Cytomegalovirus retinitis in pediatric acute lymphoblastic leukemia undergoing hematopoietic stem cell transplant: a clinical case and review of the literature

Francesca Allegrini, Elena Gusson, Giorgio Marchini

Cytomegalovirus (CMV) retinitis is a well-known complication in immunocompromised patients undergoing allogeneic hematopoietic stem cell transplant (HSCT). However, data on pediatric individuals are limited and controversial. Our aims are to describe a case of bilateral CMV retinitis in a child treated with HSCT for acute lymphoblastic leukemia (ALL) and to report a comprehensive review of the literature.

We collected and analyzed anatomical, functional and laboratory patient’s data. Treatment approaches were evaluated in a multidisciplinary team which involved pediatricians, infectiologists, oncologists and ophthalmologists in order to avoid side effects and drug toxic reactions.

A 10 years old male child developed CMV viremia 160,000 copies/ml two months after HSCT for ALL. The ocular screening examination was within normal limits and the visual acuity was 20/20 bilaterally. A systemic intravenous therapy with Foscarnet 120 mg/kg/die was first established, followed by a maintenance therapy with 90 mg/kg/die. After three months the patient complained of subacute onset of blurred vision. Slit-lamp anterior segment examination was within normal limits, but the visual acuity was 20/40 in both eyes. The fundus presented peripheral white lesions associated with hemorrhages bilaterally, which were compatible with active CMV retinitis. The value of CMV viremia was 20,400 copies/ml. In agreement with other pediatric specialists we treated the child with alternating Foscarnet 120 mg/kg and Ganciclovir 5 mg/kg every other day and anti-CMV immunoglobulin 500 UI once weekly. The systemic therapy was combined with bilateral intravitreal injections of Ganciclovir 1.0mg/0.02 ml once weekly. After six weeks of treatment his visual acuity improved at 20/25 in both eyes and the retinitis resulted inactive, in line with CNV viremia.

The prompt and appropriate treatment of CMV retinitis in children is the most important ocular prognostic factor. However, the optimal management has not yet been established and represents a challenge for the ophthalmologist and other pediatric specialists. Different protocols and dosages of intravitreal therapy in various combination with systemic anti-CMV drugs have been described, without approved uniformity among studies. In our case the treatment of CMV retinitis with a lower dose of intravitreal Ganciclovir in association with the systemic treatment resulted effective.
ABSTRACT:

Title: ROP Expert Confidence in Determining Plus Disease in Borderline Images

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Purpose

Difficulty in identifying Plus Disease (PD) in Retinopathy of Prematurity (ROP) is well documented. This study is to evaluate the confidence with which ROP experts were able to identify PD or Pre-PD among images that were categorized as borderline PD by an experienced non-physician reader.

Methods

Nine disc center images were selected by an experienced non-physician e-ROP certified grader that were judged morphologically to be between a definite PD and a definite pre-PD. These images were independently evaluated by 10 e-ROP certified ophthalmologists (ROP experts) who have extensive experience in the clinical diagnosis and treatment of ROP, for the presence of PD or pre-PD with an assessment of confidence from 1-10 (1 being not at all certain and 10 completely certain). Figure 1.

Results

The results are shown in Table 1. Among 5 e-ROP images identified as PD by both clinical examination and reading center image evaluation, one image was identified as pre-PD by one expert, another as pre-PD by two experts and a third image as pre-PD by seven experts. Among 2 images identified as pre-PD by both clinical exam and image evaluation, one was identified as PD by three experts but with low confidence. An image identified as pre-PD by image evaluation and normal by clinical examination was judged to be PD by 2 clinicians.

Conclusions

Difficulty exists even among ROP experts in identifying plus, especially in borderline cases.
Table 1. Level of confidence among expert graders in identifying plus disease in equivocal cases.

<table>
<thead>
<tr>
<th>Borderline case #</th>
<th>e-ROP Reading Center grading</th>
<th>Clinical exam Diagnosis</th>
<th># of ROP experts call plus (%)</th>
<th># of ROP experts call preplus (%)</th>
<th>Median confidence score of ROP experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Plus</td>
<td>Plus</td>
<td>9 (90%)</td>
<td>1 (10%)</td>
<td>9 (8, 9)</td>
</tr>
<tr>
<td>II</td>
<td>Preplus</td>
<td>Preplus</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td>9 (7,10)</td>
</tr>
<tr>
<td>III</td>
<td>Plus</td>
<td>Plus</td>
<td>8 (80%)</td>
<td>2 (20%)</td>
<td>8 (6, 8)</td>
</tr>
<tr>
<td>IV</td>
<td>Plus</td>
<td>Preplus</td>
<td>2 (20%)</td>
<td>8 (80%)</td>
<td>8 (6, 8)</td>
</tr>
<tr>
<td>V</td>
<td>Preplus</td>
<td>Normal</td>
<td>2 (20%)</td>
<td>8 (80%)</td>
<td>8 (6, 8)</td>
</tr>
<tr>
<td>VI</td>
<td>Preplus</td>
<td>Preplus</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
<td>6 (5, 8)</td>
</tr>
<tr>
<td>VII</td>
<td>Plus</td>
<td>Plus</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
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<tr>
<td>VIII</td>
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<td>Plus</td>
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<td>IX</td>
<td>Plus</td>
<td>Plus</td>
<td>10 (100%)</td>
<td>0 (0%)</td>
<td>10 (10,10)</td>
</tr>
</tbody>
</table>
Abstract

Abstract Purpose: To characterize the clinical features in young people with angle closure, and to determine the incidence of and risk factors for acquired anterior segment abnormality following retinopathy of prematurity (ROP) treatment. Methods: We performed two retrospective case-control series. First series – consecutive young angle closure patients without prior surgeries, with and without a history of ROP treatment; second series – consecutive patients who underwent ROP treatment, without and without acquired anterior segment abnormalities. Results: In the first series, 25 eyes of 14 consecutive angle closure patients were included. 19 eyes (11 patients, 78.6%) had a history of treated ROP, while 6 eyes (3 patients) belonged to full-term patients. The treated ROP eyes had significantly shallower anterior chambers (1.77 +/- 0.17 mm vs 2.72 +/- 0.18 mm, P < 0.0001) and thicker lenses (5.20 +/- 0.54 mm vs 3.98 +/- 0.20 mm, P = 0.0002) compared to the full-term controls. In the second series, 79 eyes of 40 patients were included, with median gestational age of 24.6 weeks. Acquired iridocorneal adhesion was noted in eight eyes (10.1%) at a mean age of 4.7 years and was associated with prior zone 1 and plus disease (P = 0.0013), a history of initial intravitreal bevacizumab treatment (IVB, P = 0.0477) and a history of requiring additional IVB after initial treatment (P = 0.0337). Conclusions: Many young angle closure patients may have a history of treated ROP, and may present with the triad of increased lens thickness, microcornea and angle closure.
Genomic Analysis of Aqueous Humor cell-free DNA in Retinoblastoma Predicts Eye Salvage: The Surrogate Tumor Biopsy for Retinoblastoma

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Abstract

- **Purpose**: To identify tumor-derived cell-free DNA (cfDNA) in the aqueous humor (AH) of retinoblastoma eyes and correlate somatic chromosomal copy number alterations (SCNAs) in the AH with clinical outcomes, specifically eye salvage.

- **Methods**: AH was extracted via paracentesis during intravitreal injection of chemotherapy or enucleation. CfDNA was isolated; shallow whole genome sequencing performed to assess tumor DNA fractions and highly recurrent SCNAs including gain of 1q, 2p, 6p, loss of 13q, 16q and focal MYCN amplification. Clinical features, treatment regimen and eye salvage were recorded. Clinical analysis was retrospective.

- **Results**: Sixty-three samples of AH from 29 eyes of 26 patients were evaluated; 13 eyes were enucleated and 16 were salvaged. The presence of detectable SCNAs was 92% in enucleated eyes versus 38% in salvaged eyes (p=0.006). 6p gain was the most common SCNA found in 77% of enucleated versus 25% of salvaged eyes (p=0.0092). 6p gain was associated with a ten-fold increased odds of enucleation (OR=10.95%CI:1.8-55.6). The mean amplitude of 6p gain was 1.47 in enucleated versus 1.07 in salvaged eyes (p=0.001). The probability of ocular survival was higher in eyes without detectable SCNAs in the AH (p=0.0028).

- **Conclusions**: This is the first study to show that clinical outcomes correlate with highly-recurrent SCNAs in the AH from retinoblastoma eyes. These preliminary results suggest that AH can reliably serve as a surrogate to tumor biopsy. This novel approach may provide additional objective information beyond clinical classification to determine the likelihood of globe salvage for patients with advanced retinoblastoma.
Neurodevelopmental Outcomes of Neonates with Retinopathy of Prematurity Treated with Primary Intravitreal Bevacizumab.

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Abstract

- **Purpose:** To evaluate neurodevelopmental outcomes among infants treated for retinopathy of prematurity (ROP) at (1) our institution and (2) in the whole of the United States.

- **Methods:** Part 1: Before-and-after retrospective chart review identified 40 infants treated with laser and 46 treated with primary intravitreal bevacizumab (IVB). Primary outcomes were death, hearing loss, bilateral visual impairment (BVI), and cerebral palsy (CP); odds ratios were calculated to determine factors associated with CP. Secondary outcomes were mean Bayley-III scores. Part 2: Using Marketscan, a national claims database, neurodevelopmental and ocular outcomes among infants treated from 2011-2014 with at least 2 years follow-up were evaluated.

- **Results:** Part 1: Overall, there were no significant differences in primary outcome measures. However, adjusted odds of BVI were significantly higher with laser compared to IVB (OR 13.2, p = 0.038). Although IVB was not associated with CP, both hydrocephalus and BVI were strongly correlated with CP. Mean Bayley-III scores were similar comparing 9 laser-treated infants to 13 IVB-treated infants. Part 2: Of 18,384 infants identified with ROP, 224 received laser and 59 received injections. Four patients in the laser group and no patient in the IVB group expired. There was a trend towards less retinal detachment with injections than laser (5% and 11%, p=0.19). Comparing injection to laser, rates of any developmental delay were 93% and 91%; other delays were motor (19% and 22%, p=0.541), cognitive (37% and 34%, p=0.676) and language (63% and 49%, p=0.063). Rates of CP were 37% with injections and 17% with laser, p=0.001, although infants receiving injections were more also likely to have severe intraventricular hemorrhage (29% and 17%, p=0.05). The difference in CP by treatment group was not statistically significant after propensity score matching (OR = 1.96, p=0.06).
Conclusions/Discussion: Visual outcomes are an important aspect of neurodevelopment. BVI and retinal detachment were more frequent after laser. IVB was not associated with severe developmental disabilities at our institution. Across the US, although developmental outcomes seem to favor laser treatment, severe intraventricular hemorrhage likely represents a confounding factor. There appears to be a propensity to treat sicker infants with injections.
The clinical course and progression of incontinentia pigmenti retinopathy in treated and untreated patients.

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PURPOSE: To describe the clinical course and progression of consecutive patients with incontinentia pigmenti.

METHODS: An observational cohort retrospective study was performed with consecutive patients with incontinentia pigmenti (IP) identified at a tertiary care academic medical center between 2011 and 2019. Patients diagnosed with IP that had undergone at least two examinations under anesthesia (EUA) with fundus imaging and fluorescein angiography (FA) were included. Twenty eyes of ten females were followed for a minimum of 6 months of follow-up.

RESULTS: The median duration of follow-up was 40 months (range 6 months – 81 months). Median age at last follow-up examination was 5-years-old (range 1 year – 26 years). Four eyes of 2 patients had normal examinations and normal FA without avascularity, vascular staining or leakage. Ten eyes of 5 patients demonstrated abnormal vascular findings on initial FA that were not detected with indirect ophthalmoscopy. Only 3 eyes demonstrated pathology on initial indirect ophthalmoscopic exam (two vitreous hemorrhages, one tractional retinal detachment) and 2 of these eyes were of older age at presentation (18 and 22-years-old). Avascular retina was treated with laser photocoagulation only if associated with vascular staining or leakage on FA. Nine eyes of 5 patients received laser photocoagulation and 1 eye required vitrectomy and membrane peel. No eyes developed increased avascularity, vascular leakage or staining than what was present on initial examination. No eyes developed retinal detachment that was not present on initial examination.

CONCLUSION: Examination under anesthesia with FA detects pathology in patients with IP that is not detected with indirect ophthalmoscopy alone. Two of 3 eyes with severe pathology did not receive EUA with FA in the first few years of life. Eyes that received EUA and FA with prompt laser photocoagulation if needed did not develop progression of retinopathy or retinal detachment during the follow-up period. Of eyes with avascularity only that did not require laser, none developed worsening increased avascularity, vascular leakage or staining during the follow-up period.
Aggressive Posterior Retinopathy of Prematurity (APROP) in India: insights from quantitative analysis using deep learning in the US and India

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Abstract

Purpose: To use a deep learning based ROP severity score to quantitatively evaluate ROP disease severity in the US and India.

Methods: We conducted a retrospective analyses of the Imaging and Informatics in ROP (i-ROP) cohort from 7 North American centers (between 2011 – 2018) as well as within the Aravind Eye Hospital (AEH) ROP telemedicine network (between 2002 – 2018). Institutional review board approval was obtained at all sites. Widefield digital fundus photographs were obtained using the Retcam camera (Natus Medical Incorporated, Pleasanton, CA). Two separate AEH cohorts were analyzed: 1) all patients with a clinical diagnosis of APROP between 2002-2018, and 2) all patients screened in the telemedicine program between 2014 – 2017. Images from the i-ROP cohort and the latter AEH cohort were analyzed using a deep-learning based ROP vascular severity score from 1-9.

Results

In the North American cohort, infants with APROP tended to be more premature by birthweight (BW, mean 617 gm) and gestational age (GA, mean 24 weeks) than other babies with non-APROP treatment-requiring (TR) ROP (mean 736 gm and 26 weeks) and those without TR-ROP. The mean ROP vascular severity score correlated with the degree of ROP severity for each ROP disease category including APROP (Figure). In the AEH cohort, the mean BW was 1400 gm and mean GA was 31 weeks in patients with APROP. There were significant differences between mean ROP severity between hospitals in the AEH telemedicine network, even after controlling for BW and GA.

Conclusions

The key findings are: 1) Infants in North America with APROP tend to be younger and smaller, and develop peak disease earlier than infants with non-APROP TR-ROP. 2) Disease severity (including APROP) is quantifiable with a deep learning based ROP vascular severity score. 3) In India, infants often develop APROP at birthweights and gestational age that would confer zero risk of any ROP in the US. 4) Hospital level disease severity can be quantified using the ROP vascular severity score to identify outlying hospitals, which may lead to improved primary prevention.
Figure: Box plot showing distribution of ROP vascular severity within the i-ROP cohort study by ROP disease category including APROP.
Novel autosomal dominant disease associated to EFEMP1 gene mutation with choroidal calcification, peripheral hypopigmentation, and ocular hypertension: report of two pediatric cases.

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Purpose: To define two pediatric cases from a novel autosomal dominant disease associated to EFEMP1 gene mutation with choroidal calcification, peripheral hypopigmentation of the retina, and ocular hypertension.

Methods: We performed a cross-sectional study of the family from the same pedigree. Complete ophthalmological examination, fundus pictures, fluorescein angiogram (4 affected eyes), optical coherence tomography (6 affected eyes), autofluorescence (6 affected eyes) were recorded. A whole exome sequencing was performed to the two proband siblings and after extensive study one strong candidate gene emerged. Sanger sequencing was used to corroborate the mutation in the rest of the family.

Results: A total of 42 members of the family (84 eyes) were examined. We found eleven affected patients (22 eyes). Mean age 34.9 years (range 9 to 62). Mean BCVA 1.4 LogMAR (range 0 to 2). Patients were classified into 3 groups according to clinical findings: complete if they had posterior pole calcification of the choroid, peripheral hypopigmentation of the retina and ocular hypertension; partial when one or two of the previous characteristics were present; probable if no other cause such as trauma, previous surgery, systemic disease or uveitis explained the cause of phthisis bulbi.

A whole exome sequencing was performed to the two proband siblings and after extensive study one strong candidate gene emerged: EFEMP1. All family members with the disease (except for the youngest where the mother refuses testing) are positive to EFEMP1 mutation. None of the non-affected individuals have abnormal EFEMP1 gene.

The youngest affected patient was a 13 year old female with peripapillary calcification and mild peripheral hypopigmentation without ocular hypertension (partial). The next youngest affected kid is a 13 year old male already with the complete phenotype.

Conclusion: To our knowledge there is no other family with the same clinical picture in the literature. The youngest patient has the mildest form of the disease. These are the first reports of the pediatric cases from this autosomal dominant disease (Tabasco syndrome) with: choroidal calcification, peripheral hypopigmentation and ocular hypertension associated to a mutation of the EFEMP1 gene. Further research is mandatory both in vitro and in vivo.
Capturing Macular Neurovascular Development in Infants with Retinopathy of Prematurity

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Abstract

- **Purpose:** Histopathological studies laid the foundation for our current understanding of human macular development. The advent of bedside handheld optical coherence tomography (OCT) imaging offers an opportunity to observe *in situ* human retinal development.

- **Methods:** Under IRB-approved protocol, we report the use of an investigational handheld noncontact swept source OCT system capable of OCT angiography (OCT-A, 200 kHz swept source OCT engine, 300 A-scans/B-scan, 4 repeated B-scans at 300 lateral locations, 2.4 seconds scan duration) to capture at the bedside human macular development.

- **Results:** We imaged at the bedside and in clinic with research structural and angiography OCT in 15 preterm infants as young as 33 weeks postmenstrual age (PMA). We captured vascular flow in the superficial perifoveal capillaries surrounding the impending fovea at the temporal notch, as well as the formation of a foveal avascular zone in the same eye 1 and 2 weeks later. We also obtained imaging of both superficial and deep vascular complexes in other preterm infants with or without pharmacological dilation. While these *in vivo* observations are consistent with our prior knowledge from histopathological studies, we document noninvasively the timing and phases of macular development.

- **Conclusions/Discussion:** OCT-A images from preterm infants of 33 weeks PMA document the earliest views of capillary vascular flow in the developing perifoveal retinal vasculature. We have captured with and identified methods to improve bedside noncontact handheld OCT-A imaging. These advancements will contribute to our understanding of the timing and variation of early human retinal neurovascular development and pathology.
Effect of anti-VEGF therapy on persistent vascular leakage and neovascularization in familial exudative vitreoretinopathy

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Abstract

- **Purpose:** To describe the effect of anti-vascular endothelial growth factor (VEGF) therapy on persistent vascular leakage and on neovascularization in familial exudative vitreoretinopathy (FEVR) previously treated with peripheral laser photocoagulation.

- **Methods:** A retrospective chart review was conducted of patients with FEVR treated between 2005 and 2015. Those who received intravitreal anti-VEGF therapy during the study period were included. The main outcome measure was progression to retinal detachment.

- **Results:** A total of 404 patients with FEVR were treated between 2005 and 2015. Of these, 32 patients (39 eyes) received intravitreal anti-VEGF therapy during the study period (7.9%). All study eyes underwent fluorescein angiography and had been treated with peripheral laser photocoagulation (average: 3 sessions/eye) before the first intravitreal anti-VEGF injection. The indications for anti-VEGF treatment included: persistent/refractory peripheral vascular leakage (26 eyes), retinal neovascularization (8 eyes), and neovascular glaucoma (5 eyes). The mean number of anti-VEGF injections was 3.5 in the persistent vascular leakage group, 2.8 in the retinal neovascularization group, and 1.6 in the neovascular glaucoma group. The mean length of follow-up was 5.5 years (range 1 – 11 years). Combined tractional-exudative retinal detachment developed in 30.8% of eyes in the persistent vascular leakage group, 62.5% of eyes in the retinal neovascularization group, and 80% of eyes in the neovascular glaucoma group.

- **Conclusions/Discussion:** Persistent peripheral vascular leakage, and neovascularization after peripheral laser photocoagulation in familial exudative vitreoretinopathy portend a poor prognosis. Anti-VEGF therapy has limited effect on preventing the progression to retinal detachment.
Prethreshold ROP - VEGF Inhibition Without VEGF Inhibitors

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**Purpose:** To discuss addressable patient-care factors, early and late in the course of the initial hospitalization of premature newborns, that may encourage more physiologic retinal vessel formation, hopefully reducing the rate of progression to Type I ROP.

**Methods:** Discussion of several modifiable systemic factors during hospitalization after premature birth, both early in the course of hospitalization and later on, when Prethreshold ROP appears.

**Results:** The following will be discussed as potential interventions during the early and late phases of ROP development:
- **Oxygen management** - What are the optimal settings early and late? Is there a role for supplemental oxygen for prethreshold ROP?
- **Anemia management** - Is there an advantage to maintaining or correcting anemia, early and late?
- **Light Adaptation State** - Given the effect of light adaptation on rod photoreceptor oxygen consumption, what light levels are best early and late?
- **Nutrition** - What do we know about the potential value of supplementing IGF, PUVA, Arachidonic Acid, Erythropoietin, and perhaps other nutritionals early and late?

**Conclusions:** Increasingly anti-VEGF agents are being used either as a monotherapy or in conjunction with laser. Anti-VEGF agents may be better than laser for the initial treatment of Aggressive Posterior ROP, and may be associated with less myopia than laser, but they have potential risks, including late recurrence of ROP, retinal vascular arrest, and prolonged systemic VEGF suppression, causing loss of fenestrations in the capillary beds of the choriocapillaris, choroid plexus, renal capillaries and capillaries in the pancreas and thyroid. We have found that a combination of supplemental oxygen, light adaptation to reduce rod oxygen consumption, and correction of severe anemia often leads to regression of Prethreshold ROP and full retinal vascularization. The objective with this approach is to lower pathologically elevated VEGF levels into a physiologic range, without profoundly suppressing VEGF, as occurs with currently used anti-VEGF doses. Recent evidence that dramatically lower doses of bevacizumab are at least as effective, and perhaps superior to higher doses supports the notion that the aim should be reduction in VEGF levels to a physiologic range, not prolonged, complete inactivation of VEGF.
Pre-treatment vs. Post-Treatment Optical Coherence Tomographic Angiography in children with strabismic and anisometropic amblyopia.

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Abstract

• Purpose: Amblyopia is a significant cause of visual deficits in childhood. Previous studies of children with amblyopia have shown lower vessel density in the superficial and deep capillary retinal plexuses (SCP and DCP, respectively) using optical coherence tomographic angiography (OCTA). No studies of children with amblyopia have used OCTA to compare pre- and post-treatment vascular density to determine whether there are any changes after treatment for amblyopia.

• Methods: This is a case series of full-term children with strabismic and anisometropic amblyopia (>2-line interocular difference in visual acuity (VA)). Subjects underwent OCTA (Optovue, Fremont, CA) during pre-treatment and post-treatment clinical visits. Age, VA, and retinal vessel densities from 3x3mm and 6x6mm macular OCTA scans of both eyes were recorded.

• Results: 4 amblyopic eyes and 3 fellow non-amblyopic eyes of 4 subjects were included. Median follow up was 135 days (range: 104-181). The mean age of subjects was 6.5 years (range: 3-9). The mean LogMAR VA differed in pre-treatment versus post-treatment setting for the amblyopic eye (0.39+/-0.07 vs. 0.23+/-0.13, p<0.05) but not for the fellow eye. OCTA of pre-treatment amblyopic eyes revealed significantly decreased vessel density compared to non-amblyopic eyes in the SCP Parafoveal (PF) superior region on the 3x3mm scans, the SCP PF inferior and nasal hemispheres, the whole image DCP, and the DCP superior and inferior hemispheres on the 6x6mm scans (p<0.05 for all). Follow-up OCTA of post-treatment amblyopic eyes revealed that none of these significant differences persisted when comparing vessel densities to the original OCTA images of non-amblyopic eyes. In the amblyopic eye, the SCP PF nasal vessel density on 6x6mm scans increased significantly from pre-treatment to post-treatment (52.175+/-3.204% vs. 55.75+/-2.35%, p<0.05). No similar vessel density changes were noted in fellow non-amblyopic eyes.

• Conclusions/Discussion: Our results demonstrate that the differences in retinal vessel density that exist between amblyopic and fellow eyes in a pre-treatment setting resolve following amblyopia treatment. Understanding changes in retinal vasculature in amblyopes may lead to earlier diagnosis and treatment. Additionally, vascular changes that resolve with treatment could lead to novel therapeutic targets for amblyopia. Further studies, with larger sample sizes, are necessary to confirm these findings.
Late Onset Retinal Findings and Complications in Untreated Retinopathy of Prematurity

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Abstract

Purpose:
To investigate late onset findings and complications of eyes with history of retinopathy of prematurity that did not receive treatment at infancy, presenting with retinal findings and complications.

Methods:
This is a retrospective, non-consecutive, non-comparative, multi-center case series of premature patients with history of ROP that did not receive treatment at infancy and did not meet established criteria for treatment at infancy, presenting with late retinal findings, manifestations or complications.

Results:
203 patients were submitted from 18 sites, of which 17 patients were excluded. A total of 363 eyes were included in the study. The average age was 34.5 years (7-76), average reported gestational age was 26.6 weeks (23-34) and average birth weight was 875 g (425-1590). Common findings included lattice like change in 196 eyes (54.0%), atrophic holes in 126 eyes (34.7%), retinal tears in 111 eyes (30.6%), retinal detachments in 140 eyes (38.6 %), tractional retinoschisis in 44 eyes (11.9%) and visible ridge tissue in 112 eyes (30.5%). Fluorescein Angiograms (FA) were performed in 113 eyes (31.1%), of which 59 eyes (52.2%) had leakage and 16 eyes (14.2%) had neovascularization. Incomplete vascularization posterior to zone 3 was common (71.6% of eyes). Patients with RD were slightly more premature than patients without RD (26.2 wks and 832 g vs 27.1 wks and 907 g). Eyes with RD that had an FA done were more likely to have neovascularization (32.4% vs 6.3%).

Conclusion/Discussion:
Significant late findings and complications were common in premature patients with regressed ROP without treatment at infancy and not meeting treatment threshold during infancy, with RDs observed in 38.6%. Significant contributing factors to RDs include atrophic holes within peripheral avascular retina, ridge tissue with residual traction as well as premature vitreous syneresis. We recommend regular exams, ultra-widefield FAs to assess for vascular activity, and consideration or prophylactic laser treatment in some cases as well as educating the parents and patients on the life-long risk of retinal detachments and complications. Prospective studies are needed to explore the frequency of complications as well predictive factors, and weather similar findings are seen in anti-VEGF treated eyes.
Vitreoretinal separation occurs in an abnormal fashion in abusive head trauma

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Purpose: To compare the pattern of vitreoretinal separation in abusive head trauma compared to physiologic age-related posterior vitreous detachment.

Methods: Two patients with a history of abusive head trauma and subhyaloid hemorrhage who underwent pars plana vitrectomy are compared to retina clinic patients by multimodal imaging.

Results: A two-year old male presented with altered mental status and was found to have subdural hemorrhage and bilateral macula-obscuring preretinal hemorrhages. His case was determined to be highly suspicious for abusive head trauma by the child advocacy specialist. Three months later, the child was found to have a persistent subhyaloid hemorrhage in the right eye by optical coherence tomography obscuring the foveal center. The area of vitreoretinal separation encompassed the optic nerve and fovea, but did not extend peripherally. The child underwent pars plana vitrectomy and the subhyaloid hemorrhage was entered and unroofed.

A three-month old male presented with seizures and was found to have acute on chronic subdural hemorrhage and bilateral preretinal hemorrhages in the posterior pole and near-confluent retinal hemorrhages in the entire fundus. The child's parent admitted to shaking the child. One month later, the patient was found to have persistent subhyaloid hemorrhage in the left eye obscuring the macula and optic nerve. Ultrasound demonstrated the posterior vitreous cortex spanning the optic nerve. The child underwent pars plana vitrectomy and prior to entering the hyaloidal space, the hemorrhage began to clear through the Weiss ring and the area of Martegiani, suggesting a direct connection. The subhyaloid space was entered and unroofed, and circumacular folds became apparent.

Wide-angle optical coherence tomography of 66 retina clinic patients indicated that vitreoretinal separation occurs in the mid-periphery before involving the macula.

Discussion: In physiologic partial posterior vitreous detachment, vitreoretinal separation begins in the mid-periphery. In two cases of abusive head trauma, we observed a non-physiologic pattern of vitreoretinal separation, which was limited to the posterior pole. The area of distribution of pre-retinal hemorrhage can be used to distinguish subhyaloidal and sub-inner limiting membrane hemorrhages.
Predictive angiographic features of Retinopathy of Prematurity

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Abstract

- Purpose
To evaluate the fluorescein angiography as a predictive tool for the development of treatment-requiring retinopathy of prematurity (ROP).

- Methods
All infants born in 5 academic institutions in Italy between 2004 and 2017 with retinal vascularization limited to zone I or to zone II with a high risk of developing clinically significant ROP underwent fluorescein angiography (FA) at around 31 weeks of postmenstrual age (PMA), and then every 15 days until discharge. Angiograms taken before 34 weeks PMA were anonymized and indexed as sets of eyes in a randomized fashion. Two ROP experts evaluated the images independently grading a list of FA findings using criteria reported in our previous paper. If discordant grading, a consensus grading was reached by the two graders. Univariate and multivariate models were used to determine the correlation of these FA findings with the development of treatment-requiring ROP.

- Results
A total of 184 eyes from 102 infants were selected for this study. 23-47% of the images were graded as ungradable per each evaluated FA feature. Vascular abnormalities at the junction between vascular and avascular retina, but not anomalies in the vascularized retina, were associated with future development of treatment-requiring ROP.

- Conclusions/Discussion
Some early angiographic features correlate with the evolution of ROP. This study is another important building block towards understanding the pathophysiology of ROP and these data may open the doors to many future applications of FA in the management of ROP.
Optical Coherence Tomography Measurements of Retinal and Choroidal Thickness In Preterm Infants

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Abstract

- Purpose: To obtain retinal and choroidal thickness of neonates with retinopathy of prematurity (ROP).
- Methods: An observational consecutive case series was performed at a single hospital in the neonatal intensive care unit (NICU). An examination consisting of retinoscopy and indirect ophthalmoscopy was performed. In addition, optical coherence tomography (OCT) was performed with and without general anesthesia using the arm-mounted Spectralis Heidelberg Flex Module.
- Results: Images were obtained from 28 eyes of 15 patients. Nine (60%) of patients were male. The infants presented with varying levels of ROP ranging from Stage 1 to Stage 4A treated with anti-VEGF, panretinal photocoagulation, and/or scleral buckling. The average gestational age was 27 weeks and 5 days; the average post menstrual age at the first image capture was 48.7 weeks. The average refractive error was +0.97 Diopters. The average central macular thickness (CMT) based on ETDRS 1mm² at the first image was 231.56μm +/- 108.16μm. In ten eyes, serial OCT images were obtained; there was no statistically significant difference between CFT at baseline (183.1μm +/- 122.1μm) and final follow up (163.9μm +/- 52.3μm, p = 0.65). In 17 eyes (61%), a retained inner retina was appreciated and in 8 eyes (28.6%) cystoid macular edema was present. In 9 eyes, choroidal thickness measured with an average of 250μm. Notably there was no correlation between refractive error and central macular or foveal thickness or choroidal thickness. There was also no correlation between gestational age or birth weight with foveal or choroidal thickness.
- Conclusions/Discussion: Our study demonstrated that OCT imaging using the arm-mounted Spectralis Heidelberg Flex Module was possible in the NICU setting. We found no correlation between refractive error, gestational age, birth weight and retinal or choroidal thickness.
Vitrectomy for pediatric toxocariasis assisted by preoperative ultrasonic bimicroscope

Jinghua Liu

Purpose: to explore the clinical effects of pediatric toxocariasis underwent vitrectomy assisted by preoperative ultrasonic bimicroscope.

Methods: the medical records of 88 patients of pediatric ocular toxocariasis who underwent vitrectomy and preoperative ultrasonic bimicroscope (UBM) in Beijing Tongren Hospital between March 2012 to March 2018 were retrospectively reviewed, with a postoperative follow-up of at least 5 months.

Results: A total of 88 patients (88 eyes) were included with a mean age of 7.33 years, and 65.9% (58/88) of the patients were boys. Preoperative UBM revealed that 48.9% (43/88) of the patients had peripheral vitreous condensations that more than 6 clock-hours, and the inferior temporal and nasal quadrants were frequently involved. Scleral incisions were adjusted according to preoperative UBM results and 51.1% (45/88) of the patients underwent vitrectomy combined with lensectomy. At last follow-up, visual acuity remained stable in 19 eyes (19/88, 21.6%) and improved in 67 eyes (67/88, 76.1%); 61 eyes had tractional retinal detachment preoperatively, among which 47 eyes had retinal reattachment or partial retinal reattachment.

Conclusions: Preoperative UBM seems to valuable in detecting the extent and range of peripheral vitreoretinal pathologies of pediatric ocular toxocariasis. Vitrectomy with adjusted scleral incisions assisted by preoperative UBM seems to be beneficial for the short-term prognosis of visual acuity and anatomic outcomes of pediatric ocular toxocariasis.
Patient Outcomes in Coats’-like Retinitis Pigmentosa

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Abstract

Purpose: Retinitis Pigmentosa (RP) is a heterogeneous group of retinal disorders characterized by nyctalopia followed by progressive peripheral visual field constriction. A Coats’ Disease like exudative vitreoretinopathy is reported in up to 5% of all patients diagnosed with RP. Since originally described in 1956, very little data has been reported on the outcomes of patients with Coats’-like RP. We evaluated the diagnostic and clinical course of patients with Coats-like RP managed with various different surgical and non-surgical modalities, with a sub-focus to identify associations, characteristics, and risk factors (i.e., modes of inheritance).

Methods: This was a multicenter, interventional, retrospective case series of patients diagnosed with RP with a documented history of Coats-like exudative vitreoretinopathy. A corresponding, in-depth analysis of mutation analysis and multimodal ocular imaging were included.

Results: Outcomes after treatment with cryotherapy, laser photocoagulation, scleral buckle with subretinal fluid drainage, vitrectomy, and anti-VEGF injection, alone or in combination, were comparatively analyzed. Critical diagnostic and clinical findings, including the results of genetic testing, family history, and performance on ophthalmic testing, were evaluated to identify important trends and prognostic factors during patient course.

Conclusions: To the best of our knowledge, this is the largest cohort of RP patients with Coats-like phenotype in the era of small gauge vitrectomy and modern genetic sequencing. The results of this study are expected advance our understanding of the pathogenesis of Coats-like reaction in the setting of RP, as well as our potential to manage and treat this condition via both surgical and non-surgical intervention. We anticipate the information and data generated may serve as a framework for prospective clinical studies in the future.
Outcomes of Voretigene Neparvovec-rzyl for Leber Congenital Amaurosis in Eleven Patients: The CHLA Experience

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Introduction: Voretigene neparvovec-rzyl is an AAV2-based gene replacement therapy for RPE65-mediated retinal dystrophies recently approved by the Food and Drug Administration (FDA) based on positive Phase 3 trial results. Visual and anatomic outcomes of patients treated with voretigene neparvovec-rzyl since FDA approval have not been reported.

Methods: Retrospective case series of 11 Leber congenital amaurosis (LCA) patients, of which 8 were children, treated with voretigene neparvovec-rzyl at Children’s Hospital Los Angeles in 2018. Both eyes were treated 7 days apart with 23-gauge vitrectomy and optical coherence tomography (OCT)-guided subretinal voretigene neparvovec-rzyl injection followed by full air-fluid exchange.

Results: Eleven LCA patients (22 eyes) with biallelic RPE65 mutations underwent bilateral gene therapy surgery with voretigene neparvovec-rzyl. Patient age at surgery ranged from 3 years to 44 years old (median age: 12 years) and 8/11 patients were children. Mean follow-up period since first surgery was 62.5 days (range: 35 – 205 days). All patients had significantly diminished or absent visual function in dim lighting. Preoperative best-corrected visual acuity (BCVA) ranged from 20/80 to hand motions with a mean BCVA of 20/300. Additional functional testing included Goldmann visual fields and full-field scotopic testing (FST). Following treatment all patients had greatly improved subjective improvements in low-light visual function, especially the pediatric patients under age 10. Postoperative BCVA improved slightly to 20/200 (p=0.055). FST obtained in 10 eyes of 5 patients improved from a mean -2.04 log cd.s/m² preoperatively to -4.52 log cd.s/m² postoperatively with a mean improvement of 2.47 log units (p<0.0001). Constricted isopters on Goldmann visual field testing expanded by approximately 50% with treatment. Safety issues included elevated intraocular pressure (5 eyes), inflammation (5 eyes), retinal breaks (2 eyes), and retinal detachment (1 eye), but these resolved spontaneously or with treatment with no obvious effect on treatment effect.

Conclusion: Treatment with voretigene neparvovec-rzyl in the post-approval period appears to mirror the results obtained in the Phase 3 clinical trial. Young patients appear to reap the maximum benefit of this treatment compared to older patients with more advanced degeneration. Long-term data on visual outcomes and surgical complications may guide the design of future trials.
Abstract

- **Purpose:** Describe the importance of developing a team approach to pediatric retina care in order to help streamline the process of the complexity required by this service.

- **Methods:** A 7-year retrospective review of the rate of success of managing the pediatric retina service at Bascom Palmer Eye Institute and Jackson Memorial Hospital/NICU, including the clinical and surgical setting.

- **Results:** The use of the different key element to manage and improve the service over the last seven years will be presented. A flow chart taking these and other factors into consideration will be discussed.

- **Conclusions/Discussion:** Understanding the complexity of the service, and developing a team approach with a clearly defined role of all parties involved in pediatric retina care, will help to streamline the process and tailor the clinical management to add significantly to the improvement of patient care and treatment outcomes.
The Role of Vitreous Surgery in Anterior Segment Dysgenesis

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Anterior segment dysgenesis can be a devastating problem in the pediatric patient. Not only is there obscuration of the visual pathway, but oftentimes there are significant developmental anatomic abnormalities that make attempting to improve the optics very challenging. Abnormalities in the angle, iris root, and ciliary body require altering the surgical approach to the eye. In the more severe cases, keratopasty almost uniformly fails. The mechanism of this corneal opacification is usually cyclitic membrane formation and hypotony with subsequent corneal decompensation. Recently, we have been working together with the anterior segment surgeons at The Children’s Hospital of Pittsburgh to try to improve the outcome in these penetrating keratoplasties by removing the vitreous as a source of scaffolding. The techniques of our current approach will be presented as well as the outcomes in the series that we have collected to date.
Progression from Pre-Plus Disease to Plus Disease in the G-ROP Study

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IRB: Approved by all participating IRB’s

SUPPORT: NIH 1R01EY021137-01A1 and the Richard Shafritz Chair in Pediatric Ophthalmology Research

INTRODUCTION: Limited data are available describing progression of pre-plus changes to plus disease in retinopathy of prematurity (ROP). We sought to determine the rate and characteristics of eyes that progress from pre-plus to plus.

METHODS: Secondary analysis of retrospective G-ROP-1 data from infants undergoing ROP examinations at 29 North-American hospitals between 2006-2012. Outcomes included proportion of eyes progressing from pre-plus to plus, based upon clinical assessment by examining ophthalmologists; days between pre-plus and plus diagnoses; and ROP stage at time of plus diagnosis. Stratified analyses by stage/zone and postmenstrual-age (PMA) at first pre-plus diagnosis were performed.

RESULTS: 946 eyes of 512 infants were diagnosed with pre-plus. 286(30.2%) eyes progressed to plus disease, or 338(35.7%) assuming progression for eyes treated at pre-plus whose fellow eye had plus. Progression rates by stage/zone were 21% St-0; 33% St-1/Zn-I; 43% St-2/Zn-I; 28% St-1/Zn-II; 32% St-2/Zn-II; 29% St-3/Zn-II. Progression rates by PMA at first pre-plus were 5.7% PMA<33; 31.7% PMA 33-40; 34% PMA>40. Mean days to progression were 12-14 days for St-1/Zn-II, St-2/Zn-I, and St-2/Zn-II; 125/159(79%) of these eyes had progressed to stage 3 at time of plus diagnosis. Mean days to progression for St-3/Zn-II was 7.3 days (range 1-35).

DISCUSSION: Although pre-plus and plus diagnoses were not based upon photographic assessment, these data represent the real-life determinations being used by clinicians to make treatment decisions.

CONCLUSION: Approximately one-third of eyes with pre-plus vascular changes progress to plus disease. The large majority of these eyes will develop stage 3 ROP by the time plus disease develops.
Retinopathy of prematurity: Incidence report of outliers based on international screening guidelines

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Abstract

- **Purpose:**
  The objective of this study is to report the incidence of ROP in infants who fall outside the screening criteria from the guidelines of the American Academy of Ophthalmology. This may help us identify at risk infants in Mexico and other middle-income countries.

- **Methods:**
  Retrospective review of 549 records from premature-born infants who were screened for ROP at our institution. All the examinations were included in our database. We analyzed by subgroups based on gestational age (GA), birth weight (BW) and stage, focusing on the outliers that don’t meet the criteria of the screening guidelines (GA >30 weeks, BW > 1500 grams).

- **Results:**
  Out of the 549 records, 294 infants were diagnosed with ROP. Mean gestational age at delivery was 30.09 ± 2.27 weeks, mean birth weight was 1238.75 g ± 340.43g. 91.49% had bilateral involvement and 116 (39.45%) required treatment. 42 infants (80 eyes, 14.2% of the total) fell outside the screening and 26.5% of them required treatment.

- **Conclusions/Discussion:**
  ROP diagnosis among infants weighing >1500g at birth and/or with a gestational age of >30 weeks is not uncommon in Mexico and possible in other middle-income countries. Modification of screening guidelines should be considered in order to reach all at risk infants.
SAFER-ROP™: Updated Protocol for Anti-VEGF Injections for ROP

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Purpose: To describe a safe and dependable protocol for intravitreal injections for the treatment of retinopathy of prematurity (ROP). Despite improved outcomes from utilizing anti-VEGF, complications induced by needle insertion technique include but are not limited to keratitis and corneal ulcers, injury to and displacement of the crystalline lens, endophthalmitis, and retinal damage to the contralateral wall resulting in retinal tears, detachments or even scleral perforations. Current standardized needles used for Anti-VEGF delivery include the 31-gauge 5/16 inch (7.93 mm) as published by the BEAT-ROP study, the 30-gauge 1/2 inch (12.7 mm) needle used in the prospective RAINBOW study comparing Ranizumab to laser treatment, and the 32-gauge 3/16 inch (4.76 mm) needle (TSK STERiJECT, Japan). Although there have been many published standardized intravitreal injection techniques for adults to ensure safe and reproducible delivery, standardized techniques in ROP anti-VEGF administration is lacking.

Methods: SAFER is an acronym used to describe the injection protocol and includes Short needle (4 mm length), Antiseptic/antibiotic (5-10% topical betadine), Follow-up (48-72 hours post-injection to rule out endophthalmitis), Extra attention to detail (sterile environment, assess for conjunctivitis, determination of safe injection site 0.75 -1.0 mm posterior to limbus using the ora nonogram), and Recheck (1-2 weeks following injection and until mature vascularization is complete. Advocate for the use of fluorescein angiogram for all treated patients between 60 and 65 weeks postmenstrual age and subsequent laser treatment if necessary.).

Results: No cases of cataract formation, endophthalmitis, vitreous hemorrhage, or corneal infections using this technique were reported in a recent retrospective chart review of 220 eyes.

Conclusion: Anti-VEGF injections are becoming more frequently used for treatment of ROP. This necessitates a practical protocol that is dependable and standardized in order to help ensure the safest outcome possible given the variation across gestational age (GA) anatomy. This protocol establishes for the first time a safe and systematic way to both inject anti-VEGF and to monitor ROP progression potential complications associated with injections.
Aggressive Posterior Retinopathy Of Prematurity: Long-Term Outcomes Following Intravitreal Bevacizumab

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PURPOSE
The purpose of this study is to review the neonatal and early childhood course of children who were treated with intravitreal bevacizumab for APROP and identify any chronic functional limitations these children face years after treatment.

METHODS
This retrospective consecutive case series included 43 eyes of 22 premature infants born over a 2-year period. The study included 13 males and 9 females. All infants were diagnosed with APROP and treated with a single intravitreal injection of bevacizumab. Patient records were reviewed to identify the gestational age, average birth weight, gender, post-menstrual age (PMA) at the time of injection, regression status, rescue therapy events, final visual acuity, final refraction, ophthalmologic diagnoses and complications, neurologic diagnoses, and duration of follow up.

RESULTS
The average gestational age was 24 weeks (range: 23-27 weeks) and average birth weight was 625.2g. The average PMA at time of bevacizumab injection was 35.59 weeks. 35 eyes eventually received laser photocoagulation at an average PMA of 53.17 weeks. All eyes ultimately demonstrated regression. The average follow-up was 4.08 years (range: 1.85-7.36 years). At last follow-up, 23 eyes were able to discern letters or shapes, with an average acuity of 20/53. 19 eyes developed subsequent ocular pathology. 13 infants developed chronic neurologic impairment, and the spectrum of neurologic disease was broad. 12 of these children also sustained frank neonatal neurologic insult during the neonatal period.

CONCLUSION
Many premature infants with APROP developed chronic neurologic disease, but nearly all of whom sustained significant neurologic disease as neonates. Treatment of APROP with intravitreal bevacizumab, often with adjuvant panretinal photocoagulation, led to regression without detachment in all eyes.
Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO) in pediatric retina

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Abstract

- **Purpose:** Fluorescence lifetime imaging ophthalmoscopy (FLIO) aids in the diagnosis of different inherited retinal diseases in adults. However, early fundus appearances of diseases in children do not always have the same characteristic findings as those in adult. This study investigates FLIO-associated changes in different pediatric retinal diseases with the goal to establish the first database for investigating pediatric patients with FLIO.

- **Methods**
  Human subjects approval was obtained from the University of Utah Institutional Review Board to image healthy adult and pediatric participants, as well as those with retinitis pigmentosa, X-linked retinoschisis, Stargardt disease, choroideremia, cone-rod dystrophy, Bardet-Biedl syndrome, or other congenital diseases using a prototype Heidelberg FLIO device. Fundus autofluorescence (FAF) was excited with a 473 nm laser, and lifetime and intensity images were recorded in short (SSC, 498-560 nm) and long (LSC, 560-720 nm) spectral channels. The mean fluorescence lifetime ($\tau_m$) was calculated and analyzed qualitatively as well as quantitatively using a t-test.

- **Results**
  FLIO shows distinct and highly disease-specific patterns of FAF lifetimes in different retinal diseases. Short lifetimes, as found in X-linked retinoschisis and cone-rod dystrophy, can clearly be distinguished from long-lifetime patterns in choroideremia or ring-like patterns of short and long lifetimes in retinitis pigmentosa and Bardet-Biedl syndrome. In Stargardt disease, new onset flecks can be detected as short lifetimes that progress to long lifetimes over time along with a loss of function in these areas.

- **Conclusions:**
  FLIO detects different fluorescence lifetime patterns characteristic for different pediatric retinal conditions that can be distinguished from one another using FLIO. Not only the appearance of the images is different, but there are also quantitatively significant lifetime differences between diseases. This novel technique aids with initial diagnosis and in recommendations for individualized genetic testing, particularly in children in whom the classic phenotypes may not have yet manifested. FLIO may be a promising tool to characterize pediatric retinal diseases early, which may be amenable to therapeutic strategies, such as gene therapy. Furthermore, it may help to discriminate between early disease stages better than current imaging modalities can.
Bevacizumab or laser for Aggressive Posterior Retinopathy of Prematurity

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Abstract

- **Purpose:** To report rate of reactivation and structural outcome after laser or bevacizumab treatment for aggressive posterior ROP (APROP).
- **Methods:** Retrospective chart review was conducted on consecutive infants with APROP treated with 1) laser or 2) bevacizumab, followed by fluorescein angiography (FA) and prophylactic laser to persistent avascular retina. APROP patients between 1/1/2006 – 6/30/2016 were included. Starting in the spring of 2010 all patients with APROP were treated initially with bevacizumab, so a direct before and after comparison is made herein.
- **Results:** 36 eyes of 19 patients were included. Mean gestational age was 24.5 weeks with mean birth weight of 632 g in the bevacizumab group and 24.7 weeks and 777 g in the laser group. Unfavorable outcome occurred in 1 of 22 eyes with treated with bevacizumab and in 5 of 14 eyes in the laser group (p=0.002). Reactivation requiring treatment was common in both groups, 9/22 after bevacizumab and 6/14 after laser (NS).
- **Conclusions/Discussion:** Regardless of initial treatment reactivation requiring retreatment is common in eyes with APROP. Unfavorable structural outcome was significantly more common after initial laser treatment than after initial bevacizumab treatment.
Inner Retinal Fenestration for Pediatric Optic Disc Pit Maculopathy
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Abstract

Purpose: To evaluate the efficacy of inner retinal fenestration as a surgical technique for the treatment of optic disc pit maculopathy in the pediatric population.

Methods: This retrospective, interventional case series included pediatric patients with optic disc pit maculopathy treated at two tertiary hospitals in London. All patients underwent pars plana vitrectomy with the creation of two inner retinal fenestrations. The partial thickness retinotomies were made radial to the optic disc pit using a 25-gauge MVR blade. Anatomic and visual outcomes were determined by optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Germany) and best-corrected visual acuity (BCVA), respectively.

Results: A total of four eyes were included. Average patient age was 12.8±3.6 years. Preoperatively all eyes demonstrated subretinal and intraretinal fluid in the central macula. Mean preoperative BCVA was logMAR 0.74±0.26 (20/100). Patients were followed for a mean of 20.5±11.0 months after surgery (range 10-36 months). Mean postoperative BCVA was 0.58±0.29 (20/80) at two weeks, 0.40±0.32 (20/50) at three months, and 0.20±0.27 (20/32) at one year. Progressive resolution of intraretinal and subretinal fluid was observed in all eyes (Figure 1). Recurrence of macular detachment or intraretinal fluid was not observed.

Conclusions: Inner retinal fenestration is an effective technique that resolves fluid and restores vision in pediatric patients with optic disc pit maculopathy. These results support the hypothesis that allowing an egress of fluid into the vitreous cavity can achieve long-lasting amelioration of the pathologic findings often associated with this condition.

Figure 1: Pre- and Post-operative OCT scans for all four cases with corresponding best-corrected visual acuity. These images demonstrate the progressive resolution fluid and improved visual acuity after vitrectomy with inner retinal fenestrations.
AAV2/4-RS1 gene therapy in the retinoschisin knockout mouse model of X-linked retinoschisis

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Abstract

- Purpose: Human gene therapy for X-linked retinoschisis (XLRS) has shown promise using intravitreal injection of adeno-associated virus AAV2/8-RSI vector, which was originally tested in the retinoschisin knockout mouse model. We tested the hypotheses that subretinal and intravitreal injections of a novel vector, AAV2/4-RSI, could correct photoreceptor cells in the Rs1-KO mouse detectable by electroretinography (ERG) and swim assay. We also studied whether brinzolamide, which reduces cysts in humans, potentiates the effects of AAV2/4-RSI.

- Methods: AAV2/4-RSI with a CMV promoter (2x10^{12} viral genomes/mL) was delivered to the right eyes of Rs1-KO mice (National Eye Institute) either via intravitreal (N= 5; 1µL) or subretinal (N=5; 2µL) injections in vivo. Six additional mice received subretinal gene therapy plus topical brinzolamide two times a day to the treated eye for the first two weeks after AAV2/4-RSI injection. Injections were performed at P60-90. Full field ERG dark adapted latency/intensity protocol was performed at day 50-60 post-injection. The treated groups were compared to untreated Rs1-KO mice (N=3) and wild-type (WT) mice (N=2) using a visually guided swim assay. Synapse labeling was performed on Rs1-KO and WT mice using anti-PSD95.

- Results: Compared to untreated eyes, treated eyes tended to have higher ERG amplitudes in subretinal gene therapy, subretinal gene therapy plus brinzolamide, or intravitreal gene therapy. Treated eyes had a less electronegative b-wave on dark adapted 10 cd.sec/m^2 flash than untreated eyes. The b/a ratio was significantly higher in the subretinal plus brinzolamide (p=0.016) and intravitreal (p=0.049) eyes compared to untreated eyes, but not the subretinal group without brinzolamide (p=0.58). There was a significantly higher b/a ratio in the subretinal plus brinzolamide group compared to those treated with subretinal gene therapy alone (p=0.025). Rs1-KO eyes had retraction of synaptic terminals into the ONL compared to WT. Swim assay showed a significant difference between WT and Rs1-KO (p=0.0003 to p=0.05).

- Conclusions: In the Rs1-KO mouse, subretinal and intravitreal injections of AAV2/4-RSI resulted in improved ERG b/a-wave ratio, and brinzolamide potentiated the effect of subretinal therapy.
Bilateral Total Retinal Detachments from Giant Retinal Tears in an Infant with Abusive Head Trauma

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Abstract

Purpose: To report a rare complication of abusive head trauma and its association with a genetic disease with ocular and systemic findings. Methods: Case presentation with surgical video. Genetic testing was performed on whole blood with microarray and exome sequencing of genes associated with hereditary vitreoretinopathy with deletion/duplication analysis. Results: A 2 month-old female victim of abusive head trauma presented with rare findings of bilateral total retinal detachments (RD) associated with extensive giant retinal tears (GRT) OU, hyphema, and vitreous hemorrhage OU. Although she had chronic cortical contusions, subdural hematomas, and rib fractures at various stages of healing indicative of shaken baby syndrome, retinal hemorrhages were not observed. A total closed funnel RD with 360 GRT OS was determined inoperable. The total RD OD without posterior vitreous detachment was repaired with scleral buckling, vitrectomy, encircling endolaser, and intermediate term perfluorocarbon liquid (PFCL). The PFCL was removed two weeks later and replaced with air. The retina remains reattached through 1 year of follow-up, although a moderate epiretinal membrane formed. Genetic testing confirmed Stickler syndrome with COL2A1 mutation associated with anterior polar cataracts and congenital hip dysplasia. Microarray testing revealed a duplication in chromosome 22q11.21 causing congenital melanotic nevus syndrome with giant hairy nevus on her left thigh extending to her calf. Conclusions/Discussion: Hereditary vitreoretinopathy may be associated with bilateral RDs from GRTs rather than hemorrhagic complications of abusive head trauma. Intermediate term PFCL and supine positioning may facilitate retinal reattachment in infants with complicated forms of RD.
APROP: Variations in Definitions Among Clinical Studies

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Abstract

- **Purpose:**
  Review the definition of APROP used in the ophthalmic literature in order to determine its uniformity, diagnostic implementations, and documentation.

- **Methods:**
  1. A PubMed database list was generated using the term: Aggressive Posterior Retinopathy of Prematurity
  2. Case studies, articles without primary data, and articles not in English were excluded from data collection
  3. Coauthors reviewed articles
  4. The following factors were determined for each article
     a. Definition of APROP, Method of Diagnosis, Enhanced Practices for Reliability, and Additional Documentation
  5. If there was any disagreement between reviewers, MJS, reviewed the article and made a final determination
  6. The data was then compiled into an excel sheet
  7. A slide show of manuscript images which included diagnosis of APROP was reviewed and rated

- **Results:**
  Search yielded 144 articles, 10 were excluded because they were not in English. Of the remaining 134 articles, 32 were excluded they were from case studies and 23 were excluded because they did not have primary patient data. Of the remaining 79 articles, 25 had a specified definition that conformed with r-ICROP, 18 cited r-ICROP but had no specified definition, 18 provided a definition that was unclear or deviated from r-ICROP, and 18 articles did not provide any specified or cited definition. In regards to methods of diagnosis, 43 did not disclose how a diagnosis was made, 18 reported using Binocular Indirect Ophthalmoscopy, 9 reported using BIO and fundus photos, 6 reported only using fundus photos, and 2 reported performing a fundus examination, but the tools used were unspecified.
Conclusions/Discussion:

R-ICROP provided a definition of APROP to be used across the literature. Despite r-ICROP, we found APROP was not uniformly defined across the literature and there were clear cases of deviation from r-ICROP. In order to reach the goal of standardization required for clear communication regarding APROP. Adjustments to r-ICROP will be required.
Phenotype-genotype correlation in patients with Familial Exudative Vitreoretinopathy carrying genetic variants in \textit{NDP, FZD4, LRP5}, and \textit{TSPAN12}.

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Abstract

Purpose: To investigate and compare the clinical phenotypes of patients with familial exudative vitreoretinopathy (FEVR) carrying confirmed genetic variants in \textit{NDP, FZD4, LRP5}, and \textit{TSPAN12} genes.

Methods: Diagnosis and clinical staging of FEVR was established by clinical examination and fundus fluorescein angiography. Data collected from medical records included age, clinical stage at diagnosis, angiographic findings, and treatment modality. Blood samples were collected from probands and their parent(s). Genomic DNA was analyzed by next-generation sequencing, and the sequence of selected variants were validated by Sanger sequencing. Only probands with identified variants were included in the study.

Results: Total of 161 consecutive FEVR patients met the inclusion/exclusion criteria and were included in the study. Of total of 146 variants identified, 97 were pathogenic variants (PVs), 20 were variants of unknown significance, and 29 were benign. PVs in \textit{NDP, FZD4, LRP5, TSPAN12} were found in 22.6\%, 25.3\%, 13.7\%, and 4.8\% of the cohort, respectively. 11\% of the probands had variants in more than one gene. History of premature birth was present in 9\% and 30\% of probands with variants in \textit{NDP} and \textit{FZD4}, respectively. Median age of diagnosis was 0.6 years for patients with \textit{NDP} variants compared to 3 years for patients with \textit{FZD4} variants. 69\% of probands with \textit{NDP} variants had stage 5 FEVR, and of those 93\% was bilateral. Asymmetric staging, as defined by different severity of disease between the two eyes, was present in 12\%, 48\%, 42\% and 5\% of patients with PVs in \textit{NDP, FZD4, LRP5, and TSPAN12}, respectively. Surgical intervention was required more commonly in patients with PVs in \textit{NDP} vs. \textit{FZD4} gene (56\% vs. 24\%).

Conclusion: Patients with PVs in \textit{FZD4} and \textit{LRP5} show significantly more clinical variation than patients with \textit{NDP} and \textit{TSPAN12}. Patients with PVs in \textit{NDP} appear to have more severe phenotypes with earlier disease diagnosis and advanced stage at presentation.
Prevalence and Risk Factors of Retinal Detachment from Retinopathy of Prematurity

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IRB Approved by CHOP IRB

**SUPPORT**
NIH 1R01EY021137-01A1

**INTRODUCTION:** Retinal detachment (RD) can develop from retinopathy of prematurity (ROP) despite treatment for Type 1 ROP. We sought to determine the prevalence, timing, and risk factors for RD from ROP.

**METHODS:** Retrospective “G-ROP Study” at 29 North-American hospitals between 2006-2012. Primary outcomes were prevalence of eyes developing RD (stage 4 or 5) and onset post-treatment. Birth weight (BW), gestational-age, postnatal-weight gain, surgical necrotizing enterocolitis (NEC), sepsis, and days of oxygen supplementation were evaluated as risk factors among treated eyes using multivariable regression.

**RESULTS:** RD developed in 70/14,996 eyes (0.47%, 95% CI 0.37-0.59%) and 46/7,483 infants (0.61%); 37 stage 4, 33 stage 5; 52% had bilateral RD. 6 eyes/3 infants developed RD without Type 1 ROP diagnosis or treatment. 64/885 eyes developed RD following laser (7.2%, 5.8-9.3%): 56/742 Type 1, 8/128 Type 2. RD occurred at median 5.6 weeks (range 0.7-19 weeks) following treatment. 10 (15.6%) RD’s were within 2 weeks of treatment. #Treated within 72 hours of Type 1 diagnoses was similar between RD and non-RD eyes. In multivariable analysis, lower BW (OR 1.03 per-10 gram-decrease (1.01-1.05)) and NEC (OR 3.0, 1.5-5.9) were significant risk factors for RD following treatment. RD rates were, for example, 11.9% for BW<500g without NEC; 16.9% for BW<700g with NEC.

**DISCUSSION:** Further investigation of infants at increased risk for RD could lead to modifications of treatment criteria or timing for such infants.

**CONCLUSION:** 7.2% of eyes progress to RD despite treatment for ROP. Infants with low BW and/or NEC are at increased risk for RD.
Coats like response in Retinitis Pigmentosa

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Purpose

To report the clinical and imaging findings of an exudative retinopathy associated with retinitis pigmentosa in two children.

Methods

Retrospective chart review of two patients.

Results

The first case is a 3 year old child with photoreceptor dystrophy. His visual acuity was 20/190 in both eyes. Examination revealed retinal pigment epithelium disturbance in the macular and perivascular region. Peripheral exudates were noted. Fluorescein angiography confirmed retinal ischemia and laser photocoagulation was performed. The retina remained stable since. The second case is an 11 year old boy with right eye worsening vision for 3 weeks. He had a positive family history with his maternal grandfather having a similar problem. Visual acuity was counting fingers closely in the right eye and 20/40 in the left eye. Examination showed extensive lipid deposition involving the macula in the right eye. Fluorescein angiography showed bilateral peripheral telangiectasia with leakage in the right eye. Peripheral capillary non perfusion was noted in the left eye. Bilateral laser photocoagulation was performed for both eyes.

Conclusion

In a pediatric patient with retinitis pigmentosa, it is important to detect exudative complications that may only be possible with careful examination of the retina periphery. On the other hand, in a child who presents with coat’s like disease, one should consider the possibility of RP.
Fluorescein Angiography Findings in Children with Congenital Zika Syndrome

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Abstract

Background and Objective To evaluate the retinal and vasculature changes in infants with congenital Zika syndrome (CZS) using fluorescein angiography (FA).

Material and Methods This consecutive case series included six infants with CZS. FA and color fundus imaging were performed under general anesthesia in both eyes of all infant using a contact wide-field digital imaging system. All color fundus images were obtained using a 130° field of view lens and the FA images were captured using either a 130° or 80° field of view lens. The IgM antibody capture enzyme-linked immunosorbent assay was positive for ZIKV in the cerebrospinal fluid samples of all infants. Other congenital infections were ruled out.

Results The mean ± standard deviation (SD) age of the infants at the time of examination was 1.4 ± 0.1 years (range, 1.3-1.5 years). Contact fundus photographs showed macular abnormalities in seven eyes (58%) and retinal vasculature changes in two eyes (17%). FA detected macular abnormalities in all 12 eyes (100%) and retinal vasculature changes in five eyes (42%). The main retinal vasculature changes were peripheral avascularity in five eyes (42%) and microvasculature abnormalities in three eyes (25%).

Conclusion FA may be an important tool for detecting subtle macular and retinal vasculature changes in CZS.
Fluorescence Lifetime Imaging Ophthalmoscopy (FLIO) in X-linked retinoschisis

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Purpose: Fluorescence lifetime imaging ophthalmoscopy (FLIO) discriminates among different inherited retinal diseases and is useful in their diagnosis. As more is understood about the relationship of FLIO and pathophysiology, FLIO may also provide insight into disease evolution. This study investigates FLIO-associated changes in patients with X-linked retinoschisis.

Methods: Human subjects approval was obtained from the University of Utah Institutional Review Board to image adult and pediatric participants. 20 eyes of 11 male patients with X-linked retinoschisis (mean age 15 ± 6 years, range 7 to 26 years) and a healthy control group were investigated using a prototype Heidelberg FLIO device. Fundus autofluorescence (FAF) was excited with a 473 nm laser, and lifetimes were recorded in short (SSC, 498-560 nm) and long (LSC, 560-720 nm) spectral channels. The mean fluorescence lifetime (τm) was calculated and analyzed qualitatively as well as quantitatively using a t-test. X-linked retinoschisis was genetically confirmed, and all subjects underwent OCT imaging.

Results: FLIO shows a distorted pattern of short lifetimes in the fovea, which has a star-like appearance. FAF images obtained in both spectral channels illustrate a very clear picture of the distortion. Hypofluorescent areas correspond to areas of short FAF lifetimes.

Conclusions: FLIO detects fluorescence lifetime patterns characteristic of X-linked retinoschisis, which are different from other inherited retinal diseases. FLIO can aid in the diagnosis and especially in children who have not yet been genetically tested. Understanding different lifetime distributions within retinoschisis may eventually add to our evolving understanding of the pathophysiology of the condition.
Surgical management of advanced Coats’ disease: From beginning to end

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Abstract – Case report

To present a case-based presentation of the surgical management of Advanced Stage 4 Coats’ disease in a 28 mo-old male with neovascularization of the iris and early neovascular glaucoma with bullous retina to the lens. This presentation will highlight the complexity and challenges associated with advanced Coat’s management using a single patient example and a “beginning to end” approach. The talk will include dynamic images and videos to walk the audience through the preoperative and perioperative planning stages as well as intraoperative technique and post-operative follow up. Importantly, the patient’s course through the stage of oil removal and subsequent follow up will be shared. Additional video/photos can be provided for review.
Practice patterns changes in the treatment of retinopathy of prematurity

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Purpose:
There are limited patient-level data describing ROP-treatment-modality preferences. We sought to describe recent ophthalmologist practice patterns for ROP treatment choice and identify changes over the past decade.

Methods:

Results:
Treatment rates were similar in G-ROP-1 (514/7483 (6.9%) infants, 1008 eyes) and G-ROP-2 (256/3981 (6.4%) infants, 500 eyes), and majority treatment was bilateral (96.1% in G-ROP-1, 95.3% in G-ROP-2). The treated infants in two studies had similar mean BW (715g/705g), GA (25.0/24.7) and PMA at first treatment (36.8/36.8 weeks). Initial treatment was 96%-laser, 4%-anti-VEGF in G-ROP-1; but 60%-laser, 40%-anti-VEGF in G-ROP-2. Zone I treatment increased slightly (from 15% to 23%) between studies, as did eyes receiving >1 treatment (from 11% to 16%). In G-ROP-2, eyes receiving anti-VEGF (n=202) were treated earlier than laser (n=298) (mean PMA 35.8 versus 37.5) and were more often in zone I (42% versus 10%). 73% of Zn-I cases and 30% of Zn-II cases were treated initially with anti-VEGF injection. Re-treatment by 50 weeks PMA was more common following anti-VEGF than following laser (29% vs. 7%).

Conclusion/Discussion:
Anti-VEGF injections now account for 40% of first-line treatments for ROP. For posterior disease, ophthalmologists are predominantly choosing anti-VEGF agents over laser. The significantly increased use of intravitreal anti-VEGF agents highlights the need for further study of appropriate dosage, systemic effects, and long-term visual outcomes.
A Survey of Stickler Syndrome Practice Patterns

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Abstract

Purpose
The purpose of this study is to clarify basic aspects of Stickler Syndrome (SS) practice patterns among pediatric retina specialists and SS experts.

Methods
A survey was constructed containing questions pertaining to practice patterns such as age at which to schedule exams, recommended examination intervals, conditions to perform prophylaxis, preferred method of prophylaxis, and suggested activity modifications. The survey was sent to active pediatric retina specialists and corresponding authors identified through PubMed search. Responses were recorded over a period of 3 months. Survey results were compiled and shared with survey respondents after data was analyzed.

Results
35 respondents out of 70 specialists contacted completed the survey. The most common reasons for referral of SS patients were retinal detachment, family history of SS, and early onset myopia. The preferred age to begin regular office exams ranged from 0 years to 10 years with a median of 1.5 years. The preferred age to begin exams under anesthesia ranged from 0 to 5 years with a median of 2 years. Recommended examination intervals ranged from 3 months to 12 months, with the most common interval being 6 months (57% of respondents (R)). The most common cases to perform prophylaxis for retinal detachment included fellow eye of blind eye (83% R) and fellow eye of retinal detachment (80% R). The preferred method of prophylaxis was laser, 8-10 row from ora to equator, 360 degrees (60% R). The most commonly suggested activity modifications were “eye protection for sports” (86% R), followed by “no martial arts” (49% R) and “no contact sports” (40% R).

Conclusions/Discussion
There is a dearth of literature that addresses nonsurgical management of Stickler Syndrome, and the wide range of practice patterns observed in this study illustrate the variety of expert opinions. Increased attention to tracking preferences among pediatric retina specialists may help optimize care for patients with SS.