Current Management of Pediatric Retinal Diseases

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VRS Retinal Update
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Pediatric retinal diseases
- ROP
  - Current Management
  - Modified laser
  - Anti-VEGF resistant ROP
  - Neurological/Ophthalmic outcomes
- Coats disease
  - Coats plus
- Familial Exudative Vitreoretinopathy
- Sticklers and Pediatric RD
  - Iris registry data
- Stargardts
- TEASE trial

Retinopathy of Prematurity (ROP)

Scope of the Problem: USA
- #1 cause of blindness in children in the US
- ≈500,000 infants/year born premature
- Occurs in smaller and younger infants
  - GA of 23 weeks or less – 75% with ROP
  - GA of 24 weeks – 70%
  - GA of 25 weeks – 50%
- Severe ROP is more common (AP-ROP)
  - 500-700 babies a year with severe visual loss

Retinopathy of Prematurity
- Aberrant retinal development
  - Arrest of retinal vascularization
  - Co-development of retina and vasculature
- Severity:
  - Gestational age
  - Birth weight
  - Systemic health
  - Genetic predisposition

Aggressive, Posterior ROP (AP-ROP)
- Low BW, early GA
- Zone 1 disease
- Vascular activity with high VEGF levels
- Increases risk of RD
Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity

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Laser vs Avastin – Zone 1

Stalled retinal development

Active NV

Double ridge reactivation

Stage 5
Typical Treatment Course

- APROP treated with a single intravitreal injection of bevacizumab
- Perform EUA/FA at 55 weeks
- Laser to areas of avascular retina or presence of NV
- Follow until PMA 70 weeks
- Late reactivation of ROP can lead to retinal detachment and vision loss

Anti VEGF is not enough

- 90% need laser

Case #1

45 6/7 weeks old female infant referred for evaluation of retinal detachment OU

- PMHx: born at 24 weeks 2 days at 580 g
- Respiratory distress syndrome, malnutrition, cholestasis, ileal stricture, rhinovirus and S. Aureus infections
- Surgical Hx: s/p PDA ligation, abdominal surgery s 3. colon resection, neck surgery
- Systemic Meds: oxygen, pulmicort, chlorothiazide, lorazepam, glycerin
- Ocular Meds: cyclomydrl, prednisolone
- Allergies: NKDA

Ocular History

At 34 weeks - APROP
- Received Avastin OU
- Good initial response

At 45 weeks – reactivation of disease
- Underwent PRP OU
POD#5 s/p PRP: OD

Started on IV methylprednisolone
Increased prednisolone gtts to q2h
Started atropine daily

POD5 s/p PRP: OS

POD#12 s/p PRP: OD

POD12 s/p PRP: OS

POW#10: OD
POW#10: OS

Case #2
- Preterm 24 2/7, 420g surviving twin
- APROP s/p anti-VEGF now POW #1 s/p laser for reactivation at 42w

Case #3
- Preterm 24w, 460g
- APROP s/p bevacizumab, POW #1 s/p laser for reactivation at 42w
- Bilateral corneal edema- with no view posteriorly
- Exudative RD OD, hypotony RD OS related to anterior segment ischemia and exudative RD OU

Review of cases:
- All eyes received anti-VEGF for APROP
- Laser was:
  - Confluent
  - OR time extensive
  - “hot” parameters – power 400mW, duration 0.2/0.3ms, spots >3500

- Our data:

Retrospective review of data: Is modified PRP better?
- Retrospective review of 43 eyes of 22 children diagnosed with APROP which were treated with one intravitreal injection of bevacizumab.
- All underwent EUA/FA at 55 weeks
- Laser to avascular retina/NV

Recommendation: Modified PRP
- 1-1½ spot size spacing
- Nonconfluent
- No RD, no reactivation at last f/u average 4 years
Ophthalmologic Outcomes

- At last follow up: 67% (29/43) of eyes were able to discern letters or shapes, with an average visual acuity of 20/37

Final Visual Acuity Distribution (Chart Readers)

Why does this happen in APROP eyes?

- Are eyes s/p anti-VEGF more anatomically susceptible to exudation?

Laser more traumatic to choriocapillaris and RPE -->> incompetent blood-retinal barrier (Malviya, Moshfeghi et al.)

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SD-OCT – ACTIVE ROP DECREASES THICKNESS OF CHOROID

Higher the stage – more reduced choroidal thickness
Thickness correlates with birth weight but not age of birth

CHOROIDAL THICKNESS IN INFANTS WITH RETINOPATHY OF PREMATURITY.

Prematurity and anti-VEGF

- Extreme prematurity is associated with thinning of choroid and retina
- Injection of anti-VEGF decreases thickness of choroid and retina
- Eyes with APROP may be more susceptible to exudative RD s/p confluent laser of high intensity – modified PRP recommended
- In our hands, anti-VEGF, often with adjuvant modified peripheral laser photoagulation, led to regression in 100% of eyes and vision >20/30 in majority of eyes

ANTI-VEGF DECREASES CHOROIDAL THICKNESS

Is it a thin choroid s/p anti-VEGF more susceptible to injury from laser photocoagulation in APROP eyes?

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The GOOD

The BAD

The Ugly
Anti-VEGF Resistant APROP

Triplets born at 22 weeks
Caucasian, male
Mother - 25 year old prima gravida - IVF
Complicated pregnancy - emergency C-section
No family history

Complicated hospital course

Triplet #1
- BW – 480g
- Septic, PDA
- IVH
- Resp distress

Triplet #2
- BW – 550
- PDA, IVH
- Resp distress

Triplet #3
- BW – 520
- Resp distress

Triplet #2 - first exam, PMA 30 weeks

Triplet #2 2nd exam – PMA 32 weeks

s/p anti-VEGF PMA=33 weeks, More active!

Inject anti-VEGF OU

Re-inject OU
Triplet #2 s/p anti-VEGF x2 PMA 35

Laser and anti-VEGF OU

Triplet #2 PMA 37

PMA 38 weeks with 4A OS

PPV, MP/AB, OS

PMA 42 weeks – POM #1 s/p PPV

TRIPLET#3 - FIRST EXAM, PMA 30 WEEKS

TRIPLET#3 - PMA 33 WEEKS

Anti-VEGF OU

Inject anti-VEGF OU
Summary

- 22 week triplets with complicated course
  - #1 - anti-VEGF x3, laser OU – RD OD
  - #2 – anti-VEGF x3, laser OU – RD OS
  - #3 – anti-VEGF, laser OU – no RD

APROP resistant to anti-VEGF
Vasculogenesis vs Angiogenesis- process not VEGF driven
VEGF load too high?
Role for early vitrectomy

Concerns: Anti-VEGF Revolution

- Late Reactivation-
  - Extensive areas of abnormal retina require laser
  - Develop late RD – 6-18 m after anti-VEGF
- Use “modified PRP”
- “Non responsive” disease

- Extreme prematurity is associated with significant morbidity

Coats’ Disease

- Exudative Retinopathy
- 2/3 present before 10 years of age
- 90% males, 90% unilateral

Coats’ Disease

- Treatment
  - laser ablation and anti-VEGF injection
  - Visual prognosis dependent on VA at time of diagnosis
  - 20% with vision better than 20/200
  - Vision limited by macular exudate
6 year old with 20/30 VA

Laser and anti-VEGF to protect the macula from migration of exudate

Residual macular exudate limits vision

Coats’ plus Syndrome

cerebroretinal microangiopathy with calcifications and cysts

- Exudative Retinopathy
- Presents at early age - leucocoria
- Males and females
- Bilateral
Coats’ plus Syndrome

- Defect in CTC-1 gene
- CTC-1 preserves telomeres during cell division
- Defect associated with shortening of telomeres and cell death

Coats’ plus Syndrome

- Systemic associations
  - retinal telangiectasia and exudates
  - intracranial calcification
  - leukoencephalopathy and brain cysts
  - osteopenia with predisposition to fractures
  - bone marrow suppression
  - gastrointestinal bleeding

Coats’ plus Syndrome

- Progressive
- Close monitoring
- Aggressive treatment

FEVR

- Familial Exudative Vitreoretinopathy
- Mutations in the NDP, FZD4, LRP5, and TSPAN12 genes
- Variability of disease severity in family members with same mutation
- Typically AD - check family members
- Chronic, progressive
14 year old male presents with visual loss for 6 months – thought he needed an update of contact lenses

- No health issues
- VA 20/30 OD, 20/100 OS
- “Possible ERM OS”
- Performed indirect laser to areas of avascular retina OU
- Expecting to perform PPV/MP OS in near future
- No anti-VEGF
Performed SB/PPV/MP/Sf6 OD

POM #2 s/p SB/PPV/MP/Sf6

Stickler and Stickler-like Vitreoretinopathies

Sticklers
- Most common cause of inherited RD
  - Myopic
  - Craniofacial Abnl
  - Peripheral lattice
  - Posterior tears
  - Giant retinal tears
  - Early cataract
Sticklers

- Type I – Type 2 Collagen (Collagen 2A1)
  - Worse visual prognosis
- Type II – Type 11 Collagen (Collagen 11A1)
- Type III – Collagen 11A2 – no ocular sx
- High risk of RD!!! What do we do with these children??

Natural History Data

- Known COL2A mutations
  - Group 1 – observation, no laser
  - Group 2 – prophylactic treatment
  - Group 3 – RD one eye, treatment other eye
  - 211 patients
  - Mean F/U 11.5 years

Natural history

- Group 1 (control group)
  - 73% RD
  - 48% Bilateral
- Group 2 (peripheral treatment)
  - 8% RD
  - 0% Bilateral
- Group 3 (RD one eye, treatment other)
  - 10% RD

Observation is not a good option!!

- Genetic defect, high myopia, peripheral pathology – refer for evaluation

Structural and Functional Outcomes of Vitreoretinopathy related Retinal Detachments

Peter Belin MD, Ameay Naravane MD, Polly Quiram MD, PhD

IRIS Registry – Big Data
Msp/St Paul Childrens collaboration with ENT
Stargardt disease

- ABCA4 mutation – Vit A metabolism
- Decreased vision, scotoma, decreased dark adaption
- Variable VA - 20/20-20/400 with prognosis based on age of onset
- AR – 1:10,000 affected

10 year old male

- 20/80
- 20/60
Progressive atrophy

<table>
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<tr>
<th>Vision</th>
<th>Year</th>
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<tbody>
<tr>
<td>20/80</td>
<td>2013</td>
</tr>
<tr>
<td>20/150</td>
<td>2016</td>
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<tr>
<td>20/400</td>
<td>2019</td>
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What do we have to offer?

**TEASE TRIAL**

- Novel agent- ALK-001
- Analog of Vit A-prevents toxic Vit A dimers from forming (A2E)
- Pill taken once daily
- Slow the progression of the disease

**Summary**

- Many diseases can cause visual loss in children
- Increased understanding
- Early identification=better VA
- If in doubt - refer