HEREDITARY FUNDUS CONDITIONS

Raman Bhakri, OD, FAAO
Assistant Professor
Marshall B. Ketchum University
Southern California College of Optometry

DISCLOSURES

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OUTLINE

- Technology used in hereditary disease
  - Electroretinogram (ERG) and multifocal electroretinogram (mERG)
  - Spectral Domain Optical Coherence Tomograph
  - Fundus Auto-Fluorescence
  - Fluorescein Angiography
- Conditions affecting night vision
- Conditions affecting central vision

ELECTRORETINOGRAM (ERG)

- Evaluate waveform (a-b amplitude)
  1) Photopic A: evaluate cones
  2) Scotopic A: evaluate rods
  3) Photopic B: inner nuclear layer (cones)
  4) Scotopic B: inner nuclear layer (rods)
  5) Flicker ERG: macular cones

For additional information, Dr. Creel at the University of Utah has good online review:
- http://webvision.med.utah.edu/book/electrophysiology/the-electroretinogram-clinical-applications/

EQUIPMENT USED
**MULTI FOCAL ERG**

- Variation of ERG:
  - allows assessment of ERG activity in small areas of retina
  - The mfERG is particularly valuable in cases in which the fundus appears normal

**MULTIFOCAL PRINTOUT**

- Measures electrical potential generated by the RPE
- Compares the potential difference in dark versus light. ratio is obtained (light peak-dark trough)
- If ratio is reduced then RPE disease is suggestive (<1.6:1)

**ELECTROOCULOGRAM (EOG)**

- EOG recording of a normal person
- Measures electrical potential generated by the RPE
- Compares the potential difference in dark versus light. ratio is obtained (light peak-dark trough)
- If ratio is reduced then RPE disease is suggestive (<1.6:1)

**SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHPER**

- Multifocal ERG recordings transformed into color-maps of the macular area in a patient with AMD compared to a normal patient

**FUNDUS AUTO-FLUORESCENCE**

- Fundus auto-fluorescence image
Fluorescein angiography

CONDITIONS AFFECTING PERIPHERAL VISION

HEREDITARY FUNDUS CONDITIONS
- Retinitis Pigmentosa
- Choroideremia
- Gyrate Atrophy
- Stargardt disease
- Albinism
- Achromatopsia
- Best disease

CASE 1
- 15 year old female
- CC: near and distance blur
- Family and ocular history unremarkable
- VA: 20/40 OD and OS, NPHI OD and OS
- External Examination:
  - Pupils: equal, round, reactive, no APD
  - CVF: constricted OD and OS
  - Motilities: FROM OD, OS
  - Slit Lamp Exam: unremarkable
  - IOPS: 10mm Hg OD and OS

IMPORTANT OF FAMILY HISTORY
- Inheritance patterns: autosomal dominant, autosomal recessive, x-linked
- Introduction to pedigree analysis
- Importance of genetic counselling

RETINITIS PIGMENTOSA: FUNDUS PHOTO
## Retinitis Pigmentosa

- RP includes a wide variety of disorders that cause progressive degeneration of the photoreceptors and eventually the retinal pigment epithelium (RPE).
- Nyctalopia
- Visual field defects/constrictions and vision loss
- RP is the most common inherited retinal condition in the world
  - 1 in 3000-5000 people are affected
  - Estimated that 1.5 million people worldwide are affected

## Pathophysiology of RP

- Mutations in more than 60 genes are known to cause non-syndromic retinitis pigmentosa.
- Research has shown that photoreceptor death can be induced by different pathways due to different gene mutations (retinal metabolism, photo transduction, transcription factors...)
- The final common pathway of all these diseases is photoreceptor cell death.

## Symptoms

- Nyctalopia: due to degeneration of the rods which are found more abundantly in the mid periphery
- Peripheral visual field loss: manifest in teenage years, symmetric
- Central field and vision loss: does not manifest until the later stages of the condition
- Photophobia: due to retinal hypersensitivity
- Photopsia: due to improper photoreceptor signaling
- Color vision: acquired, therefore more tritan anomalies seen

## Signs

- RPE Pigmentary changes (early)
- Bone spicules
- Vessel attenuation
- Optic nerve pallor (waxy)
- Foveal lesions (RPE, photoreceptor atrophy)
- Cystoid Macular Edema (CME)
- Vitreous cells
- Cataracts
  - Most common is posterior subcapsular
- Testing:
  - ERG
  - VF
  - FAF

## Classification

- No uniform classification system exists
- Previous nomenclatures have classified RP based on what area of the retina was involved:
  - Central, pericentral, sector, and peripheral
- Mode of inheritance and photoreceptor involvement:
  - Autosomal recessive, autosomal dominant, X-linked, digenic, mitochondrial
- Better to classify as primary and syndromic and then further classify with previous classification systems
- Syndromic RP is beyond the level of this lecture, can discuss at a later time if interested
TREATMENT

- Vitamin A
- 15,000 IU reduced rate of ERG loss
- Low vision
- Genetic research
- Prosthetic devices
  - Only for those who have profound vision loss

CHOROIDEREMIA

- Description:
  - X-linked condition with progressive retinal, RPE, and choroidal damage
  - Females-mild fundus changes
  - Incidence estimated to be between 1:50,000 to 1:100,000

- Pathophysiology:
  - Mutations in the CHM choroideremia gene. It provides instructions for producing the Rab escort protein 1 (REP-1).
  - REP-1 is responsible for movement of proteins and organelles within cells (intracellular trafficking).
  - Without REP-1 retinal cells do not form or die prematurely.

CASE 3

- 15 year old male
- CC: routine examination
- Family and ocular history unremarkable
- VA: HM OD and OS, NPHI OD and OS
- External Examination:
  - Pupils: equal, round, reactive, no APD
  - CVF: constricted OD and OS
  - Motilities: FROM OD, OS
  - Slit Lamp Exam: unremarkable
- IOPS: 11mm Hg OD and OS

CHOROIDEREMIA

- Genetics are understood, but the pathogenesis is not completely understood.
  - Different theories are postulated:
    - Abnormalities in RPE results in damaged photoreceptors and choroid.
    - RPE and photoreceptors degenerate independently, choroid damaged secondary to RPE degeneration.
    - Photoreceptors are source of degeneration
    - Choroid first to degenerate with resulting RPE and photoreceptor damage

- Symptoms:
  - First to second decade patients experience nyctalopia
  - Visual field restrictions progressing to tunnel vision
  - Acuity loss, central vision preserved until 40-55 years of age
  - One line acuity every five years according to one study

- Signs:
  - Pigmentary changes (RPE loss) in mid periphery
  - Choroidal atrophy then spread towards periphery and posterior pole
  - Bare sclera seen
    - 3 types usually seen:
      - Light complexion: bare sclera seen, large choroidal vessels
      - Dark complexion: RPE, pigment loss, choroidal pigment intact
      - Scattered areas of black pigmentation
CHOROIDEREMIA

- Additional testing:
  - FA, genetic testing, ERG
- Management:
  - No known treatment
  - Varying stem cell research
  - New study published in Lancet

GYRATE ATROPHY

- Description:
  - Progressive condition that involves the peripheral retina and then the posterior pole
  - Condition is inherited in an autosomal recessive pattern
  - Very rare (around 200 cases)
- Pathophysiology:
  - Mutations in ornithine amino transferase (OAT) gene: provides instructions for making the enzyme ornithine amino transferase
  - Helps convert ornithine into pyrroline-5-carboxylate (P5C). Deficiency in this enzyme leads to increased levels of ornithine (hyper-ornithine).

CASE 2

- 15 year old female
- CC: routine examination
- Family and ocular history unremarkable
- VA: 20/25 OD and OS, NPHI OD and OS
- External Examination:
  - Pupils: equal, round, reactive, no APD
  - CVF: constricted OD and OS
  - Motilities: FROM OD, OS
- Slit Lamp Exam: unremarkable
- IOPS: 11mm Hg OD and OS

GYRATE ATROPHY

- Symptoms:
  - Nyctalopia: first to second decade
  - Peripheral field loss
  - Acuity loss
- Testing:
  - ERG: reduced rod and then cone response
  - Hyper ornithine levels: normal range being 28-110 nmol/mL
- Signs:
  - Myopia: >80%
  - Retinal and choroidal atrophy, smaller spots that eventually coalesce
  - Posterior subcapsular cataracts: 40%
- Management:
  - Vitamin B6 (pyridoxine)
    - Among approximately 70 Finnish GA cases reported to date, none have been responsive to vitamin B6
CONDITIONS AFFECTING CENTRAL VISION

CASE 4

- 19 year old female
- CC: gradual loss of vision over the last year
- Family and ocular history unremarkable
- VA: 20/200 OD and OS, NPHI OD and OS
- External Examination:
  - Pupils: equal, round, reactive, no APD
  - CVF: constricted OD and OS
  - Motilities: FROM OD, OS
- Slit Lamp Exam: unremarkable
- IOPS: 11mm Hg OD and OS

STARGARDT DISEASE

- **Description:**
  - Most common inherited macular dystrophy
  - Affects all races and genders, with varying age of onset
  - Acuity ranges from 20/20 to 20/400

- **Pathophysiology:**
  - Autosomal recessive condition caused by mutation to ABCR (ABCA4)
  - Gene which is responsible for transport of retinoids through a protein called rim protein (RmP)
  - Transport of all trans retinal inhibited, no formation of all trans retinol
  - all trans retinal accumulates in the photoreceptors giving rise to lipofuscin and A2E

- **Symptoms:**
  - Acuity loss, photophobia, nyctalopia, central scotoma (relative then absolute)

- **Signs:**
  - Normal in early stages, disappearance of foveal reflex
  - RPE mottling
  - Deposition of flecks (pisciform) in RPE
  - Macular atrophy (beaten bronze appearance)
  - Bulls eye maculopathy

- **Testing:**
  - FA-hyper fluorescent flecks, dark choroid, hyper fluorescence with large amounts of RPE atrophy
STARGARDT DISEASE

- ERG, FAF, VF
- OCT
- Disorganization of the retinal layers, thinning of the retinal outer layers and enhanced choroidal reflectivity associated with overlying atrophic retina.
- Loss of photoreceptors would correlate with a decrease in central visual function.

Management:
- No cure but low vision consult is indicated
- Studies at UCLA
  - Sub-retinal Transplantation of RPE Cells in Patients With Stargardt's Macular Dystrophy
  - Studies in Oregon and France
  - Phase I/IIa Study of StarGen in Patients With Stargardt Macular Degeneration

CASE 5

- 20 year old female
- CC: gradual loss of vision over the last year
- Family and ocular history unremarkable
- VA: 20/200 OD and OS, NPHI OD and OS
- External Examination:
  - Pupils: equal, round, reactive, no APD
  - CVF: constricted OD and OS, pendular horizontal nystagmus
  - Motilities: FROM OD, OS
  - Slit Lamp Exam: unremarkable
  - IOPS: 11mm Hg OD and OS

STARGARDT DISEASE

OCT OF STARGARDT DISEASE

- Early Stargardt patients may have a thickened ELM as suggested by Sherman et al:

ACHROMATOPSIA
ACHROMATOPSIA

Description:
- Inherited autosomal recessive condition that results in total or near total color discrimination
- Acuity ranges from 20/80-20/200
- Prevalence: 1:30,000

Pathophysiology:
- Changes in the CNGB3, CNGB1, and GNAT2 genes are responsible for achromatopsia
- Mutation results in the cone ion channels not being able to close and regulate ion transport which results in improper cone function and formation.
- Partial mutations are also seen accounting for incomplete achromats

Symptoms:
- Reduced visual acuity
- Photophobia
- Central scotoma (small)
- Loss of color discrimination

Signs:
- Nystagmus
- Normal appearing fundus, loss of foveal reflex, pigment mottling

Testing:
- Color vision testing with Panel D15, best option is anomaloscope
- ERG: reduced photopic response
- Visual field: small central scotoma
- Genetic testing

Symptoms:
- Reduced visual acuity
- Photophobia
- Central scotoma (small)
- Loss of color discrimination

Differentials:
- Blue cone monochromatism
  - X linked not AR
  - Rarer, 1:50,000 to 1:100,000
  - Have only S-cone and rods that function
  - Better acuity than achromats

Management:
- Low vision options, especially red tints
**BEST DISEASE (VITELLIFORM DYSTROPHY)**

- **Description:**
  - Inherited autosomal dominant
  - Slow, progressive macular dystrophy with onset in childhood although an adult onset Best disease exists.

- **Pathophysiology:**
  - Due to mutations in bestrophin gene (BEST1)
  - Regulates the movement of chlorine into and out of RPE cells.
  - Mutations leads to improper regulation.
  - Researchers have not determined how these malfunctioning channels are related to the buildup of lipofuscin in the macula and progressive vision loss.

**BEST'S VITELLIFORM DYSTROPHY**

**BEST DISEASE (VITELLIFORM DYSTROPHY)**

- **Symptoms:**
  - Reduced acuity
  - Metamorphopsia
  - Scotomas

**BEST'S VITELLIFORM DYSTROPHY**

**CLASSIFICATION OF BESTS DISEASE**

- **Staging:**
  - Previtelliform: Accumulation of lipofuscin but no fundus abnormalities
  - Vitelliform stage: Yellow to light red central macular lesion consisting of lipofuscin
  - Pseudohypopyon: yellowish material occupies lower portion of lesion
  - Vitelliruptive or scrambled egg stage: Uniform disruption of yellow material
  - Fibrotic Stage: scarring and subretinal fibrosis, CNVM

**BEST'S VITELLIFORM DYSTROPHY**

**RESOLVING BEST'S VITELLIFORM DYSTROPHY**
BEST DISEASE (VITELLIFORM DYSTROPHY)

- Testing:
  - EOG: low Arden ratio
  - Reflects RPE function, is the most diagnostic test for evaluating Bests
  - Normal ratio is >1.6
  - Genetic
  - FA: rarely used expect when CNVM is suspected
  - FAF: hyper auto fluorescence as lipofuscin accumulates
  - OCT: will show extent of lesion, accumulation of lipofuscin, and possible CNVM

- Management:
  - Low vision aids
  - Anti-Vegf for any CNVM

X-LINKED RETINOSCHISIS

- Description:
  - X-linked recessive disorder in which males develop splitting of the nerve fiber layer in both eyes, possibly related to a Müller cell defect
  - Female carriers have normal vision and are normal on ophthalmic examination
  - Affects 1/25,000, slowly progressive condition.

- Pathophysiology:
  - Caused by mutation in the retinoschisis gene, RS1.
  - The RS1 gene provides instructions for producing a protein called retinoschisin, which is found in the retina (responsible for retinal development and maintenance)
  - Mutation can cause tiny splits (schisis) or tears to form in the retina leading to vision loss.

NORMAL OCT

X-LINKED RETINOSCHISIS

- Symptoms:
  - Progressive acuity (average 20/70), plateaus to 20/200
  - Visual field loss: central and peripheral

- Signs:
  - Macular retinoschisis: spoke like appearance
  - Very slowly progressive reduction from macular atrophy, until the fifth or sixth decade
  - Peripheral retinoschisis in 50% of patients
    - Most evident inferior temporal
  - Potential late stage findings:
    - RPE changes, macular hole, vitreo-retinal traction resulting in vitreous hemorrhage and rhegmatogenous retinal detachment
    - Strabismus and nystagmus have been noted
X-LINKED RETINOSCHISIS

Testing:
- OCT
- Visual Field
- ERG
- Genetic testing
- FA-more so to rule out macular edema

Treatment:
- Low vision aids
- Consult with retinal specialist to manage vitreous hemes and retinal detachments

CONE DYSTROPHIES

- Broken into two categories:
  - Stable cone dystrophy: Achromatopsia
  - Progressive Cone Dystrophies
  - AD, but can be recessive and X-linked

- Symptoms
  - decreased visual acuity (20/60-20/400)
  - color vision defects
  - photophobia
  - central scotomas

- Signs
  - Early on patients have no fundus abnormalities
  - Three typical types of fundus lesions:
    - "bullseye" appearance
    - Patchy central RPE defects with pigment stippling and clumping
    - Localized central RPE and choriocapillaris atrophy
  - Possibility of further macular atrophy and optic atrophy

- Management
  - Low vision devices
  - Pedigree and genetic counseling
CONE DYSTROPHIES

ALBINISM

**Description:**
- Involves the hair, skin, and eyes
- Abnormality of Tyrosinase - deals with depigmentation

**Pathophysiology:**
- OCA1 or tyrosinase-related albinism genetic defect in an enzyme called tyrosinase. This enzyme helps the body to change the amino acid tyrosine into pigment.
- OCA2 or P gene albinism results from a genetic defect in the P protein that helps the tyrosinase enzyme to function.
- Oculocutaneous albinism type 3 (OCA3)
- Oculocutaneous albinism type 4 (OCA4)

**Symptoms:**
- Reduced vision
- Photophobia

**Signs**
- Foveal and fundus hypoplasia
- Nystagmus at birth
- Iris transillumination defects
- Large refractive errors
- Strabismus
- Blond, white hair
- Pink and white skin
- Blue to blue-grey irides
- Iris transillumination

**Symptoms:**
- Reduced vision
- Photophobia

**Signs**
- Foveal and fundus hypoplasia
- Nystagmus at birth
- Iris transillumination defects
- Large refractive errors
- Strabismus
- Blond, white hair
- Pink and white skin
- Blue to blue-grey irides
- Iris transillumination

**Management**
- Best refraction, low vision, sunglasses, sunscreen
- Consider reading add

**Rule out systemic diseases such as hemorrhagic diathesis, lung disease, gram positive infections**
- Hermansky-Pudlak Syndrome
- Chediak-Higashi
<table>
<thead>
<tr>
<th>OCULAR ALBINISM (OA)</th>
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<tr>
<td>- Signs and symptoms are similar to OCA but less severe</td>
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<td>- Typically X-linked so males will be affected, females do not usually show signs.</td>
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