarely seen in other conditions.

Risk of Cataract Development among Children with Juvenile Idiopathic Arthritis-Related Uveitis Treated with Topical Corticosteroids

Thorne JE, Woreta FA, Dunn JP, Jabs DA

Ophthalmology 2010;117:1436-1441 (July)

Design: A retrospective cohort study of 75 patients with JIA-associated uveitis observed from July 1984 through August 2005 at the Wilmer Eye Institute.

Results: Of the 60 eyes in 40 patients who received topical corticosteroid therapy, there was a dose-dependent increase in the rate of cataract development among eyes receiving topical corticosteroids. Presence of posterior synechiae, active uveitis, and use of topical corticosteroids at presentation were significantly associated with cataract development after controlling for confounding variables. Use of topical corticosteroids was associated with cataract formation independent of uveitis activity. Treatment with ≤ 3 drops daily of topical corticosteroid was associated with an 87% lower risk of cataract formation compared with eyes treated with >3 drops daily.

Reviewer's Comments: These data imply that in the setting of suppressed uveitis, patients with JIA-associated chronic anterior uveitis may be treated with low doses of topical corticosteroids (≤ 3 drops daily) over moderate periods of follow-up with a low risk of developing cataract.

Incidence, Ocular Findings, and Systemic Associations of Ocular Coloboma :A Population-Based Study

Kelly M. Nakamura, BS; Nancy N. Diehl, BS; Brian G. Mohny, MD

Arch Ophthalmol. January 2011;129(1):69-74.

This paper describes the incidence, ocular findings, and systemic associations of coloboma in a population-based cohort of children. The authors retrospectively reviewed the medical records of pediatric (aged <19 years) patients diagnosed as having ocular coloboma from January 1, 1968, through December 31, 2007, as residents of Olmsted County, Minnesota. They found a total of thirty-three children who were newly diagnosed as having ocular coloboma (annual incidence, 2.4 per 100 000 residents <19 years old; prevalence, 1 in 2077 live births). Median patient age at diagnosis was 3.9 months (range, 2 days to 18.4 years), and 22 patients (67%) had unilateral involvement. Twelve patients (36%) had involvement of the anterior segment only, 13 (39%) of the posterior segment only, and 8 (24%) of both. During median ophthalmologic follow-up of 9.2 years (range, 13 days to 35.9 years), 19 patients (58%) had other ocular disorders, including amblyopia in 11 (33%) and strabismus in 10 (30%). During median medical follow-up of 16.8 years, 22 patients (67%) were diagnosed as having a nonocular disorder, including abnormal development in 12 (36%) and CHARGE (coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies) syndrome in 4 (12%). The authors conclude that ocular coloboma occurred in 1 in 2077 live births. More than half of the patients in their study were diagnosed as having an ocular disorder other than coloboma, including strabismus and amblyopia in approximately one-third. Two-thirds of patients were diagnosed as having a nonocular disorder, including CHARGE syndrome in 1 in 8 patients.

Ocular manifestations of congenital toxoplasmosis.

[Melamed J](#), [Eckert GU](#), [Spadoni VS](#), [Lago EG](#), [Uberti F](#). *Eye* 2010 April;24(4), 528-534

This is a study of 44 Brazilian children with a confirmed diagnosis of congenital toxoplasmosis. In all patients, complete ophthalmological examinations were performed under sedation. RESULTS: The mean age of patients was 4.2 months. 70% had ocular involvement. 66% of them had chorioretinal lesions. The chorioretinal lesions were bilateral in 76% of patients and unilateral in 24%. These lesions were active in 16% of eyes and inactive in 84%. 76% of the lesions were concentrated in the papillomacular area. Other associated ocular alterations were present in 50% of the children; the most prevalent being cataract (14%), microphthalmia (11%), nystagmus (16%) and strabismus (27%). The authors note that since the view of the fundus was obscured by a cataract in some children, the incidence of chorioretinal lesions may in fact be higher. Of the mothers about whom the timing of the infection could be ascertained, 48% occurred in the first trimester of pregnancy, 7% in the second trimester and 2% in the third trimester.

XXI. INFANTILE DISEASES

Urine catecholamine levels as diagnostic markers for neuroblastoma in a defined population: implications for ophthalmic practice.

[Smith SJ](#), [Diehl NN](#), [Smith BD](#), [Mohnney BG](#). *Eye*, 2010 Dec;24(12):1792-6.

The purpose of this population-based study is to report the percentage of cases of neuroblastoma with elevated urinary catecholamine levels at presentation and to suggest a recommended work-up for cases of idiopathic pediatric Horner syndrome. The medical records of all pediatric (<19 years) residents of Olmsted County, Minnesota diagnosed with neuroblastoma from January 1, 1969 through December 31, 2008 were retrospectively reviewed. A total of 14 patients were diagnosed with neuroblastoma during the 40-year study period. A total of 10 (71%) of the 14 cases manifested elevated urinary catecholamine metabolites at the initial presentation. Urinary vanillylmandelic acid (VMA) levels were greater than twice the upper limit of normal in eight (57%) of 14 cases, whereas homovanillic acid (HVA) levels were greater than two times the upper limit of normal in 10 (71%) of the 14 cases. Three (75%) of the four cases without significantly elevated urinary VMA or HVA levels were diagnosed with stage IV disease, whereas one (25%) had stage II neuroblastoma. The authors conclude that negative urine screens in cases of idiopathic Horner syndrome in children are not sufficient to rule out underlying malignancy. They suggest that greater emphasis be placed on performing a thorough physical examination, specifically, careful palpation of the neck, abdomen and axilla with close follow-up and obtaining imaging studies in cases of worsening disease.

Visual Function in Congenital and Childhood Myotonic Dystrophy Type 1 (DM1)

Ekström AB, Tulinius M, Sjöström A, Aring E.
Ophthalmology 2010;117:976-982 (May)

Objective: To investigate visual function in a group of individuals with congenital and childhood myotonic dystrophy type 1 (DM1), to correlate the results to the size of the cytosine-thymine-guanine (CTG) repeat expansion and the onset form, and to compare the results with those of a control group.

Participants: Forty-nine individuals from Sweden with severe and mild congenital and childhood DM1.

Main Outcome Measures: Visual acuity, refractive error, pathology of lens, fundus, and VEP pathologic features.

Results: The study shows a higher prevalence of low visual acuity, hyperopia, and astigmatism in the study population. The size of the CTG repeat expansion had an impact on BCVA in all subgroups. In childhood DM1, individuals with high hyperopia and astigmatism and had greater CTG repeat expansion size than those without. No true cataract was found. Subtle nonspecific fundus changes were present in addition to VEP pathology.

Nathan M. Kerr, MBChB; Hamilton R. Cassinelli, MD; Linda A. DiMeglio, MD, MPH; Cristina Tau, MD; Beyhan Tüysüz, MD, PhD; Tim Cundy, MD; Andrea L. Vincent,

MBChB. Ocular Manifestations of Juvenile Paget Disease. *Arch Ophthalmol.* 2010;128(6):698-703.

This purpose is to determine the prevalence and spectrum of retinal changes in juvenile Paget disease. Observational case series and literature review with analysis. Patients with clinical and molecular evidence of juvenile Paget disease were recruited by members of the International Hyperphosphatasia Collaborative Group. Participants underwent ophthalmic examinations consisting of at least best-corrected Snellen visual acuity and dilated fundal examination or color fundus photography. A MEDLINE literature search was performed, and all identified case reports were reviewed for information regarding ocular phenotype. Fourteen eyes from 7 patients were examined. The mean (SD) patient age was 22 (8) years, and 4 patients were female. Retinal abnormalities were evident in 12 of 14 eyes and were reported among an additional 12 patients in the literature. Retinal abnormalities included mottling of the retinal pigment epithelium, peripapillary atrophy, angioid streaks, and choroidal neovascularization. Cumulative number of retinal abnormalities was strongly associated with increasing age. Juvenile Paget disease is associated with progressive retinopathy characterized by the development of angioid streaks, which may be complicated by choroidal neovascularization, the predominant cause of visual loss. Osteoprotegerin or its signaling pathway may have a role in calcification of Bruch membrane and in the pathogenesis of angioid streaks. Retinopathy in patients with juvenile Paget disease may be a sign of a more generalized vascular disorder.

**Systemic and ophthalmological anomalies in congenital anophthalmic or microphthalmic patients
Br J Ophthalmol 2010;94:487-493 (Apr).**

This paper reviewed 75 patients with congenital anophthalmos or blind microphthalmos. The authors recorded data on pregnancy, birth and family history. Patients were screened for any pathology in the fellow eye in unilateral disease and for any systemic anomaly. Sixteen patients had blind unilateral microphthalmos. To date there has been only one case of bilateral microphthalmos. Congenital anophthalmos was unilateral in 38 and bilateral in 20 patients. Only one of the children had a positive family history for anophthalmos. None of the mothers had had problems in pregnancy or during delivery. There were more associated systemic findings in anophthalmic (50%) than in microphthalmic (17.6%) patients. The most common pathology was characterised by Goldenhar's syndrome, facial clefts and developmental cerebral anomalies. Four out of 16 patients with unilateral microphthalmos (25%) and 18 out of 38 patients with unilateral anophthalmos (47.4%) had anomalies in the fellow eye, predominantly coloboma, dermoid, sclerocornea and glaucoma. On account of this pathology in a single eye, two (12.5%) of the patients with unilateral microphthalmos and 13 (34.2%) of the patients with unilateral anophthalmos, as well as all 20 patients with bilateral anophthalmos, were classified as legally blind. The overall blindness rate was 17.6% in microphthalmos and 3.4 times higher (56.9%) in anophthalmos. The authors concluded that all children born with congenital anophthalmos or microphthalmos require a thorough clinical examination by an experienced ophthalmologist to rule out pathology in the fellow eye in unilateral disease and by a paediatrician to screen for any associated systemic anomalies.

Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy.
Br J Ophthalmol 2010;94:696-700 (June)

This paper describes the combined ophthalmology and visual electrophysiology findings in 20 infants and children who were exposed to substitute methadone and other drugs of misuse in utero. This is a descriptive case series of 20 patients, all of whom had been referred to a paediatric visual electrophysiology service because of concerns regarding visual function, and all of whom had been exposed to methadone in utero. All children underwent a full ophthalmic and orthoptic examination as well as visual electrophysiology testing deemed appropriate on an individual basis. A review was undertaken of paediatric case notes and of maternal antenatal urine toxicology. The authors found the following ophthalmic abnormalities: reduced acuity (95%), nystagmus (70%), delayed visual maturation (50%), strabismus (30%), refractive errors (30%), and cerebral visual impairment (25%). Visual electrophysiology was abnormal in 60%. A quarter of the children had associated neurodevelopmental abnormalities. The majority of children with nystagmus (79%) had been treated for neonatal abstinence syndrome (NAS). The authors concluded that infants born to drug-misusing mothers prescribed methadone in pregnancy are at risk of a range of visual problems, the underlying causes of which were not clear. They also state infants with NAS severe enough to receive pharmaceutical treatment may be at particular risk of developing nystagmus.

XXII SYSTEMIC

Visual and Systemic Outcomes in Pediatric Ocular Myasthenia Gravis

Stacy L. Pineles, Robert A. Avery, Heather E. Moss, Richard Finkel, Thane Blinman, Larry Kaiser, Grant T. Liu *American Journal of Ophthalmology*

Volume 150, Issue 4, Pages 453-459.e3 (October 2010)

Purpose: To evaluate visual and systemic outcomes in pediatric patients with purely ocular myasthenia gravis (OMG) treated at the Children's Hospital of Philadelphia.

Design: Retrospective chart review.

Methods: Pediatric patients with OMG seen at a single institution over a 16-year period with a minimum follow-up of 1 year were reviewed. Associations of demographic and clinical characteristics with disease resolution, amblyopia, and development of generalized symptoms of myasthenia gravis were analyzed.

Results: Thirty-nine patients were identified, with a mean age of 5.4 ± 4.8 years and mean follow-up of 4.8 ± 4.3 years. Fifteen patients were treated with pyridostigmine only, 19 (49%) also received steroids, and 15 (38%) underwent thymectomy. Four patients (10%) received steroid-sparing immunosuppressive therapy. Resolution occurred in 10 patients, and generalized symptoms eventually occurred in 9 patients. Although 10 patients were treated for amblyopia, only 1 had amblyopia at the final visit. There was no correlation between sex or age with amblyopia or development of generalized symptoms. Thymectomy, when performed before the onset of generalized symptoms, showed a trend toward protection from the development of generalized symptoms ($P = .07$).

Conclusions: In our series, 24% of patients had disease resolution and 23% had generalized symptoms. Our larger cohort confirms previous findings that treated and untreated pediatric patients with OMG have a relatively low risk of developing generalized symptoms and that related amblyopia is readily reversible. Although our treatments were more aggressive than those previously reported, our rates of amblyopia and development of generalized symptoms are comparable.

Comment: This is a relatively large series (39) of children with ocular myasthenia. Most of us will encounter such a case only occasionally, so this paper will be useful resource when that occurs. It is interesting that generalized symptoms occurred only about one-quarter of the time, and that thymectomy showed a trend for protecting against development of generalized symptoms.

Neuroendocrine tumor (carcinoid) metastatic to orbital extraocular muscle: case report and literature review.

MATSUO T, ICHIMURA K, TANAKA T, TAKENAKA T, NAKAYAMA T: *Strabismus* 2010; 18: 123-128.

The authors presented a patient who showed neuroendocrine tumor (carcinoid) metastasis to the medial rectus muscle, as well as reviewed patient characteristics of carcinoid metastases to the extraocular muscles. A 72-year old woman initially presented with spindle-shaped enlargement of the belly of the right medial rectus muscle and was followed for 3 years with a diagnosis of idiopathic orbital myositis. Biopsy of the medial rectus muscle showed only inflammation. She had right proptosis and eyelid swelling which responded to oral and intravenous steroids, but continued to reoccur once taken off treatment. Three years later, the patient underwent a CT scan for ischemic colitis. This scan revealed a large retroperitoneal mass located anterior to the left kidney, diagnosed as a nonfunctioning neuroendocrine tumor for which she underwent total extirpation. The medial rectus muscle gradually enlarged, leading to optic nerve compression and decreased visual acuity to count fingers. The patient developed an esotropia in primary with total restriction of abduction of the right eye. A second biopsy of the medial rectus mass and partial resection of the anterior half of the mass was performed. Pathology revealed a neuroendocrine tumor metastasis. The residual mass responded to radiation to the right orbit, however vision was reduced to light perception. Literature review found 15 patients (including this case) with neuroendocrine tumor metastases to the extraocular muscles, 7 male and 8 female with a mean age of 65 (range 42-74 years). One extraocular muscle was involved in 9 patients and multiple extraocular muscles were involved in 6 patients (5 bilateral and 1 unilateral). The most common symptoms and signs were diplopia, proptosis, limitations in ocular motility, and visual acuity impairment. The authors concluded that neuroendocrine tumor may have a propensity to extraocular muscle metastases, and its slow growth may make it difficult to differentiate from orbital myositis.

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XXIII VISUAL IMPAIRMENT

A population-based study of visual impairment among pre-school children in Beijing: the Beijing study of visual impairment in children.

Lu Q, Zheng Y, Sun B, Cui T, Congdon N, Hu A, Chen J, Shi J.
Am J Ophthalmol 2009 Jun; 147(6):1075-81.

Purpose: To evaluate the prevalence and causes of visual impairment among Chinese children aged 3 to 6 years in Beijing.

Methods: Presenting and pinhole visual acuity were tested using picture optotypes or, in children with pinhole vision < 6/18, a Snellen tumbling E chart. Comprehensive eye examinations and cycloplegic refraction were carried out for children with pinhole vision < 6/18 in the better-seeing eye.

Results: All examinations were completed on 17,699 children aged 3 to 6 years (95.3% of sample). Subjects with bilateral correctable low vision (presenting vision < 6/18 correctable to \geq 6/18) numbered 57 (0.322%; 95% confidence interval [CI], 0.237% to 0.403%), while 14 (0.079%; 95% CI, 0.038% to 0.120%) had bilateral uncorrectable low vision (best-corrected vision of < 6/18 and \geq 3/60), and 5 subjects (0.028%; 95% CI, 0.004% to 0.054%) were bilaterally blind (best-corrected acuity < 3/60). The etiology of 76 cases of visual impairment included: refractive error in 57 children (75%), hereditary factors (microphthalmos, congenital cataract, congenital motor nystagmus, albinism, and optic nerve disease) in 13 children (17.1%), amblyopia in 3 children (3.95%), and cortical blindness in 1 child (1.3%). The cause of visual impairment could not be established in 2 (2.63%) children. The prevalence of visual impairment did not differ by gender, but correctable low vision was significantly ($P < .0001$) more common among urban as compared with rural children.

Conclusions: The leading causes of visual impairment among Chinese preschool-aged children are refractive error and hereditary eye diseases. A higher prevalence of refractive error is already present among urban as compared with rural children in this preschool population.

Anasaini T. Cama, MBBS, MSc; Biu Telaite Sikivou, DSM, MSc; Jill E. Keeffe, OAM, PhD. Childhood Visual Impairment in Fiji. *Arch Ophthalmol.* 2010;128(5):608-612.

The purpose of this paper is to establish the prevalence and causes of low vision and blindness in children aged 0 to 15 years in Fiji using existing data and new surveys. Childhood visual impairment data on both low visual acuity (<20/60-20/400) and blindness (<20/400) were obtained from existing records at hospital clinics, the school, an outreach service for visually impaired children, primary school screening records, and surveys in high schools and schools for children with multiple disabilities. Crude prevalence was derived and,

using 5-year age range and age at onset of vision loss, the probable prevalence per 1000 children was calculated. A total of 81 children were identified; causes were established for 70 children, showing that 69% had unavoidable causes of vision loss (retinal, 39.7% and cortical, 15.5%), with the avoidable cause of low vision and blindness mainly being cataract (15.5%). Probable prevalence was 1.134 per 1000 children (95% confidence interval [CI], 1.115-1.153), with low vision, 0.774 per 1000 children (95% CI, 0.758-0.790) and blindness, 0.36 per 1000 children (95% CI, 0.349-0.371). The rate of severe visual impairment (<20/200) was 0.522 per 1000 children (95% CI, 0.509-0.535), only half of the total vision loss. Both the low to moderate prevalence and mainly unavoidable causes of visual impairment indicated that Fiji, a developing country, has prevalence and causes of visual impairment similar to more resourced, industrialized countries.

Lee, H et al. Complications and Visual Prognosis in Children with Aniridia. *JPOS* July-August 2010; 47:205-210.

A retrospective study of a cohort of 11 patients (22 eyes) with aniridia was undertaken at Temple Street Children's Hospital (Dublin) from 1985-2007. Incidence of aniridia varies between 1:64,000 and 1:100,000. Two-thirds of all cases are familial and one third are sporadic. It occurs due to mutations on the PAX6 gene on 11p13. In this study group aniridia was associated with corneal dystrophy (54.5%), cataracts (72%), glaucoma (45.5%), nystagmus (81.8%), poor vision (81.8%), optic nerve hypoplasia (36.4%), macular hypoplasia (54.5%), and retinal breaks or detachments (18.2%). Aniridia-associated keratopathy occurs secondary to limbal stem cell deficiency. Penetrating keratoplasty leads often to unsatisfactory results, but the Boston keratoprosthesis improved vision in two patients in this study group. Overall, this study demonstrates the panocular nature of aniridia and its poor visual prognosis despite early diagnosis and aggressive management. Aniridia is a pro-fibrotic process and as a result many surgical interventions fail. Thus, surgery should be performed in aniridia only when absolutely necessary.

The 'mirror test' for estimating visual acuity in infants Br J Ophthalmol 2010;94:882-885 (Jul)

This paper investigated the association between the distance at which infants fixate on their own reflections and visual acuity card testing, and determined whether this could form the basis of a new clinical test of visual function in infants. They examined 78 healthy infants under 9 months of age (range 1–266 days, mean 56.5±64SD) and they were held close to a mirror such that they attended their own reflections. The distance from the mirror was increased until they no longer held fixation. Binocular acuities were also tested with the Teller acuity card procedure. The reliability was rated 'good' in 58 and 60 infants respectively, for mirror distances and for the acuity cards. Data were also included for moderate reliability (n=20 and 14 respectively). The mean mirror distance was 54.9 cm (range 13.5–178, SD=42.8). The mean Teller acuity was 2.19 cycles per degree (range 0.2–14.5, SD=2.8). (Snellen equivalent 6/82, range 6/900–6/12). Mirror distance showed linear correlation with both Teller acuity (R²=0.69, p<0.0005) and with age (R²=0.73, p<0.0005) by univariate analysis. Using multivariate analysis, only age retained significance. Using logarithmic scales and a logistic growth function for age, correlations were even stronger (log mirror distance vs log Teller acuity, R²=0.86, p<0.0005; logistic regression of log mirror distance vs log age, R²=0.88, p<0.0005), and both retained independent significance in a multivariate model. The

authors concluded that mirror fixation distance increases with age in infants and has a good correlation with acuity card results. The portability and ease of use would make it a useful additional tool for detecting impaired visual function in infants.

XXIV NYSTAGMUS

Nystagmus in infancy and childhood: Characteristics and evidence for treatment.

HERTLE RW: *Am Orthopt J* 2010; 60: 48-58.

This article was based on a presentation made as part of a symposium held at the Joint Meeting of the American Orthoptic Council, the American Association of Certified Orthoptists, and the American Academy of Ophthalmology in San Francisco, CA, October 2009. The eye care professional specializing in pediatrics will see more nystagmus than any other specialist. The National Eye Institute has recently sponsored a collaboration of interdisciplinary experts known as the Classification of Eye Movement Abnormalities and Strabismus (CEMAS), which used evidence to reclassify and define eleven different types of nystagmus. The author described in detail three forms of neonatal and early infantile nystagmus: Infantile Nystagmus Syndrome, Fusion Defect Nystagmus, and Spasmus Nutans Syndrome. He also discusses the indications for and uses of medical, surgical, optical, and orthoptic treatment of various types of nystagmus based on the best available evidence.

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Hobson F, Rowe FJ: Management of nystagmus by surgery and botulinum toxin options: a review. *Br Ir Orthopt J* 2009; (June) 6: 28-34.

This literature review searched articles written between 1939 and 2008, and set out to determine the success rate for botulinum toxin therapy and extraocular surgery in the management of acquired nystagmus.

Botox can be injected directly into the extraocular muscles or into the retrobulbar space. Benefits can be effective, albeit temporary. Sometimes a satisfactory improvement seen with botox can be used as a guideline for a more permanent surgical correction. It can be helpful in the presence of nystagmus with annoying subjective symptoms such as oscillopsia. Complications include ptosis, which can have the unintended benefit of creating occlusion.

If the deviation is mostly horizontal, a single injection into a horizontal muscle is applied; if the deviation has combined horizontal, vertical and torsional components, injection into the retrobulbar space may be indicated.

Acquired pendular nystagmus did better with botox than jerk nystagmus. Botox can be very valuable in selected cases.

The article summarizes all the surgical techniques that can be used when operating on patients with nystagmus. Surgery is often performed to reduce or eliminate an abnormal head posture. Specifically the best successes occur when surgery is performed to reposition a null point.
[37 references]

Br J Ophthalmol 2009;**93**:1560-1562 doi:10.1136/bjo.2009.161083

Estimating numbers of blind children for planning services: findings in Kilimanjaro, Tanzania

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6. P Courtright¹

Abstract

Aim: Childhood blindness is included in the VISION 2020 initiative. However, childhood blindness is rare, so there is limited population-based evidence to assist with the planning of services. We carried out a survey of childhood blindness in Kilimanjaro Region, Tanzania, to generate information needed for planning eye care services.

Methods: The study was carried out in parallel with a Rapid Assessment of Avoidable Blindness (RAAB) survey. Villages within Kilimanjaro Region were selected on a probability-proportional-to-size basis. Key informants in each village were trained to identify children with any vision problems; a visiting team assessed the children to determine visual status and arranged for further assessment as needed at hospital. The files of children at schools for the blind in the Region were reviewed to identify children in schools from the selected study villages.

Results: Among the 95 040 children in the 72 villages sampled, 13 children were identified as blind; an additional three children were found in the schools for the blind. The prevalence of blindness was 0.17 per 1000 children; the causes of blindness varied but there was no vitamin A- or measles-related corneal blindness and only one case of unoperated cataract.

Discussion: The low prevalence of blindness in children suggests that efforts at reducing childhood blindness in Kilimanjaro Region have been effective. Planners there should focus on community-based approaches to ensure that blind children have appropriate rehabilitation services and educational placements. While it remains impractical to carry out large childhood blindness surveys, this approach attached to a RAAB survey may be useful for generating information for planning services.

Comment: Large study, over 95,000 children screened. Screening attached to another survey already being done is a novel approach to gathering this type of data.

Two hypothetical nystagmus procedures: Augmented Tenotomy and Reattachment and Augmented Tendon Suture (sans tenotomy). Dell'Osso L et al. JPOS Nov-Dec 2009; 46:337-344.

The tenotomy and reattachment procedure directly affects only the enthesis of the tendon. The augmented tendon suture technique consists of placing several additional sutures in the tendon proximal to the tenotomy. Based on the hypothetical proprioceptive mechanisms for the beneficial effects of the T&R procedure, the authors hypothesize that the ATS technique will duplicate the therapeutic effect of T&R resulting in

a simpler procedure more suitable for single-session, multi-muscle surgery that may be required for improving the waveforms of nystagmus and less prone to cause complications.

Onset and progression of with-the-rule astigmatism in children with Infantile Nystagmus Syndrome.

Wang J, et al. Invest Ophthalmol Vis Sci 2010; 51:594-601. (Jan 2010)

Purpose: The purpose of this study was to examine the onset and progression of with-the-rule (WTR) astigmatism during the first 8 years of life in children with idiopathic infantile nystagmus syndrome (INS) or INS associated with albinism and to compare their development with that of normal children. Also explored was whether early WTR astigmatism influences emmetropization in children with INS and whether there is evidence of meridional emmetropization.

Methods: Cycloplegic refractions culled from medical records were converted into power vector components: M (spherical equivalent), J0 (positive J0 indicates WTR astigmatism), and J45 (oblique astigmatism). Two diagnostic groups (idiopathic, n = 106; albinism, n = 95) were evaluated and compared with a reference normal group (n = 495). Four age subgroups were evaluated: age ≤ 0.5 year, 0.5 < age ≤ 1 year, 1 < age ≤ 4 year, and 4 < age ≤ 8 year; in the normal group, no data were available for 4- to 8-year-olds. In addition, two longitudinal groups of children with INS (idiopathic, n = 22; albinism, n = 27) were studied.

Results: WTR astigmatism was prevalent among children with INS, even during infancy. Both the prevalence and magnitude of WTR astigmatism increased with age in both INS groups. Predicted J0 from fitted longitudinal data agreed with cross-sectional data. Spherical equivalent of children with INS demonstrated little emmetropization during the first 8 years of life.

Conclusions: Both the cross-sectional and longitudinal data showed that WTR astigmatism was common among children with INS and increased in magnitude with age during the first 8 years of life. Changes observed in meridional refractive error with age were consistent with meridional emmetropization in children with INS and WTR astigmatism.

Comment: This study is novel because it is known that WTR astigmatism has been reported frequently in school-age children and adults with INS. In normal infants, astigmatism typically decreases with age and most astigmatic infant eyes have against-the-rule (ATR) astigmatism. The authors show, through both cross-sectional and longitudinal data, that with-the-rule astigmatism is common among children with infantile nystagmus syndrome and increases in magnitude with age during the first 8 years of life.

Spectral domain optical coherence tomography for detection of foveal morphology in patients with nystagmus. Cronin TH, Hertle RW, Ishikawa H, et al. J AAPOS 2009;13:563-566.Dec

Evaluation of the retina is difficult in nystagmus patients secondary to their constant eye motion. Time domain optical coherence tomography (TD-OCT) is difficult in pediatric nystagmus patients because of the eye movement, shortened attention span and their compromised vision. Spectral domain OCT (SD-OCT) provides high-resolution 3-D macular imaging at 50x the speed of TD-OCT. This study tested 19 nystagmus patients (age 6-68 years) with SD-OCT. Two patients had latent nystagmus and 17 had infantile nystagmus syndrome (9 of whom had OCA). High-resolution macular images were obtainable in 18 of 19 patients (95%). There was a high correlation between the clinical examination and the SD-OCT findings involving the macula. Foveal hypoplasia patients showed persistence of the outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer and nerve fiber layer in the fovea.

The effect of horizontal rectus muscle surgery on clinical and eye movement recording indices in infantile nystagmus syndrome.

BAGHERI A, ALETAHA M, ABRISHAMI M: *Strabismus* 2010; 18: 58-64.

This was a prospective study designed to determine the effect of horizontal rectus muscle surgery on eye movement recordings in infantile nystagmus. Patients with Infantile Nystagmus Syndrome who had not previously undergone eye muscle surgery were assigned to one of three treatment groups. Group I consisted of those with head postures of $< 20^\circ$, binocular visual acuity worse than 20/30, and a tropia < 30 prism diopters (PD). This Group underwent recessions of all 4 horizontal rectus muscles. Group II consisted of those with head postures of $< 20^\circ$, binocular visual acuity worse than 20/30, and a tropia > 30 PD. Group II underwent large recessions of two horizontal rectus muscles. Group III consisted of patients with head postures $> 20^\circ$. Group III underwent Kestenbaum-Anderson surgery.

Fifty-eight patients with a mean age of 18.7 (SD \pm 9.10 years) were included, 29 in Group I, 23 in Group II, and 6 in Group III. Mean follow up after surgery was 18 \pm 7.4 months. Distance visual acuity improved in all three groups, but only in Group II was the change significant for both monocular and binocular acuity (p $<$ 0.001). In all three groups the velocity and amplitude of the nystagmus waveforms changed, but only in Group I was the change statistically significant (speed p=0.0; amplitude p=0.04). The authors concluded that horizontal rectus muscle surgery in patients with infantile nystagmus syndrome improves the visual acuity and nystagmus intensity.

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GENETICS/RETINOBLASTOMA ADDENDUM: LATE-BREAKING NEW ARTICLES

Intra-arterial Chemotherapy for the Management of Retinoblastoma: Four-Year Experience.

Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Arch Ophthalmol. 2011 Feb 14. [Epub ahead of print]

OBJECTIVE: To determine whether intra-arterial chemotherapy is safe and effective in advanced intraocular retinoblastoma.

DESIGN: 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.

RESULTS: 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.

CONCLUSION: Our experience suggests that intra-arterial chemotherapy is safe and effective in the treatment of advanced intraocular retinoblastoma.

Comment: This study by the experts in this technique shows that the procedure can be done, but success rates may differ in less experienced hands. The best success was for eyes that received intra-arterial chemotherapy as a primary treatment. This treatment was not nearly as successful (only 58.4%) for eyes that had previous treatment failure and therefore use as a rescue therapy requires more analysis.

Novel retinoblastoma treatment avoids chemotherapy: the effect of optimally timed combination therapy with angiogenic and glycolytic inhibitors on LH(BETA)T(AG) retinoblastoma tumors.

Houston SK, Piña Y, Murray TG, Boutrid H, Cebulla C, Scheffler AC, Shi W, Celdran M, Feuer W, Merchan J, Lampidis TJ. Clin Ophthalmol. 2011 Jan 27;5:129-37.

PURPOSE: The purpose of this study was to evaluate the effect of optimally timed combination treatment with angiogenic and glycolytic inhibitors on tumor burden, hypoxia, and angiogenesis in advanced retinoblastoma tumors.

METHODS: LH(BETA)T(AG) mice (n =30) were evaluated. Mice were divided into 5 groups (n =6) and received injections at 16 weeks of age (advanced tumors) with a) saline, b) anecortave acetate (AA), c) 2-deoxyglucose (2-DG), d) AA +2-DG (1 day post-AA treatment), or e) AA +2-DG (1 week post-AA treatment). Eyes were enucleated at 21 weeks and tumor sections were analyzed for hypoxia, angiogenesis, and tumor burden.

RESULTS: Eyes treated with 2-DG 1 day post-AA injection showed a 23% (P =0.03) reduction in tumor burden compared with 2-DG alone and a 61% (P < 0.001) reduction compared with saline-treated eyes. Eyes treated with 2-DG 1 week post-AA injection showed no significant decrease in tumor burden compared with 2-DG alone (P = 0.21) and a 56% (P < 0.001) decrease in comparison with saline-treated eyes. 2-DG significantly reduced the total density of new blood vessels in tumors by 44% compared to saline controls (P < 0.001), but did not affect the density of mature vasculature.

CONCLUSIONS: Combination therapy with angiogenic and glycolytic inhibitors significantly enhanced tumor control. Angiogenic and glycolytic inhibitors may have significant potential as alternative therapies for treating children with retinoblastoma.

Comment: This study was done in mice, so clinical trials in humans would be needed to confirm the effect, but it may offer another treatment for Rb that could avoid chemo and radiation. The side effects of these new agents would also have to be investigated.

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.

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.

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. Epub 2011 Jan 31.

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. 2011;2011:394730. Epub 2010 Dec 28.

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.

Lighting a candle in the dark: advances in genetics and gene therapy of recessive retinal dystrophies.

den Hollander AI, Black A, Bennett J, Cremers FP. J Clin Invest. 2010 Sep 1;120(9):3042-53. doi: 10.1172/JCI42258. Epub 2010 Sep 1.

Nonsyndromic recessive retinal dystrophies cause severe visual impairment due to the death of photoreceptor and retinal pigment epithelium cells. These diseases until recently have been considered to be incurable. Molecular genetic studies in the last two decades have revealed the underlying molecular causes in approximately two-thirds of patients. The mammalian eye has been at the forefront of therapeutic trials based on gene augmentation in humans with an early-onset nonsyndromic recessive retinal dystrophy due to mutations in the retinal pigment epithelium-specific protein 65kDa (RPE65) gene. Tremendous challenges still lie ahead to extrapolate these studies to other retinal disease-causing genes, as human gene augmentation studies require testing in animal models for each individual gene and sufficiently large patient cohorts for clinical trials remain to be identified through cost-effective mutation screening protocols.

Comment: This is a truly excellent review of gene therapy for retinal dystrophies. It is very well written and the illustrations are superb. It explains vision at a cellular level, as well as discussing treatment.

Gene therapy for Leber's congenital amaurosis is safe and effective through 1.5 years after vector administration.

Simonelli F, Maguire AM, Testa F, Pierce EA, Mingozzi F, Bennicelli JL, Rossi S, Marshall K, Banfi S, Surace EM, Sun J, Redmond TM, Zhu X, Shindler KS, Ying GS, Ziviello C, Acerra C, Wright JF, McDonnell JW, High KA, Bennett J, Auricchio A. Mol Ther. 2010 Mar;18(3):643-50. Epub 2009 Dec 1.

The safety and efficacy of gene therapy for inherited retinal diseases is being tested in humans affected with Leber's congenital amaurosis (LCA), an autosomal recessive blinding disease. Three independent studies have provided evidence that the subretinal administration of adeno-associated viral (AAV) vectors encoding RPE65 in patients affected with LCA2 due to mutations in the RPE65 gene, is safe and, in some cases, results in efficacy. We evaluated the long-term safety and efficacy (global effects on retinal/visual function) resulting from subretinal administration of AAV2-hRPE65v2. Both the safety and the efficacy noted at early timepoints persist through at least 1.5 years after injection in the three LCA2 patients enrolled in the low dose cohort of our trial. A transient rise in neutralizing antibodies to AAV capsid was observed but there was no humoral response to RPE65 protein. The persistence of functional amelioration suggests that AAV-mediated gene transfer to the human retina does not elicit immunological responses which cause significant loss of transduced cells. The persistence of physiologic effect supports the possibility that gene therapy may influence LCA2 disease progression. The safety of the intervention and the stability of the improvement in visual and retinal function in these subject support the use of AAV-mediated gene augmentation therapy for treatment of inherited retinal diseases.

Comment: This study reports that the effects of subretinal gene therapy in 3 patients with RPE65 LCA were long lasting and safe, which is great news for patients with this type of LCA.

Safety and efficacy of subretinal readministration of a viral vector in large animals to treat congenital blindness.

Amado D, Mingozzi F, Hui D, Bennicelli JL, Wei Z, Chen Y, Bote E, Grant RL, Golden JA, Narfstrom K, Syed NA, Orlin SE, High KA, Maguire AM, Bennett J. *Sci Transl Med.* 2010 Mar 3;2(21):21ra16.

Leber's congenital amaurosis (LCA) is a group of severe inherited retinal degenerations that are symptomatic in infancy and lead to total blindness in adulthood. Recent clinical trials using recombinant adeno-associated virus serotype 2 (rAAV2) successfully reversed blindness in patients with LCA caused by RPE65 mutations after one subretinal injection. However, it was unclear whether treatment of the second eye in the same manner would be safe and efficacious, given the potential for a complicating immune response after the first injection. Here, we evaluated the immunological and functional consequences of readministration of rAAV2-hRPE65v2 to the contralateral eye using large animal models. Neither RPE65-mutant (affected; RPE65(-/-)) nor unaffected animals developed antibodies against the transgene product, but all developed neutralizing antibodies against the AAV2 capsid in sera and intraocular fluid after subretinal injection. Cell-mediated immune responses were benign, with only 1 of 10 animals in the study developing a persistent T cell immune response to AAV2, a response that was mediated by CD4(+) T cells. Sequential bilateral injection caused minimal inflammation and improved visual function in affected animals. Thus, subretinal readministration of rAAV2 in animals is safe and effective, even in the setting of preexisting immunity to the vector, a parameter that has been used to exclude patients from gene therapy trials.

Comment: This excellent study demonstrates that in dogs that have received subretinal injection treatment with AAV in one eye, injecting the second eye is safe and effective. There is an antibody response to the AAV2 capsid, and 1/10 animals had a T cell response, but these were not clinically significant.

Mutations in chaperonin-like BBS genes are a major contributor to disease development in a multiethnic Bardet-Biedl syndrome patient population.

Billingsley G, Bin J, Fieggen KJ, Duncan JL, Gerth C, Ogata K, Wodak SS, Traboulsi EI, Fishman GA, Paterson A, Chitayat D, Knueppel T, Millán JM, Mitchell GA, Deveault C, Héon E. *J Med Genet.* 2010 Jul;47(7):453-63. Epub 2010 May 14.

BACKGROUND: Bardet-Biedl syndrome is a pleiotropic disorder with 14 BBS genes identified. BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9 form a complex called the BBSome, which is believed to recruit Rab8(GTP) to the primary cilium and promote ciliogenesis. The second group, the chaperonin-like proteins BBS6, BBS10, and BBS12, have been defined as a vertebrate-specific branch of the type II chaperonin superfamily. These may play a role in the regulation of BBSome assembly.

METHODS AND RESULTS: Using sequence analysis, the role of BBS6, 10 and 12 was assessed in the patient population comprising 93 cases from 74 families. Systemic and ocular phenotypes were defined. In the study, chaperonin-like BBS gene mutations accounted for the disease in approximately 36.5% of BBS families. A total of 38 different non-polymorphic exonic sequence variants were identified in 40.5% of BBS families (41.9% cases), of which 26 were novel (68%). Six cases had mutations present in more than one chaperonin-like BBS gene. One case with four mutations in BBS10 had a phenotype of overall greater severity. The phenotypes observed were beyond the classic BBS phenotype as they overlapped with characteristics of MKKS (congenital heart defect, vaginal atresia, hydrometrocolpos, cryptorchidism), as well as Alström syndrome (diabetes, hearing loss, liver abnormalities, endocrine anomalies, cardiomyopathy).

CONCLUSIONS: While overlap between the MKKS and BBS phenotypes has previously been reported for cases with BBS6 mutations, we also observed MKKS phenotypes involving BBS10 and BBS12 and Alström-like phenotypes associated with mutations in BBS1, BBS2, BBS6, BBS7, BBS9, BBS10 and BBS12 for the first time.

Comment: This is an excellent study with a large group of BBS patients. This disorder has such unusual findings--extra digits, obesity, retinitis pigmentosa—that it was difficult to understand how so many different genes could cause the same phenotype until the BBSome was discovered. This is a protein complex involved in intracellular trafficking which requires the protein product of multiple BBS genes to form correctly. This paper shows that other related genes cause a large percentage of BBS, and that there is phenotypic overlap with other syndromes such as MKKS and Alstrom syndrome.

PLASTICS ADDENDUM:

Hyperkalemia complicating Propranolol treatment of an infantile hemangioma. Pavalkovic H., Kietz S., Lauerer P., *et.al.* *Pediatrics* 2010;126:e1589-e1593.

The authors report of a case of 17 week old preterm female with large cutaneous-subcutaneous hemangioma of the right lateral thoracic wall. The hemangioma was 11x8x1.5 cm with extension into the pleura. Propranolol, 1 mg/kg/day divided into three doses was initiated then increased to 2mg/kg/day on day 2. There was immediate response of the hemangioma to the drug with significant decrease in size. However, after 72 hours of therapy, the patient had a significant increase in serum potassium up to 6mmol/L requiring diuretics and fluid boluses to normalize her potassium levels. It required several weeks of this therapy to completely eliminate the hyperkalemia.

[NB: I had a three week old infant with a 4 x 3 x 1cm hemangioma of the anterior lateral orbit who developed two episode of non-responsiveness and was found to be hyperkalemic. This responded to diuretics and fluid boluses. The lesion had had a rapid response to the loading doses of propranolol, but developed hyperkalemia in 48 hrs of initiating the drug.

These children need to be monitored for hyperkalemia especially if there is a rapid response of the hemangioma to the drug]