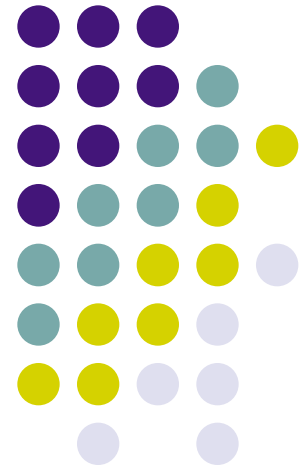
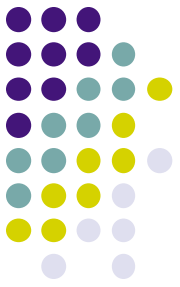


Grand Rounds

Jenny Temnogorod
SUNY Downstate Medical Center
Department of Ophthalmology
September 19, 2013

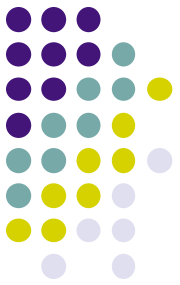


History and Examination



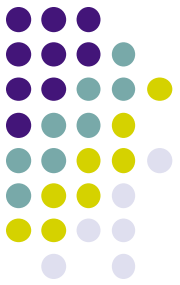
HPI: 2 day old SGA (small for gestational age, 37 weeks, BWt. 1760g) with IUGR

TORCH infection work-up was ordered to evaluate IUGR and ophthalmology was consulted to rule out chorioretinitis. In addition, there was rupture of membranes at delivery and mother had post-op fever, so baby was empirically started on IV antibiotics for presumed chorioamnionitis.



History and Examination

- Maternal history: 30F, two previous term deliveries, with routine prenatal follow-up prior to the recent delivery. Gestational age determined by LMP, confirmed by ultrasound.



History and Examination

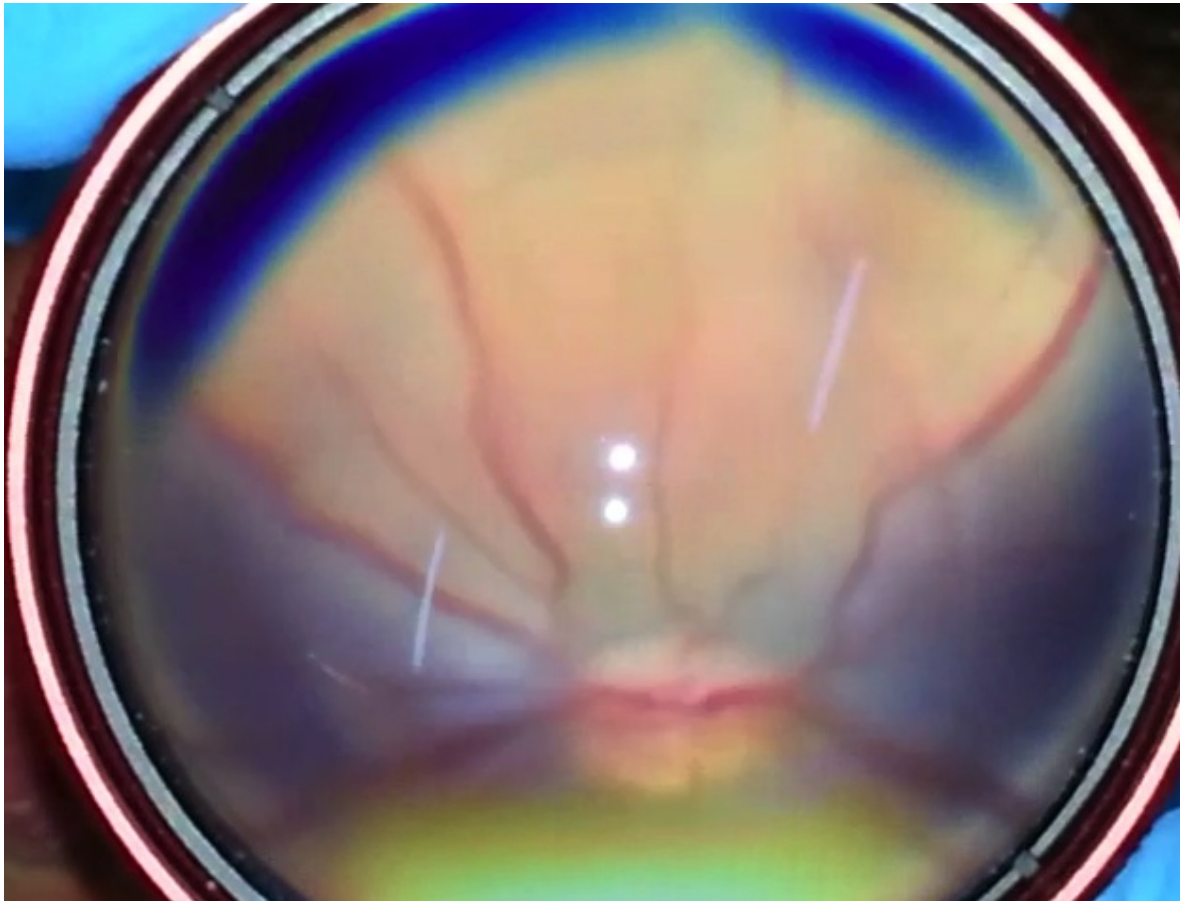
- PLE
 - LLA: wnl ou
 - C/S: w/q ou
 - K: cl ou
 - AC: f/s ou
 - IP: pharm dilated ou
 - L: cl ou

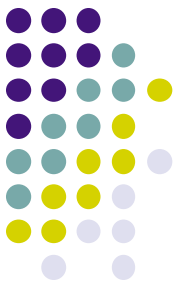


History and Examination

DFE

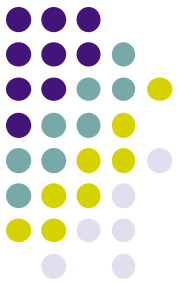
(picture: R eye taken 1 week later)



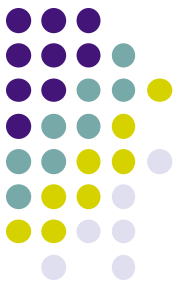


History and Examination

- Initial DFE
 - Ridge present between vascularized and small area of nonvascularized retina in temporal periphery near ora serrata ou
 - Dilation and tortuosity of posterior retinal vessels ou
 - No chorioretinitis ou
- DFE 1 week later
 - Fully vascularized retina ou
 - Decreased dilation and tortuosity of posterior retinal vessels ou

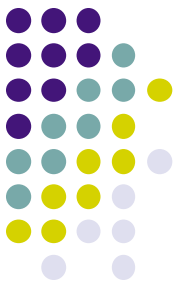


Differential Diagnosis?



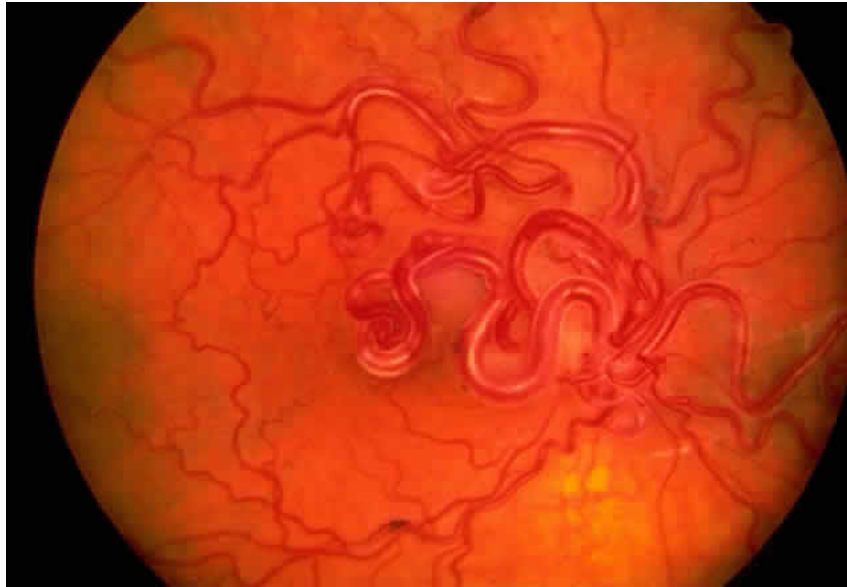
Differential Diagnosis

- Retinopathy of prematurity with plus disease
- Racemose hemangiomas (Wyburn-Mason Syndrome)
- Familial exudative vitreoretinopathy (FEVR)
- Norrie Disease

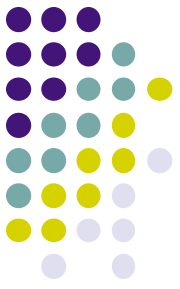


Wyburn-Mason Syndrome

- Arteriovenous malformations of the retina, optic nerve, brain, facial structures
- Retinal racemose hemangiomas: typically unilateral, nonhereditary, nonfamilial, often asymptomatic

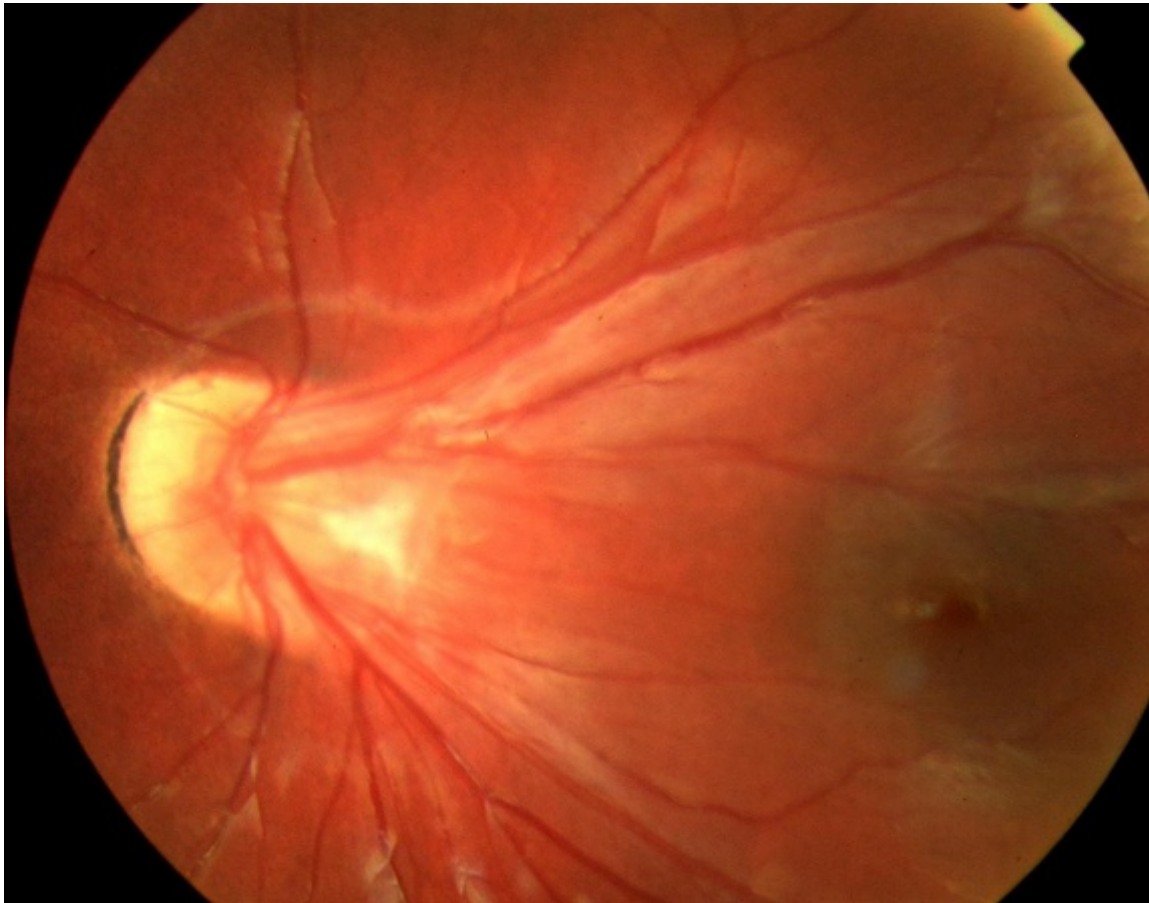
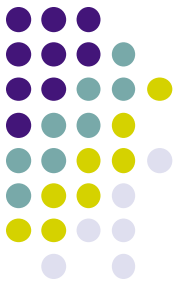


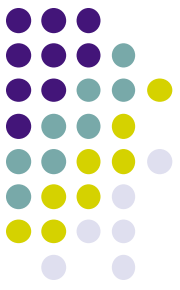
Familial Exudative Vitreoretinopathy (FEVR)



- Failure of temporal retina to vascularize
- Inherited via several gene loci; most autosomal dominant (chromosome 11), one X-linked recessive (NDP gene). Severity can vary significantly among family members.
- Retinal ischemia resulting in peripheral fibrovascular proliferation, retinal folds, retinal traction, tractional and exudative retinal detachments
- Usually bilateral, but severity often considerably asymmetric

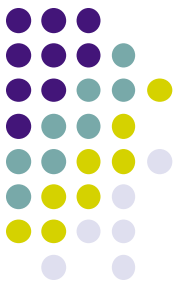
Familial Exudative Vitreoretinopathy (FEVR)





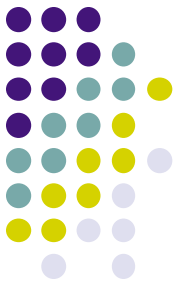
Norrie Disease

- Rare, X-linked recessive (affecting boys), NDP gene (same gene involved in X-linked FEVR).
- Severely dystrophic retina with pigmentary changes in avascular periphery. Retinal detachments early in life resulting in leukocoria. Then opacification of lens and cornea and eventually phthisis bulbi.
- Congenital blindness, hearing impairment, mental retardation
- Female carriers can show peripheral retinal abnormalities.



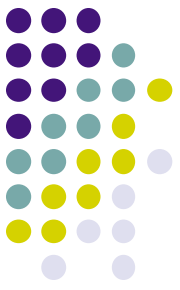
Retinopathy of Prematurity

- Incomplete retinal vascularization in premature and low birth weight infants that results in retinal ischemia, release of growth factors, and abnormal extraretinal fibrovascular proliferation.
- Plus disease: presence of retinal vascular dilation and tortuosity in at least 2 quadrants of the posterior pole



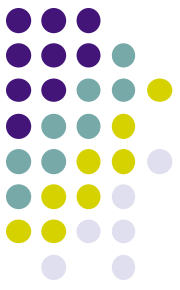
Objectives

- To review the classification and terminology associated with ROP
- To review risk factors and screening recommendations for ROP
- To review treatment strategies for ROP



Pathogenesis

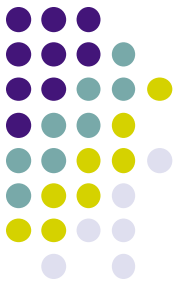
- Normal retinal vascularization: optic disc to periphery
 - Nasally by 36 weeks
 - Temporally by 40 weeks
- Retina of premature infant without ROP: vascularized and avascular areas blend together
- ROP: junction between vascularized and avascular retina is distinct due to presence of shunts and glial hyperplasia
- Retinal ischemia->release of vascular growth factors-> abnormal fibrovascular proliferation



Classification- Location

- Zone I- circle centered around optic nerve with radius 2x distance from center of optic nerve to the center of the macula
- Zone II- from edge of Zone I to the nasal ora serrata anteriorly
- Zone III- remaining temporal peripheral retina

Classification -Extent



- Extent: number of clock hours involved



From: **The International Classification of Retinopathy of Prematurity Revisited**

Arch Ophthalmol. 2005;123(7):991-999. doi:10.1001/archophth.123.7.991

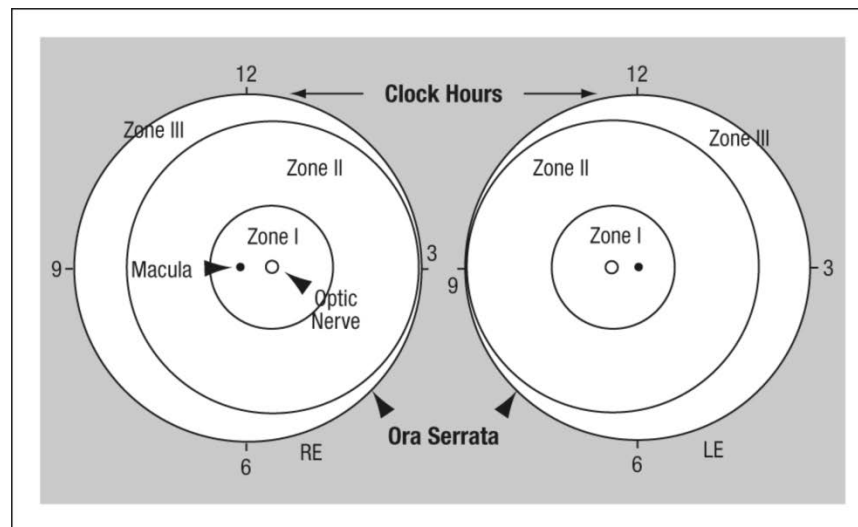
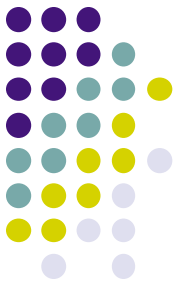


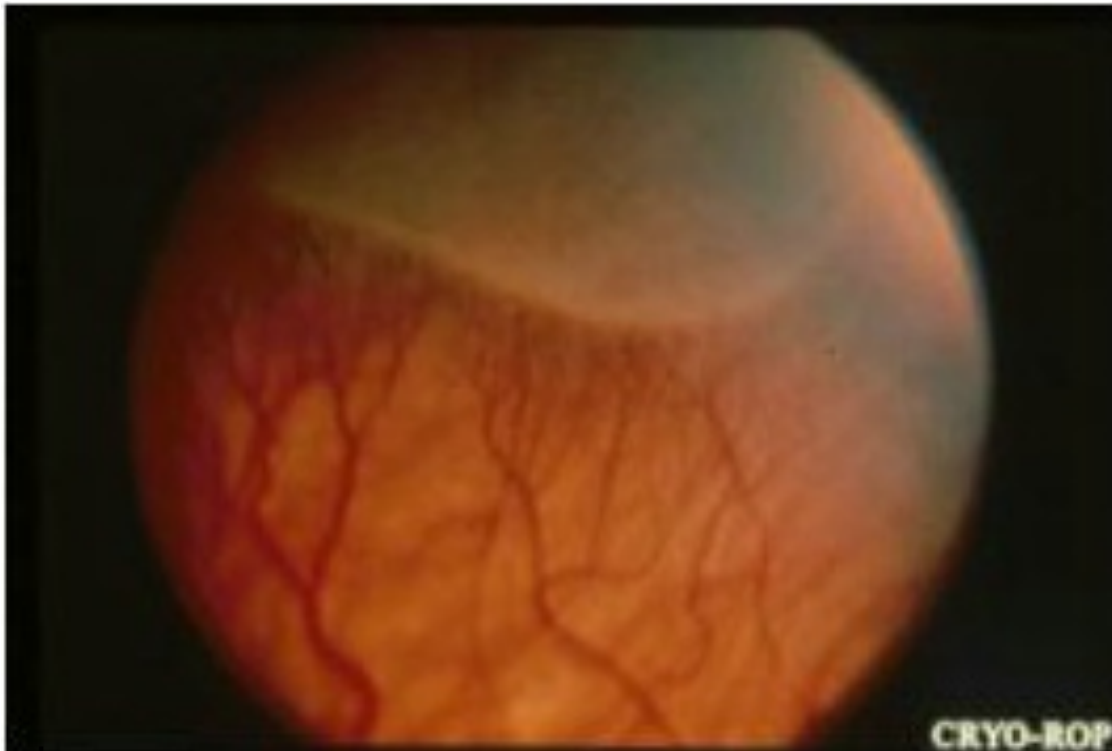
Figure Legend:

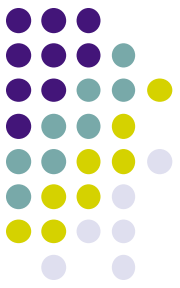
Scheme of retina of right eye (RE) and left eye (LE) showing zone borders and clock hours used to describe the **location and extent** of retinopathy of prematurity (adapted the Committee for the Classification of Retinopathy of Prematurity^[p1131]).



Classification- Severity

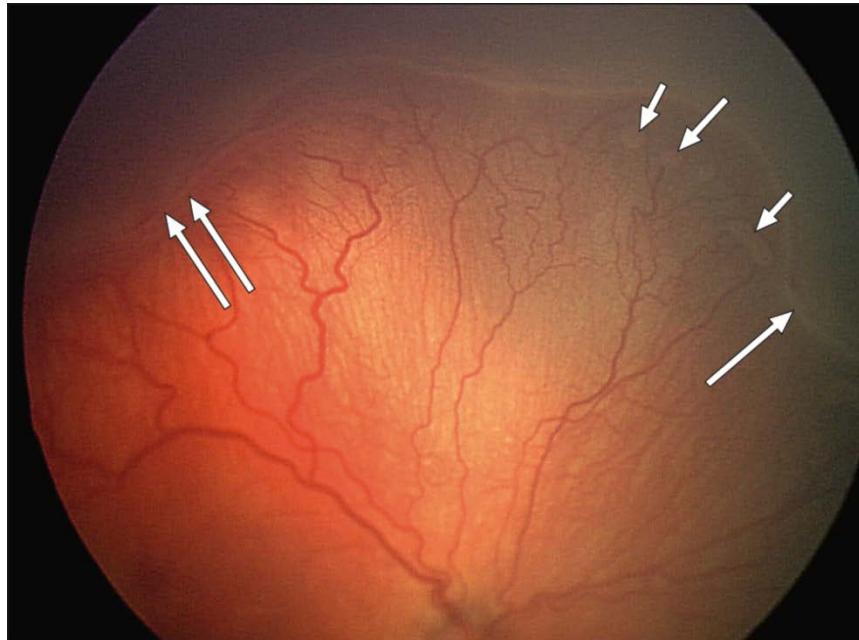
- Stage 1: demarcation line between vascularized and nonvascularized retina





Classification- Severity

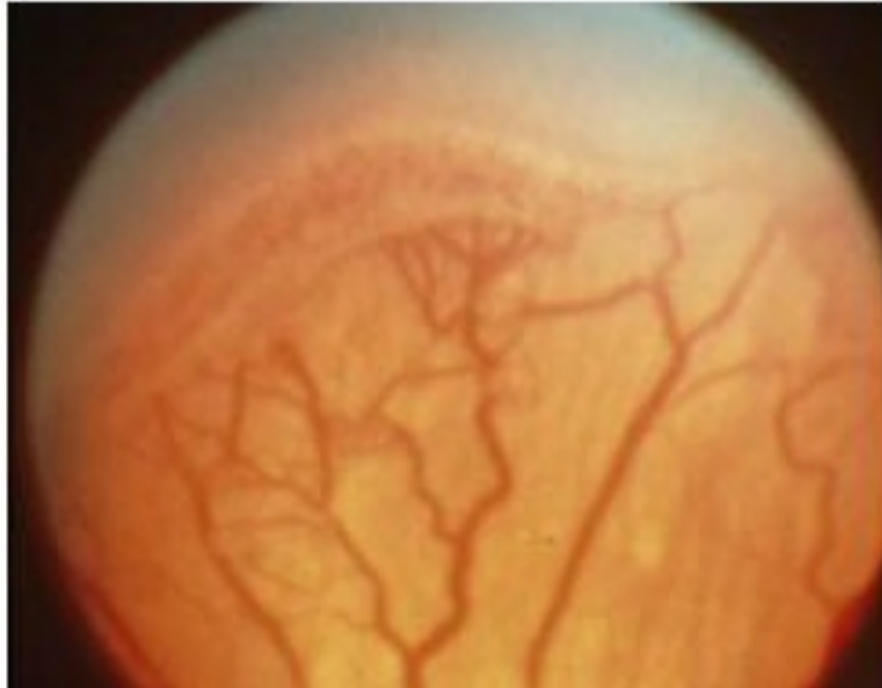
- Stage 2: an elevated ridge (long arrows) separating vascularized and nonvascularized retina. Small isolated tufts of new vessels (called “popcorn”) lie on the retinal surface (short arrows).

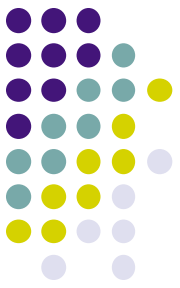




Classification- Severity

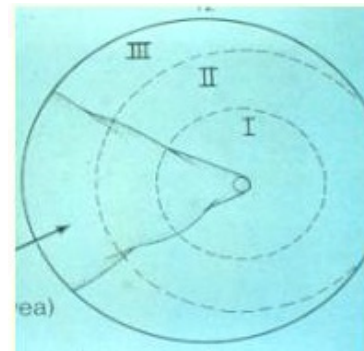
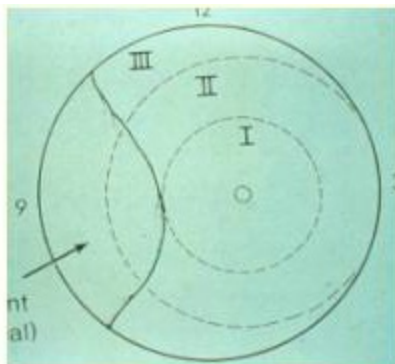
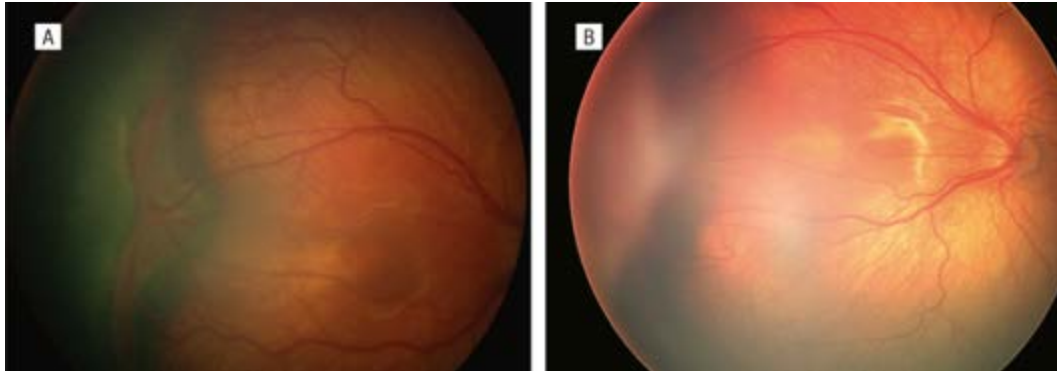
- Stage 3: a ridge with extraretinal fibrovascular proliferation (neovascularization) extending into the vitreous

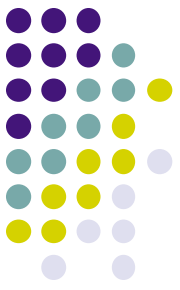




Classification- Severity

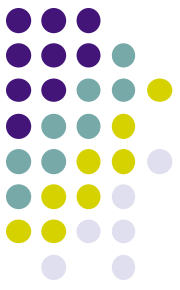
- Stage 4: partial retinal detachment
 - 4A: extrafoveal
 - 4B: including fovea



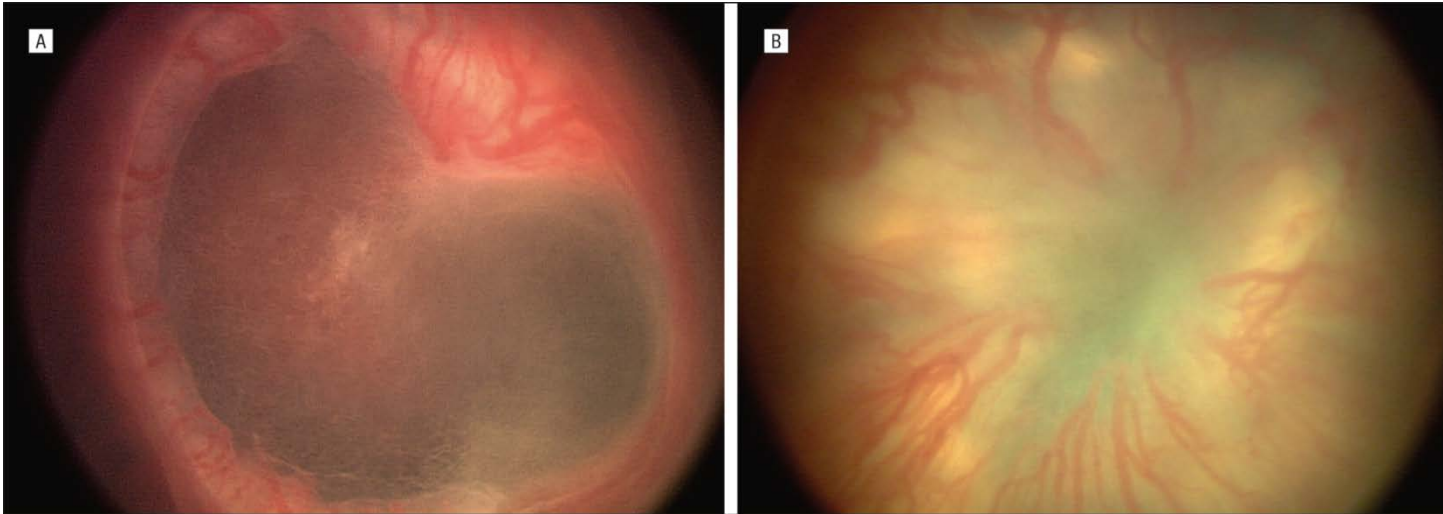


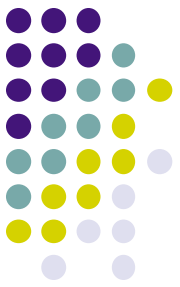
Classification- Severity

- Stage 5: total retinal detachment
 - Funnel configurations in order of frequency:
 - Anterior Open, Posterior Open
 - Anterior Closed, Posterior Closed
 - Anterior Open, Posterior Closed
 - Anterior Closed, Posterior Open
 - If closed funnel anteriorly, associated fibrosis appears as a white mass behind the lens.



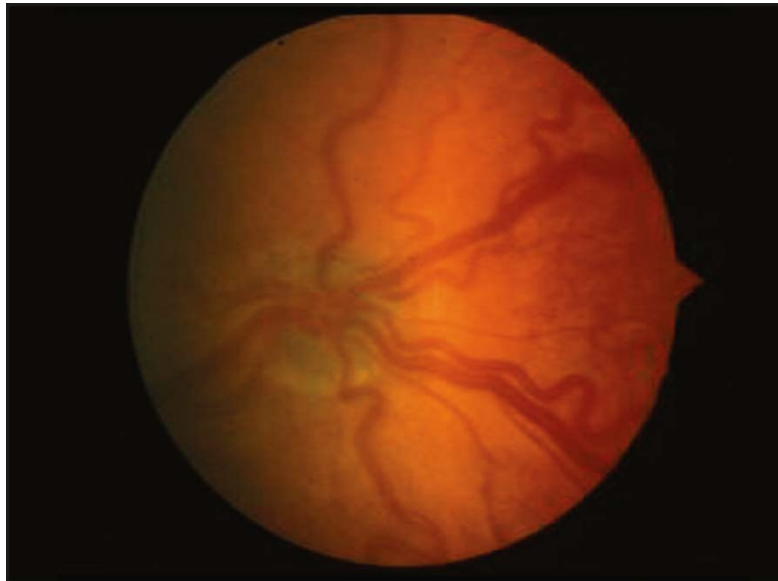
Classification- Stage 5 ROP

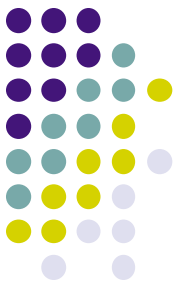




Plus Disease

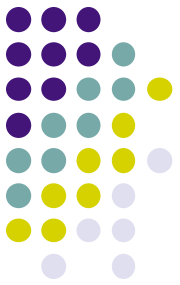
- Dilation and tortuosity of the retinal vasculature in at least 2 quadrants
- Signifies actively progressive phase
- Associated findings: iris vascular engorgement, poor pupillary dilation (rigid pupil), and vitreous haze





Rush disease (APROP)

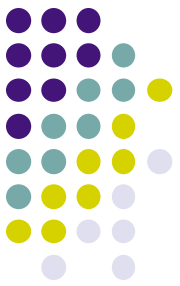
- Aggressive (rapid progression) posterior (zone I or posterior zone II) ROP with plus disease
- Usually does not progress classically through stages 1 to 3
- Neovascularization typically extends circumferentially
- If untreated, usually progresses to Stage 5



(OLD) Threshold Disease

- More than 5 contiguous clock-hours or 8 cumulative clock hours of extraretinal neovascularization
- Plus disease
- Zone I or II

- Defined by the Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) as benefiting from peripheral retinal ablation with cryotherapy treatment



Risk Factors

- Short gestational period (prematurity) (GA<32wk)
- Low birth weight (<1500g)
- Supplemental oxygen
- Illness: sepsis, low APGAR scores, blood transfusion, slow rate of postnatal weight gain, IGF-1 levels



Screening Recommendations

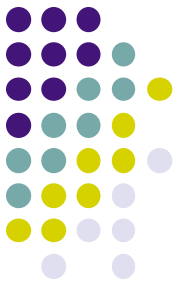
- Infants with birth weight $\leq 1500\text{g}$ or GA of $\leq 30\text{wk}$
- Infants with birth weight $1500\text{g}-2000\text{g}$ or $\text{GA} > 30\text{wks}$ with unstable clinical course
- At least 2 dilated exams should be performed. One exam sufficient only if it unequivocally shows fully vascularized retina in both eyes.
- Timing of first exam based on postmenstrual age (GA+chronologic), as serious ROP correlates better with postmenstrual age.
 - More preterm = longer time to development of serious ROP
 - Earlier screening based on severity of comorbidities

TABLE 1 Timing of First Eye Examination Based on Gestational Age at Birth

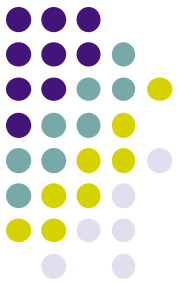
Gestational Age at Birth, wk	Age at Initial Examination, wk	
	Postmenstrual	Chronologic
22 ^a	31	9
23 ^a	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older gestational age, high-risk factors ^b		4

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 AMERICAN ACADEMY OF OPHTHALMOLOGY, AMERICAN ASSOCIATION
 AMERICAN ACADEMY OF PEDIATRICS Section on Ophthalmology,
 Screening Examination of Premature Infants for Retinopathy of Prematurity
Pediatrics 2013; 131: 189-195

Screening Recommendations

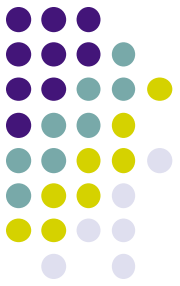


- Follow-up intervals based on severity of initial findings
- 1 Week or Less
 - Zone I, stage 1 or 2
 - Zone II, stage 2 or 3
 - Suspected presence of aggressive posterior ROP
- 1-2 Week
 - Zone I, regressing ROP
 - Zone II, stage 2
- 2 Week
 - Zone II, no ROP, Stage 1 ROP, or regressing ROP
- 2-3 Week
 - Zone III: stage 1 or 2 ROP, regressing ROP



Treatment

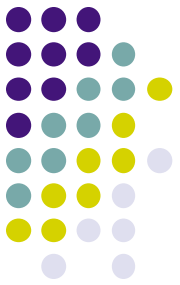
- CRYO-ROP (1988)
 - Ablation of avascular anterior retina in ROP eyes with **threshold disease** reduced the incidence of unfavorable outcomes by approximately 50%. Benefit of cryotherapy treatment still evident at 10-year follow-up.



ETROP (2000-2002)

- Type I ROP (high risk): Retinal ablative therapy recommended
 - Zone I, any stage with plus disease
 - Zone I, stage 3 without plus
 - Zone II, stage 2 or 3 with plus
- Type II ROP (low risk): Monitoring and f/up for any progression recommended
 - Zone I, stage 1 or 2 without plus
 - Zone II, stage 3 without plus

Treatment: Anti-VEGF/BEAT-ROP



Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity.

Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group.

Collaborators (83)

Department of Ophthalmology and Visual Science, University of Texas Health Science Center at Houston-Medical School, Houston, USA. helen.a.mintz-hittner@uth.tmc.edu



Abstract

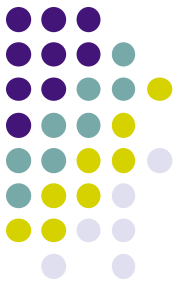
BACKGROUND: Retinopathy of prematurity is a leading cause of childhood blindness worldwide. Peripheral retinal ablation with conventional (confluent) laser therapy is destructive, causes complications, and does not prevent all vision loss, especially in cases of retinopathy of prematurity affecting zone I of the eye. Case series in which patients were treated with vascular endothelial growth factor inhibitors suggest that these agents may be useful in treating retinopathy of prematurity.

METHODS: We conducted a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age.

RESULTS: We enrolled 150 infants (total sample of 300 eyes); 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary-outcome analyses. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], $P=0.002$). A significant treatment effect was found for zone I retinopathy of prematurity ($P=0.003$) but not for zone II disease ($P=0.27$).

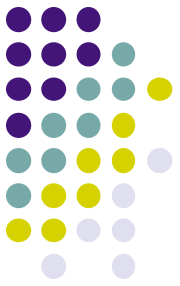
CONCLUSIONS: Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. This trial was too small to assess safety. (Funded by Research to Prevent Blindness and others; ClinicalTrials.gov number, NCT00622726.).

Reflective Practice



This case allowed me to learn about the classification, risk factors, screening recommendations and treatment of an important retinal disease process.

Core Competencies



Patient Care: The case involved thorough patient care and careful, timely and appropriate follow up.

Medical Knowledge: This presentation allowed me to review the classification, risk factors, screening guidelines, follow-up and treatment of Retinopathy of Prematurity.

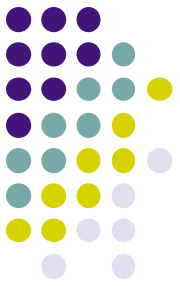
Practice-Based Learning and Improvement: This presentation included a literature search of risk factors and current treatment modalities for Retinopathy of Prematurity.

Interpersonal and Communication Skills: Every effort was made to communicate clearly with the primary pediatric team about the findings, management and further follow-up for this patient.

Professionalism: The patient was diagnosed and followed in a timely and appropriate manner.

Systems-Based Practice: The ophthalmology and pediatric services worked together to appropriately diagnose and follow the patient.

References



- et al. The International Classification of Retinopathy of Prematurity Revisited. Arch Ophthalmol. 2005;123(7):991-999.
- From the American Academy of Pediatrics. Policy Statement. Screening Examination of Premature Infants for Retinopathy of Prematurity. Pediatrics 2013; 131: 189-195
- Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011 Feb 17;364(7):603-15.
- Section 12: Retina and Vitreous. Basic and Clinical Science Course. American Academy of Ophthalmology. 2013-2014.
- William V Good, MD and on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final Results of the Early Treatment for Retinopathy of Prematurity (ETROP) Randomized Trial. Trans Am Ophthalmol Soc. 2004 December; 102: 233–250.