SUNY DMC
Department of Ophthalmology
Grand Rounds 11-20-2014

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Clinical Assistant Instructor
History

- HPI: 44 YO Greek male referred from general ophthalmologist for retina evaluation of fundus lesions.
- PMH: denies
- PSH: denies
- POH: s/p LASIK OU, episcleritis OS
- SH: social EtOH
- FH: no early blindness
- Meds: none
- Gtt: none
- All: NKDA
Exam

- DVasc: OD 20/20-2; OS: 20/20-2
- NVasc: OD 20/30; OS 20/25
- Pupils: 5-2, no APD
- EOM: Full OU
- CVF: ftcf OU
- Tapp: 15/15
Exam

- SLE: s/p lasik changes OU, otherwise unremarkable
- DFE: see photos
Differential diagnosis

- Age related Macular Degeneration (Drusen)
- Bulls eye maculopathy
- Pattern dystrophy
- Stargardt disease or Fundus Flavimaculatus
- Cone rod dystrophy
- Retinitis Pigmentosa
- White Dot syndromes
Basics

- Early 1900s Karl Stargardt describes disease in 7 patients in 2 families
- Prevalence estimated 1 per 8-10,000
- Fundus flavimaculatus (FFM) is a genetically linked clinically milder form of Stargardt
- Gene defect found in 1997 to encode for ABCA4
• Autosomal recessive disease
• ABCA4 gene on chromosome 1, 6.8 kB
• > 600 disease associated variants in the gene
• ABCA4 microarray detects all currently known disease associated genetic variants or ~70% of all disease associated alleles
• Estimated that >1/20 individuals carry ABCA4 disease associated allele
• 3 most common mutations account for <10% of disease
• ABCA4 associations: Bulls eye maculopathy, AR cone rod dystrophy, AR RP, AMD
ABC transport

- ATP Binding cassette transporters (ABC transporters) use ATP hyrolysis to translocate substrates across cell membranes

- 4 domains required: 2 nucleotide binding and 2 transmembrane

- 49 ABC transporters identified in human genome so far

- Localizes to rim of rod outer segment discs (cones as well)
ABCA4
Pathophysiology

- ABCA4 removes N retinylidene-phosphatidylethanolamine (NRPE) from disc space and transports to cytoplasm of rods and cones.

- NRPE is formed by all trans retinal binding to phospholipid phosphatidylethanolamine.

- Accumulation of NRPE in the disc space allows a second molecule of all trans retinal to bind to NRPE, forming A2E.

- Diretinoid-pyridinium-ethanolamine (A2E), a component of lipofuscin, accumulates in disc space via disc shedding and phagocytosis and is toxic to RPE.
Clinical characteristics

• Slowly progressive central vision loss, photophobia, color vision abnormality, central scotoma, slow dark adaptation

• Patients presenting over 20 years of age usually have better than 20/200 vision

• Age of onset highly variable, usually between childhood to early adulthood

• Color vision typically compromised (red-green)
4 stages

- Gerald Fishman describes 4 stages of Stargardt’s in 1976

- Stage I - pigmentary changes in fovea or parafovea (beaten metal), atrophic RPE, normal EOG/ERG, ring of flecks around fovea

- Stage II - flecks extending anterior to the arcades and/or nasal to optic disc, normal EOG/ERG but with delayed dark adaptation, normal peripheral field, possible central scotoma

- Stage III - resorption of flecks, widespread choriocapillaris atrophy, EOG abnormal, ERG may be abnormal

- Stage IV - further resorption of flecks, more widespread atrophy of choriocapillaris, greatly reduced ERG amplitudes
Fundus Autofluorescence

- Hyperfluorescence - areas of lipofuscin accumulation
- Hypofluorescence - areas of RPE atrophy
- Allows detection of RPE functional changes before clinically detectable
- Serves as a useful indicator of disease progression
- Sparing of peripapillary retina on FAF has been diagnostic criteria
  - Loss of sparing may correlate with widespread photoreceptor dysfunction and poorer visual prognosis
Fundus Autofluorescence

Red free and fundus autofluorescence
Fundus Autofluorescence
Fluorescein Angiography

- Dark choroid cited from 62 to 86% sensitive
- Background choroidal fluorescence blocked from lipofuscin accumulation in RPE
- Ring of hypofluorescence in the peripapillary region reported in 37% of 135 patients in a cohort study at Kellogg in 2009
  - May be indicator of more severe disease
Fluorescein Angiography
Optical Coherence Tomography

- Voigt looked at 49 eyes of 26 patients with FFM using FAF, OCT, and FA

- Classified flecks based on location

- Hyper reflective deposits may be: in the inner RPE (type 1), or in the ONL clearly separated from the RPE (type 2)
  - Type 2 are rare in inherited maculopathies
  - Correlation between ellipsoid and BCVA
Optical Coherence Tomography
Important Differentials

- Drusen
  - Lesions show less hyperfluorescence
  - Echolucent on OCT
- Pattern dystrophy
  - Better final VA, no dark choroid on FA
  - Hyperfluorescence tends to be more discrete, punctate and irregular
- Autosomal dominant in many cases
Progstar

- Multi-center study will characterize disease progression and facilitate data collection on progression trends

- Primary outcome: lesion growth by FAF q6 month

- Secondary outcomes: retinal function by microperimetry, SD-OCT
Potential therapies

- Deuterated vitamin A: may block formation of A2E downstream the visual cycle
  - KO ABCA4-/- mice raised on deuterated vitamin A generated less A2E and lipofuscin vs those fed vitamin A

- In phase Ia trials
Stargen

- Delivery of human ABCA4 gene to KO mice reduced accumulation of A2E in treated eyes
- Lentivirus vector used instead of adeno associated virus
- Requires subretinal injection
- Currently in phase I/IIa in US and Europe
- Studies in adult macaque and rabbit retinas indicate safety for subretinal delivery of stargen

A2E accumulation in STGD mouse model


Medical Education
Our Patient

- Patient advised of visual prognosis and treatment options and sent for second opinion with another retina specialist
- Encouraged UV blocking sunglasses and eye exams for all relatives
Reflective Practice

- Patient was examined and treated in a timely manner with respect and updated practice guidelines
- Case demonstrates presentation of a rare disease process
- After considering a wide differential diagnosis and examining the literature, the appropriate diagnostic modalities were chosen to narrow our differential, formulate a diagnosis, and monitor the patient and disease progression.
- Family and patient were educated about the disease process, natural course, and treatment options.
- Literature review was performed to ensure up to date guidelines regarding management were followed.
Core Competences

• **Patient Care:** The patient and family were treated compassionately and with respect and patient and family were included in medical decision making calculus.

• **Medical Knowledge:** Extensive literature review of corneal stingers was performed, and current practice guidelines were reviewed.

• **Practice-Based Learning and Improvement:** Close examination of patient was performed at each visit and treatment plan was altered accordingly.

• **Interpersonal and Communication Skills:** We communicated extensively with the patient and family at each clinical encounter.

• **Professionalism:** Patient and family were treated with respect during all clinical encounters.

• **Systems-Based Practice:** Appropriate and cost effective services were offered to patient.
Thank you

- Patient
- Dr Fletcher
References

  http://imagebank.asrs.org/file/5124/late-stage-stargardt-disease


• Burke TR1, Tsang SH. Allelic and phenotypic heterogeneity in ABCA4 mutations.  

• Fishman GA. Fundus flavimaculatus. A clinical classification.  

• Jayasundera T1, Rhoades W, Branham K, Niziol LM, Musch DC, Heckenlively JR. Peripapillary dark choroid ring as a helpful diagnostic sign in advanced stargardt disease.  


• Querques G1, Leveziel N, Benhamou N, Voigt M, Soubrane G, Souied EH. Analysis of retinal flecks in fundus flavimaculatus using optical coherence tomography.  

• Shroyer NF1, Lewis RA, Allikmets R, Singh N, Dean M, Leppert M, Lupski JR. The rod photoreceptor ATP-binding cassette transporter gene, ABCR, and retinal disease: from monogenic to multifactorial.  

• Tsybovsky Y1, Molday RS, Palczewski K. The ATP-binding cassette transporter ABCA4: structural and functional properties and role in retinal disease.  

• Von Rückmann A, Fitzke FW, Bird AC. In vivo fundus autofluorescence in macular dystrophies.  