INHERITED RETINAL DISEASE

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Hereditary Retinal Diseases Epidemiology

- HRDs affect about 1/2000 people worldwide
- Hundreds of causative mutations now identified
  - Most affecting photoreceptors or RPE
- Many associated with systemic syndromes
- Most cause significant visual disability

Hereditary Retinal Disease

Signs and Symptoms Based on Photoreceptors Involved:

RODS	**CONES**
• Loss of Night Vision	• Decreased Acuity
• Peripheral Field Loss	• Central scotoma
• ERG: Scotopic loss	• ERG: Photopic loss
• VA and color vision affected late	• Color Vision Affected
•Photosensitivity	• Photosensitivity

The Rod/Cone Dichotomy

Peripheral (Rod) Diseases	Central (Cone) Diseases
□ Retinitis Pigmentosa family	□ Achromatopsia
◘ Leber's Congenital Amaurosis	□ Cone Dystrophy
□ CSNB	
□ Oguchi's	□ Stargardt's (juvenile macular dystrophies)
	□ Best's (juvenile macular dystrophies)

Case History/Entrance Skills

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- 31 YR HM
- CC: referred from PCP for a possible uveitis
- LEE: 3 years ago
- PMHx: unremarkable
- Meds: Omega-3 supplements
- Entrance VA: 20/30+ OD, OS
- Refraction:
  - +0.75 -2.50 x 003 6/7.5+ (20/25+)
  - +0.25 -2.75 x 004 6/7.5+ (20/25+)
- All other entrance skills unremarkable except for difficulty doing confrontation visual fields

Health Assessment

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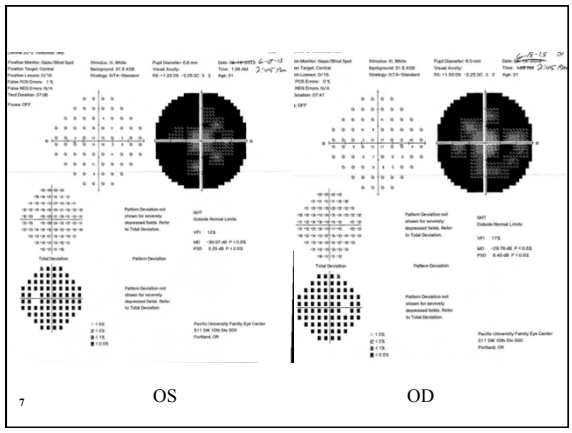
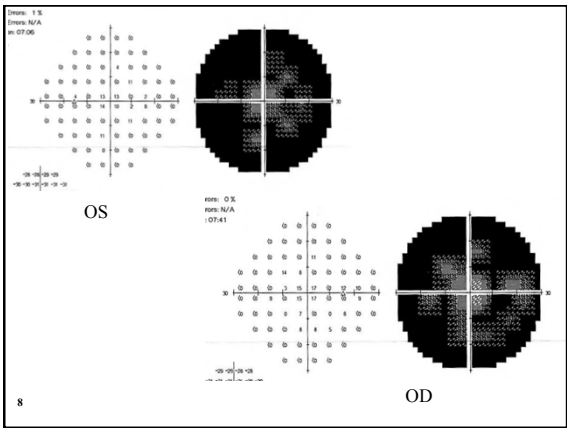
- SLE:
  - 1+ conjunctival injection in the right eye
  - Anterior chamber: deep and quiet (no cells or flare noted in either eye)
- IOP: 12 and 11 OD, OS
- DFE: see photos

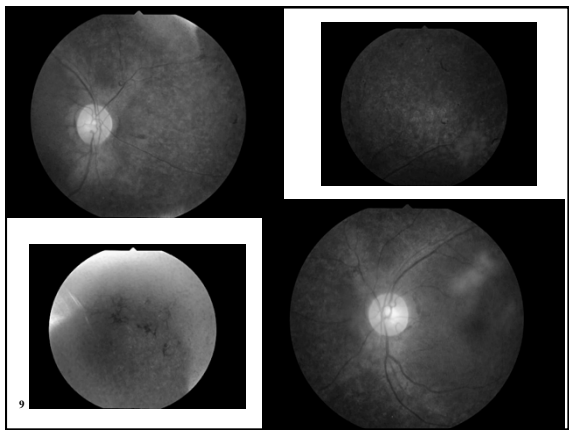


7 OS OD



OS

8 OD



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Retinitis Pigmentosa and related dystrophies (Rod-Cone Dystrophies)

- Most common hereditary retinal dystrophy
  - Prevalance 1/4000 in US
- Family of dystrophies caused by variety of genetic mutations
  - Now over 200 specific genetic mutations identified that contribute to RP
- Common end result is loss of rods with secondary involvement of cones

Retinitis Pigmentosa Types

- Many variants Including AD, AR, X-linked
- Autosomal Recessive: Most common
  - Night vision and peripheral field loss in early childhood, central vision loss by adulthood
- Autosomal Dominant
  - Least severe form with central vision intact until 40's or 50's
- X-Linked
  - Worst prognosis with severe vision loss by 4th decade

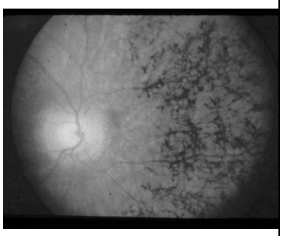
* 30-40% of cases are part of a systemic syndrome

RP Symptoms

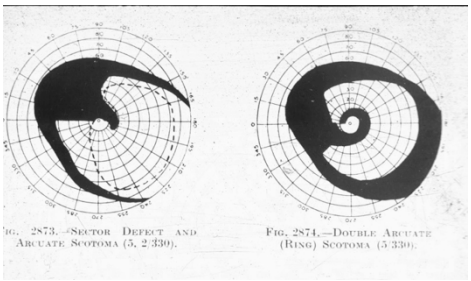
- Night blindness (Nyctalopia)
  - Initial symptom
- Reduced mobility, esp. in low illumination
- Some patients are asymptomatic even though they have significant field loss and night blindness (esp. children)
- Eventual central acuity loss

RP Signs

- Arterial attenuation (sometimes the earliest sign)
- Waxy looking optic nerve pallor (atrophy)
- Classic bone spicule pigmentary pattern
  - Begins in mid-periphery
  - Corresponding visual field loss (ring scotoma)
- Cataracts (PSC) develop in 50% of cases
- Macular edema in late stages



Typical Early RP Field Loss



IG. 2873.—Sector Defect and Arcuate Scotoma (5, 2/330).

Fig. 2874.—Double Arcuate (Ring) Scotoma (5/330).

ERG Findings

- Scotopic ERG will usually be abnormal before retinal signs are present
- Relative loss of scotopic vs photopic ERG clarifies to what degree and what types of photoreceptors are involved.
- Often necessary for firm diagnosis in early stages of disease
- Results can help determine the RP type and therefore prognosis

Photoreceptors

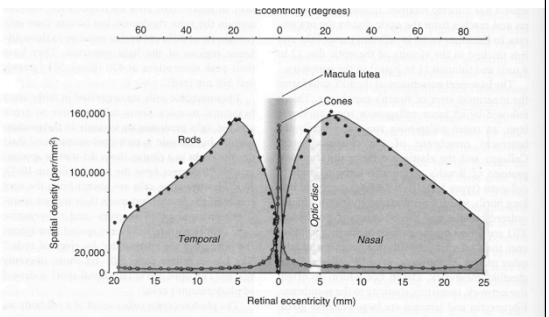


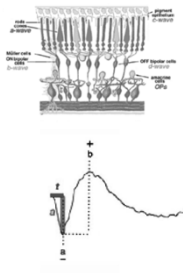
FIGURE 10-7 Rod and cone densities in the human retina. (Redrawn from Rodieck RW: *The first steps in seeing*, Sunderland, Mass, 1998, Sinauer Associates; modified from Sterberg G: *Acta Ophthalmol [Copenh]* 6:1, 1935.)

From Kaufman and Alm, *Adler's Physiology of the Eye*, 2003

Electroretinogram (ERG)

- Full field flash ERG
  - Measures the summed response of **all** photoreceptors (rods & cones)*
  - 2 main components of the clinically recorded ERG
    1. Negative A-wave
       - photoreceptors
    2. Positive B-wave
       - mid-retinal layers

  ganglion cells do not contribute

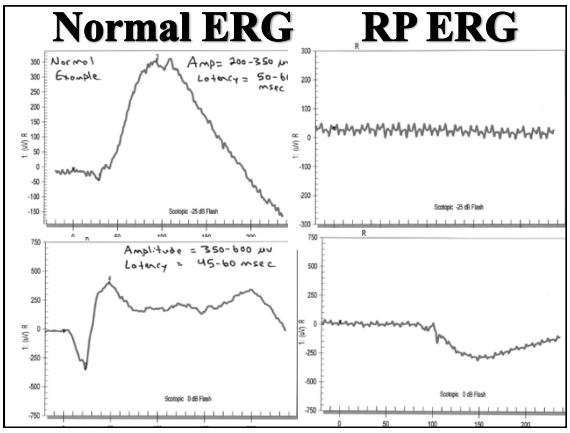


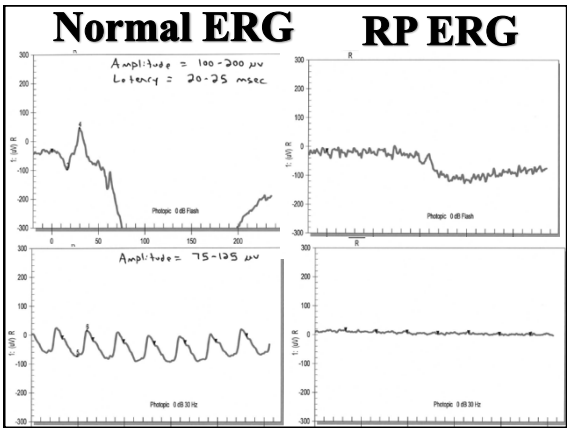
Electroretinogram (ERG)

- 4 steps/tests in the full field flash ERG

Scotopic ERG
1. Dark-adapted dim flash (rod response)
2. Dark-adapted bright flash (maximal rod-cone response – still mostly rods)

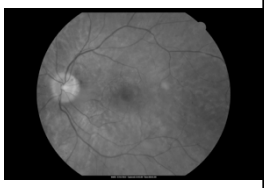
Photopic ERG
3. Light-adapted bright flash (single-flash cone response)
4. Light-adapted flicker (cone flicker response)



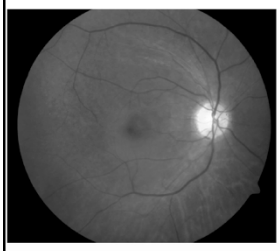


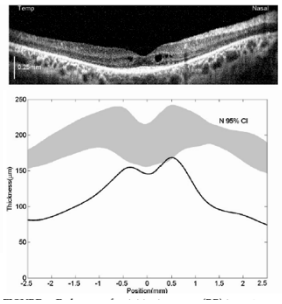
A few RP Variants...

- Retinitis Sine Pigmento
  - No or minimal pigmentary changes (may be atrophic looking retina)
  - May be just early stage of disease
  - Arterial attenuation and waxy nerve may be prominent signs
- Sector RP
  - Inferior quadrants only



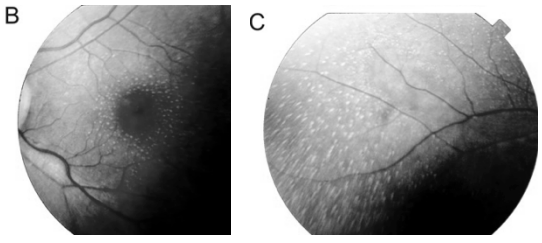
Early RP





From: A Pilot Study of Fourier-Domain Optical Coherence Tomography of Retinal Dystrophy Patients
Lim, et al. Am. J. Ophthalmol, Sept. 2008

Retinitis Punctata Albescens



Invest. Ophthalmol. Vis. Sci. November 2006 vol. 47 no. 11 4719-4724

Systemic Syndromes

- Usher Syndrome: Congenital sensori-neural hearing loss and RP
  - 1/6000 people affected, accounts for 50% of deaf-blind individuals
  - Many also have poor tactile sensation
  - Vestibular issues
  - 3 types identified (4th type debated)
    - Worst form is Type 1 with congenital deafness and vision problems beginning in first decade of life

RP Treatment

- No direct treatment…yet. Advances in molecular biology hold great promise.
- Nutrient supplements:
  - Vitamin A, lutein and Omega 3 have been proposed to slow down progression of VF loss
  - Rayapudi, et al, 2013 Cochrane Database review of literature:

    "no clear evidence for benefit of treatment with vitamin A and/or DHA for people with RP, in terms of the mean change in visual field and ERG amplitudes at one year and the mean change in visual acuity at five years follow-up"

RP Treatment

- Short-wavelength blocking tints
  - May help with photosensitivity
  - May slow progression
  - Decreases metabolism of the retina (photopigments)

RP Treatment

- Cataract removal may improve VA's
- Treatment of CME may preserve central vision
- Consult retinal specialist for prognosis, genetic testing and counseling if not already done
- Low Vision management is difficult
  - Denial may occur due to slow progression
  - As central vision loss occurs, magnification has limited efficacy due to narrow FOV
  - Field expansion devices may be helpful
- Refer to Commission for the Blind for orientation and mobility

RP Treatment/Research

- Gene Therapy:
  - Introducing a healthy gene into the retina
- Transplant Therapy:
  - Transplanting healthy retinal cells
- Retinal prosthesis:
  - Implanting a light sensitive electrode (prosthesis) into the eye which would act as a "bionic" eye

Clinical Case

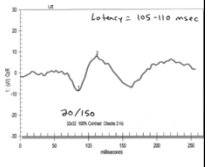
- 23 year old Male
- Sudden decrease in vision in both eyes

- Entering VA's
  - OD -> Count Fingers @ 2 feet
  - OS -> 20/300

- Pupils, EOM's, Confrontation fields normal OU
- Patient has had a MRI of brain/orbits- within normal limits

Visually Evoked Response (VER or VEP)

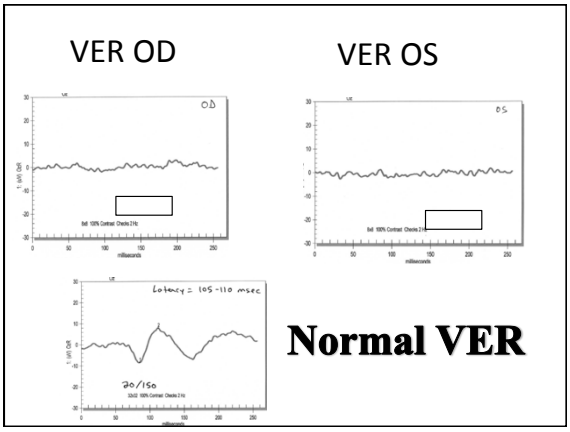
- Measures the entire visual pathway
  - From cornea to occipital lobe
- Very useful in:
  - Unexplained vision loss
  - Malingering
  - Psychogenic vision loss
  - MS/optic neuritis



- However, usually will not point to a specific diagnosis
  - Just tells you there is a problem somewhere in the visual pathway

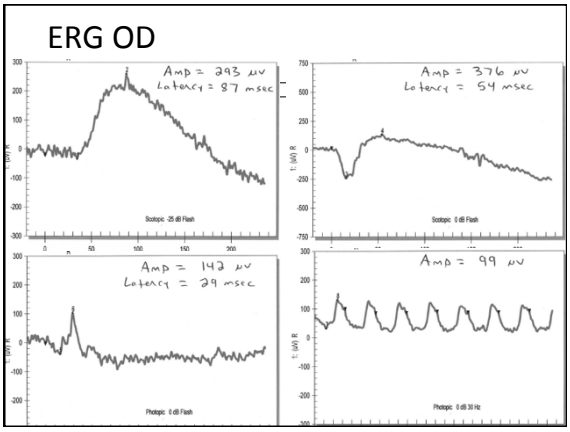
VER OD

VER OS

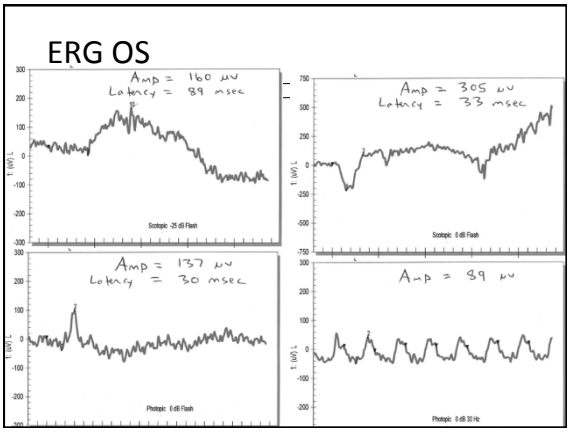


Normal VER

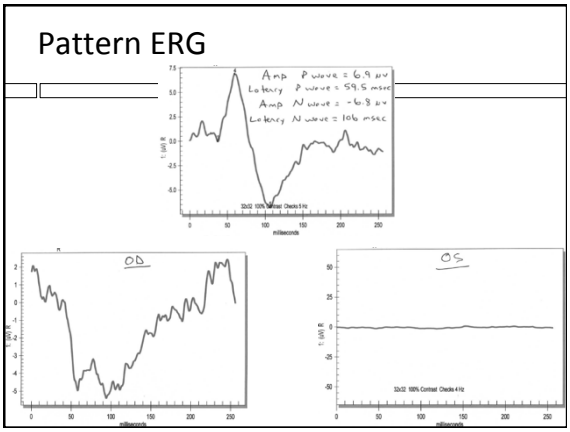
ERG OD

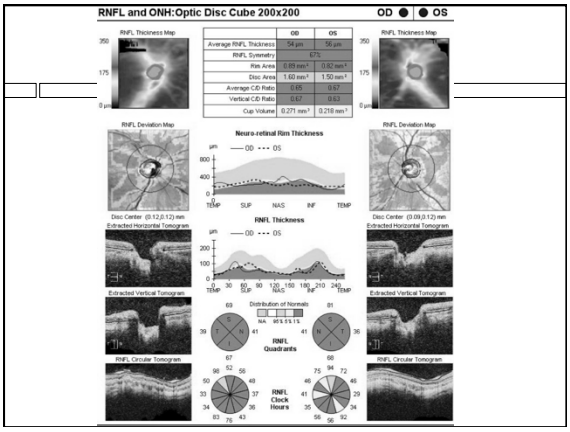


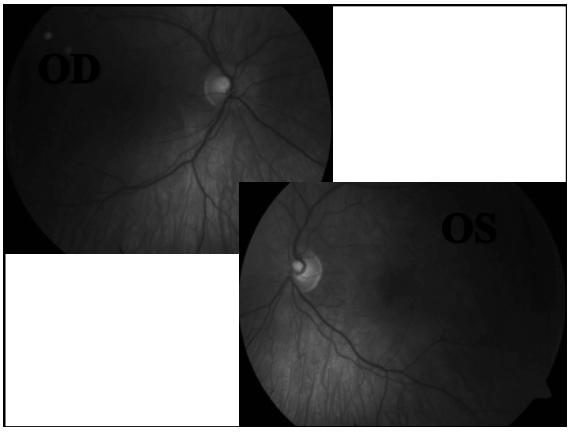
ERG OS



Pattern ERG







Case

- Diagnosis:
  - Leber's Hereditary Optic Neuropathy (LHON) OU
- Plan:
  - Low vision referral

Leber's hereditary optic neuropathy (LHON)

- 15-30 year old males
- Mitochondrial DNA mutation from the mother
  - Lifetime risk of blindness for males is 50% and only 10% for females
  - None of the males will transfer the condition
- Symptoms:
  - Rapidly, progressive painless vision loss in one eye, and then the other
  - Bilateral presentation 25%, sequential 75%
  - Other eye typically follows 6-8 weeks after the first eye
  - Vision is typically in the 20/200 (6/60) or worse
  - Central or centrocecal scotomas

Leber's hereditary optic neuropathy (LHON)

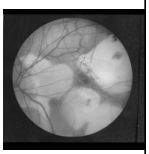
- Signs:
  - Optic nerve head pallor (typically develops 4-6 months after)
  - Telengiaectatic vessels around the nerve
- Treatment:
  - Low vision
  - Idebenone (Catena) approved in Europe (2015) for treatment of LHON
    - 900 mg/day for 24 weeks has persistent beneficial effects in preventing further vision impairment and promoting vision recovery in patients with LHON relative to the natural course of the disease.

Congenital Stationary Night Blindness

- Group of disorders:
  - 17 genes identified to contribute
- Generally non progressive
- Night Blindness is primary symptom
  - Delayed dark adaptation
- Mild acuity reduction (usually 20/30 - 20/60)
- Normal retina
- Nystagmus present in more severe cases
- ERG pattern is diagnostic

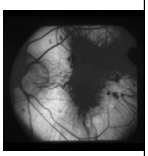
Hereditary Choroidal Disease: Peripheral Presentation

- Gyrate atrophy (very rare)
  - Associated with hyperornithinemia due to deficient enzyme activity (ornithine aminotransferase)
  - High myopia is common early in life
  - Night Blindness and RPE changes in 2nd decade
  - RPE and choroidal atrophy leaving bare sclera
  - Pattern of visual loss very similar to RP
  - Treatment: B6 supplements, diet low in protein (low arginine, precursor of ornithine) slows, may halt progression



Choroideremia

- X-linked, Affects Males only (1/50,000)
- Onset of night blindness first 5 - 10 yrs
- Diffuse RPE mottling is early sign then large patches of RPE and choroidal atrophy in mid-periphery leaving bare sclera
- Corresponding peripheral field loss
- Central field lost in 40's to 60's
- Scotopic ERG becomes non-recordable
- First Gene Therapy Trials now complete. Very promising results:

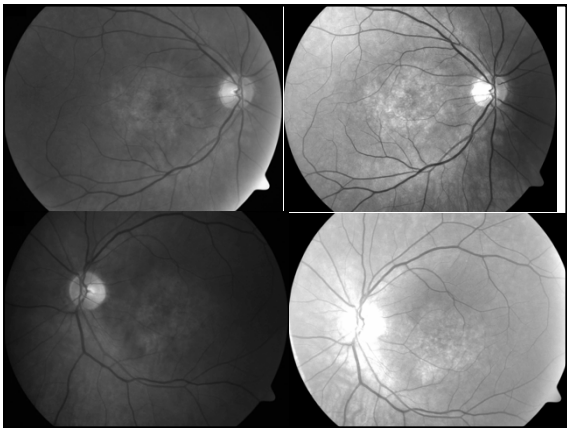


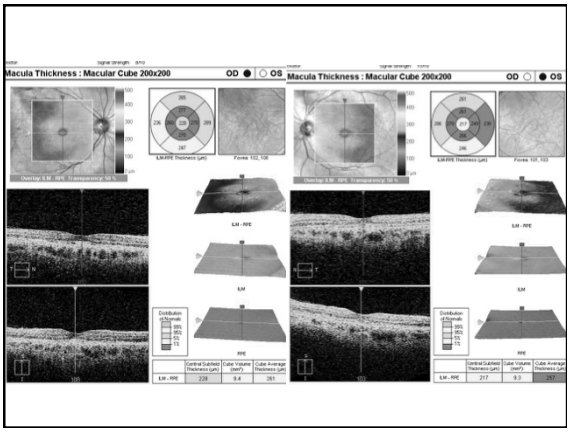
Clinical Case

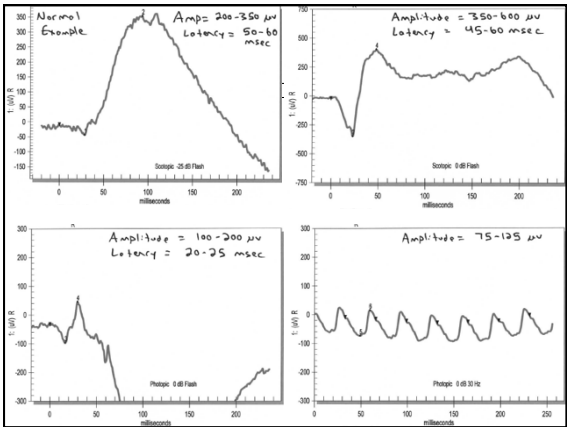
- 37 yoF
- Referred in for electrodiagnostics testing due to "RPE changes" within central macula OU
- Pt notes mildly decreased vision for past decade or so that seems to have worsened significantly in past year
- Significant sensitivity to lights

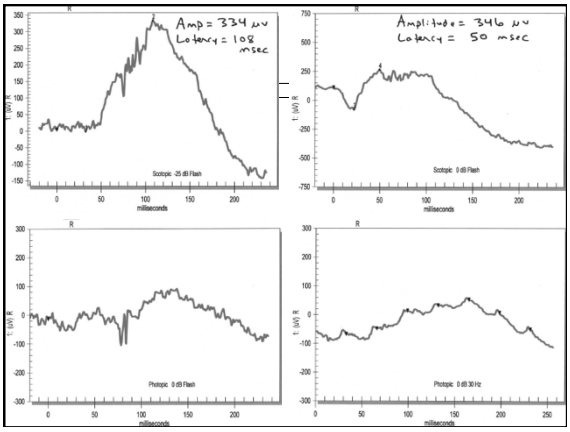
Clinical Case

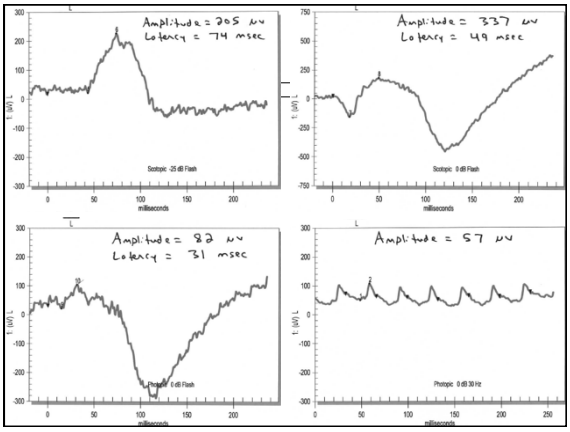
- BCVA
  - OD –> 20/30-
  - OS –> 20/40+
- Color vision
  - Severe color vision deficit OD
  - Moderate color vision deficit OS
- Anterior segment, IOP's, and peripheral retinal exam unremarkable OU











Clinical Case

- Full field flash ERG
  - Normal rod response OU
  - Severely reduced cone response OD
  - Moderately reduced cone response OS

Clinical Case

- Diagnosis:
  - Cone Dystrophy OD>OS
- Treatment:
  - Not a whole lot can be done
  - Sun protection to help with photophobia
  - Genetic testing

Central Retinal Dystrophies

Cone Dystrophy

- Sporadic & autosomal dominant inheritance
- Onset
  - 1st – 3rd decade of life
- Classic Triad
  - Decreased central vision
  - Decreased color vision
  - Photophobia
- Also
  - Central visual field defects

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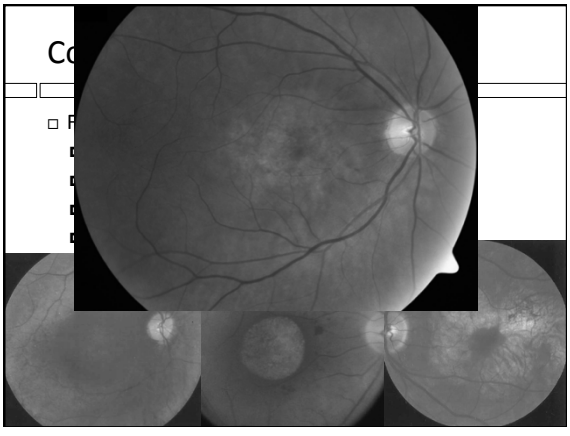


Cone Dystrophy

- DDx:
  - Congenital color blindness/Rod monochromatism
  - ARMD
  - Stargardts
  - Chloroquine/Hydroxychloroquine maculopathy
- Tx:
  - Tinted glasses/sunglasses
  - Genetic counseling
  - Low vision aids
- Prognosis:
  - 20/30 – 20/400
  - Worse if rods become involved
  - Age of patient

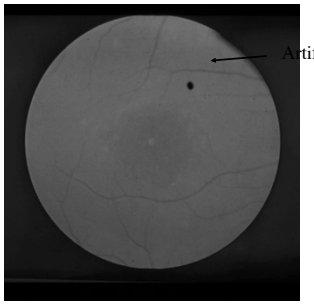
Stargardt's Macular Dystrophy

- Most common hereditary (juvenile) macular dystrophy (AR inheritance)
  - (ARMD has strong hereditary component but is multifactorial)
  - Caused by mutation in the ABCA4 gene
- Usual Onset 8 - 16 yrs with poor acuity
  - 25% of cases have later onset (less severe)
- Often exhibit delayed dark adaptation
- **Acuity loss may precede observable macular changes**
  - **Macular changes very subtle at first**

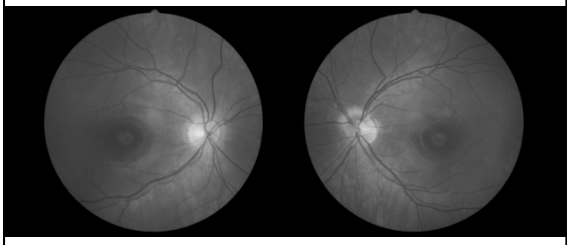
Stargardt's

- Foveal Light Reflex lost as mottling appears
- Coalesces to form oval area of atrophic RPE
- Beaten Bronze appearance at end stage
- Yellow pisciform (fishy) flecks in surrounding posterior pole vary in timing and appearance
- Usually stabilizes by early 20's with acuities in 20/200 - 20/400 range

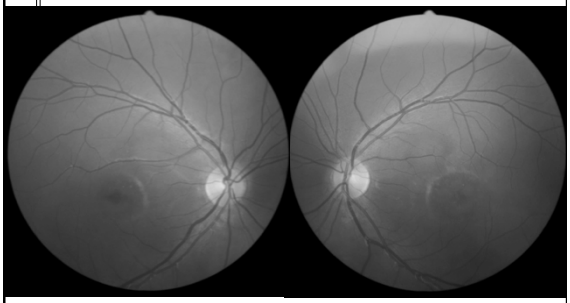
Stargardt's: Early Stage



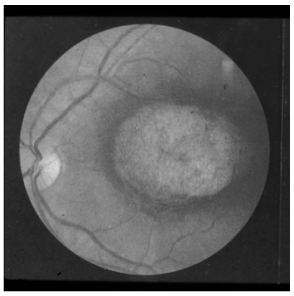
Stargardt's: 18yo w/20/50 VA's



Stargardt's: 16 yr old with 20/200 acuity

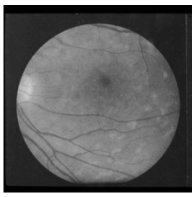


Stargardt's: Endstage

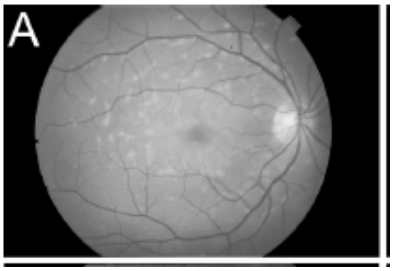


Fundus Flavimaculatus

- Variant of Stargardt's
- Pisciform lesions are primary presentation
- Macular disease and acuity loss develops later (40's - 50's)



Fundus Flavimaculatus

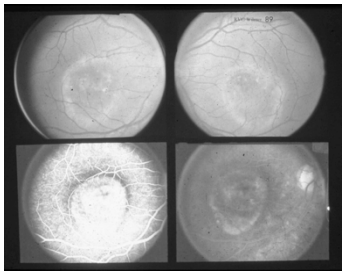


From: Westeneng-van Haaften et al. Clinical and Genetic Characteristics of Late-onset Stargardt's Disease, Ophthalmology 2012;119:1199–1210

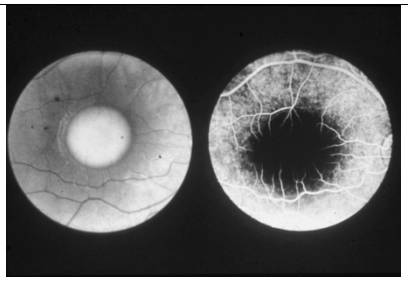
Vitelliform Dystrophy (Best Disease)

- Usually begins early childhood (AD inheritance)
- Previtelliform stage: Abnormal EOG
- Vitelliform Stage: Yellow spots coalesce into "Egg Yolk" macula appearance
  - VA still near normal (opposite of Stargardt's)
- Pseudohypopyon stage: Lesion partially reabsorbs
- Vitelliruptive Stage: Lesion breaks up in to "scrambled egg"
  - VA drops to 20/200 range

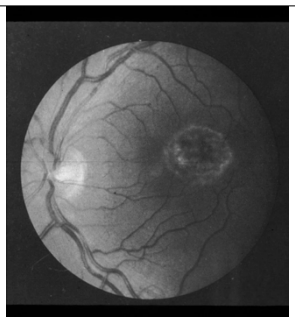
Best's: Early Stage



Best's: Vitelliform Stage



Best's: Endstage



Albinism

- Very common form of congenital visual impairment
- Varying degrees of amelanosis due to deficiency of tyrosinase (or other players in melanin biosynthesis)
- Many genetic variants
- Anomalous wiring at the chiasm limits binocularity (no global stereopsis, gross local stereo in mild cases)

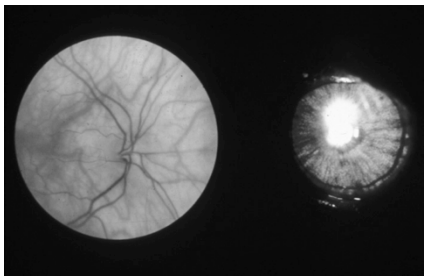
Albinism: Primary Types

- Oculocutaneous
  - Systemic, skin, hair and eyes affected
  - Several genetic variants (main types are OCA1, OCA2, and OCA3)
- Ocular Albinism
  - X-Linked: Affected males show near normal skin and hair pigment but varying degrees of ocular depigmentation
    - Acuity usually in 20/40 - 20/100 range
  - Autosomal Recessive form of ocular albinism tends to be more severe

Albinism: Visual function dependent on degree of:

- Foveal hypoplasia (major factor affecting acuity)
  - Can be appreciated on ophthalmoscopy and with macular OCT scan
- Amelanosis of iris and retina (photophobia)
- Nystagmus (and ability to dampen)
- Strabismus and impaired BV
- Astigmatism (almost all have WTR)

Albino Fundus and Iris Transillumination



Mild Oculocutaneous Albinism