Hereditary Macular Dystrophies

Diagnosis and Management

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- No financial disclosures
- I will discuss off-label use of anti-VEGF
Hereditary Macular Dystrophies

- Stargardt Disease
- Best vitelliform dystrophy
- Pattern dystrophy
- Familial (dominant) drusen
- Sorsby Macular Dystrophy
- North Carolina Macular Dystrophy
Case 1

- 48 y/o white female
- c/o blurry central vision
- BCVA 20/25 OD
- 20/25 OS
- Was told something was wrong age 32, but vision was “good” until recently
Diagnosis......

Stargardt disease
Stargardt Disease

- Most common inherited macular dystrophy
- Prevalence: 1 in 20,000
- Inheritance: AR > AD (rare)
- Genetics:
  - AR caused by mutations in ABCA4 gene on chromo 1p21-p22
    - Encodes ABC transporter protein expressed by photoreceptor outer segments role of which is transport of A2E intermediates (toxic by-product of vitamin A and component of lipofuscin)
    - Impairs processing of Vitamin A accumulated A2E
    - Leads to RPE and subsequent photoreceptor degeneration
  - AD caused by mutations in ELOVL4 gene (STGD4 and STGD3 on chromo 4p and 6q)
    - Encodes photoreceptor component of fatty acid elongation system
Lipofuscin

- By-product of Vitamin A metabolism visual cycle
- Imbalance of formation and disposal leads to:
  - Lipofuscin accumulation
  - Common mechanism in:
    - AMD
    - Stargardt disease
    - Best vitelliform dystrophy
    - Pattern dystrophy
Stargardt Disease

- Onset: 1st-2nd decade (age 6-20)
- May have decreased vision before fundus changes
- AD form more benign course
Stargardt Disease

- Classic phenotype:
  - Bilateral yellow ‘pisciform’ flecks in posterior pole
  - Atrophic maculopathy, “beaten-bronze” appearance
  - Patchy atrophy
  - Bull’s eye maculopathy
  - Late ‘salt and pepper’ pigmentary changes may occur in periphery

- ‘Fundus flavimaculatus’ if flecks are widespread
Stargardt Disease

- Color vision may be abnormal
  - deutan-tritan defects

- Visual fields
  - normal early stage
  - central scotoma over time
Stargardt Disease

- ERG: usually nml
  - Abnml if severe peripheral degenerative changes develop

- EOG: can be nml, but abnml in ¾ cases

- mERG: abnml

- OCT: loss of photoreceptor layers (ellipsoid zone, IS/OS junction)
Stargardt Disease

- FA: decreased choroidal fluorescence = dark “silent” choroid
  - In at least 80% of cases
  - Due to masking of normal choroidal fluorescence by accumulation of lipofuscin in RPE

- Hyperfluorescent spots don’t always correlate with flecks
- Various window defect/staining around flecks
Stargardt Disease

- Fundus autofluorescence:
  - hypoAF in areas of RPE loss
  - hyperAF in areas of flecks

- AF in increased w/ RPE dysfunction ie lipofuscin accumulation
- AF is decreased w/ RPE death
Stargardt Disease

- Prognosis: 20/50 to 20/200 range
- Most pts retain 20/100 in at least one eye
- Vision decline can stabilize or slow progression by 3rd
Stargardt Disease

- Targeting vitamin A cycle may lower lipofuscin levels (isoretinoin/Accutane) blocks A2E accumulation.

- On June 2, 2014, Makindus, Inc., a specialty pharmaceutical company, received orphan drug designation for their lead product MI-100 from the FDA for the treatment of Stargardt Disease.
  - 2015- Phase 3 clinical development

- On October 14, 2014, Ocata Therapeutics (formerly Advanced Cell Technology, Inc.) announced positive results from its small (18-patient) early-stage clinical trials of human embryonic stem cells (hESC) for the treatment of dry age-related macular degeneration and Stargardt disease.
Stargardt Disease

**Diagnosis:**
- Flecked retina
- Silent choroid on FA
- Pattern of FAF findings
- Genetic testing for ABCA4 mutation

**Management:**
- Protection from sunlight exposure (UVA, UVB, blue light)
- Avoid vitamin A
- Low vision aids
- Genetic counseling
Case 2

- 28 y/o male from Iraq
- c/o decreased VA OS x several weeks
- BCVA 20/60 OD
- 20/400 OS
- Was told something was wrong age 12, but vision was “good” until recently
Diagnosis......

- Best vitelliform dystrophy
- with choroidal neovascular membrane OS
Case 2

- Bevacizumab injection x 2 OS
- Vision 1 year after
  - VA sc 20/40 OD
  - 20/40 OS
Best Vitelliform Dystrophy

- Prevalence: rare
- Genetics: AD, variable expressivity/penetrance
- caused by mutations in BEST1 gene (chromo 11q12)
  - encodes for bestrophin-1
  - chloride channel expressed in RPE
- defect in this protein leads to accumulation of lipofuscin
- leads to dysfunction of the RPE/photoreceptors
Best Vitelliform Dystrophy

- Onset: childhood and sometimes in later teenage years (5-13 years)
- Affected individuals have normal vision early in life
- Characterized by loss of central visual acuity over time
- Metamorphopsia
Best Vitelliform Dystrophy

- some affected individuals remain asymptomatic
- 7-9% of patients never experience vision loss
- may be complicated by CNV (rare in children)
Best Vitelliform Dystrophy

- **Stage 1**
  - Subclinical/previtelliform
  - asymptomatic

- **Stage 2**
  - Vitelliform-yellow, egg yolk-like

- **Stage 3**
  - pseudohypopyon
  - Fluid level, yellow-colored vitelline material layers
Best Vitelliform Dystrophy

- Stage 4
  - Vitelliruptive
  - Lesion becomes less homogenous and develops a "scrambled-egg" appearance

- Stage 5
  - Atrophic
  - Cicatricial
Best Vitelliform Dystrophy

- OCT shows abnormal accumulation between photoreceptors and RPE
- FA shows variable blockage, staining, window defects depending on stage
- FAF:
  - increased AF corresponding to lipofuscin early stages
  - decreased AF with atrophic states
CHOROIDAL THICKNESS IN BEST VITELLIFORM MACULAR DYSTROPHY
MAURIZIO BATTAGLIA PARODI, MD, RICCARDO SACCONI, MD, PIERLUIGI IACONO, MD,
CLAUDIA DEL TURCO, MD, FRANCESCO BANDELLO, MD RETINA 36:764–769, 2016
Best Vitelliform Dystrophy

- Full-field electroretinogram (ERG) is normal
- mERG may be abnml
- Electro-oculography (EOG): markedly abnml in all phases
  - measures standing potential of the eye by recording the Arden ratio (AR; ratio of light peak/dark trough <1.5; normal value ≥1.8)
- Hallmark of Best Disease is abnml EOG w/ nml ERG
Best Vitelliform Dystrophy

**Diagnosis:**
- Typical macular vitelliform lesion in 1st-2nd decade
- Family history
- Abnormal EOG (decreased Arden ratio) with normal ERG
- Genetic testing for BEST1 mutation

**Management:**
- Monitor for CNV
- anti-VEGF if CNV develops
- Low vision aids
- Genetic counseling
  - Prenatal diagnosis and preimplantation genetic diagnosis
Pattern Dystrophy
Pattern Dystrophy

- Inheritance: AD
  - Incomplete penetrance and variable expression may mask dominant pattern
- Caused by various mutations in retinal degeneration slow (RDS)/peripherin gene on chromo 6p21
  - Encodes photoreceptor-specific glycoprotein
  - Development and maintenance of photoreceptor outer segments
  - Leads to build up of lipofuscin
Pattern Dystrophy

- Heterogeneous group of macular diseases
- Variable expressions of same genetic defect in RDS/peripherin gene
- Characterized by development in midlife of variety of patterns of yellow, orange, gray pigment deposits in macula
Pattern Dystrophy

- Major patterns:
  - Butterfly dystrophy
  - Reticular (Sjögren) dystrophy
  - Multifocal pattern dystrophy simulating Stargardt disease
  - Fundus pulverulentus
  - Adult-onset foveomacular vitelliform dystrophy
Pattern Dystrophy

- Utility of this classification is questioned
- Clinical pattern can vary among family members with same mutation
- One form of PD may evolve into another in the same pt
- Can even vary between 2 eyes of same pt

- PD should be considered a single disease expressed in various manners
Pattern Dystrophy

- Age of onset highly variable
- Tend to remain asymptomatic until 5th decade
- Mild impairment of central vision
- Some may remain asymptomatic
- Classically described as having “benign” course
- But may develop atrophy and CNV resulting in severe vision loss
Pattern Dystrophy

- Color vision: normal
- Visual fields: relative central scotoma
- ERG/EOG: normal to subnormal
- OCT: deposit between RPE and ellipsoid zone

- FA: hypofluorescence from blocking by lipofuscin/pig; window defects from atrophy

- FA and FAF show lesions better than ophthalmoscopy
Pattern Dystrophy

- AMD can be indistinguishable from late PD
- Some of deposits in PD resemble druse in AMD
- May have co-existing AMD
- Peripheral changes can be seen
Butterfly Pattern Dystrophy

- butterfly-shaped pigmentations in macula
- FA and FAF show lesions better than ophthalmoscopy
Case 3

- 56 y/o white female
- “I see a spot in my right eye” x 2 weeks
- VA c.c 20/20 OD
- 20/20 OS
Case 3

- 5 years later.....age 61
- asymptomatic
- VA cc 20/20 OD
- 20/20 OS
Reticular Pattern Dystrophy

- "Sjogren Reticular Pigment Dystrophy"

- Prevalence: very rare
- Inheritance: AR and AD
- Genetics: unknown***

- Characterized by fishnet/reticular pattern
- Starts centrally and spreads peripherally
- Appears in infancy
Reticular Pattern Dystrophy

- FA and FAF show lesions better than ophthalmoscopy
- Usually asymptomatic/good vision
Retina image bank from ASRS, By Thomas M. Aaberg, MD
Multifocal Pattern Dystrophy

- can simulate Stargardt disease
- characterized by irregular scattered yellow-white flecks
- posterior pole extending beyond vascular arcades
Case 4

- 41 y/o white male
- asymptomatic
- referred for abnml visual fields

- BCVA  20/20 OD
- 20/20 OS
Diagnosis......

Stargardt disease?
Case 4

- Genetic testing for ABCA4 gene mutation...  
  - Negative

- Genetic testing for RDS)/peripherin gene mutation...  
  - Positive
Diagnosis......

Multifocal Pattern Dystrophy simulating Stargardt disease
Multifocal Pattern Dystrophy

- **Distinguishing characteristics from Stargardt disease:**
  - Late onset (5th decade)
  - AD pattern
    - Incomplete penetrance and variable expression may mask dominant pattern
  - Comparatively good/stable vision
  - Absence of “dark choroid”
  - Genetic testing to rule out ABCA4 gene mutation
Case 5

- 89 y/o white female
- Decreased vision for months
- BCVA 20/60 OD
- 20/40 OS
Diagnosis......

Adult-onset Foveomacular Vitelliform Dystrophy
Adult-onset Foveomacular Vitelliform Dystrophy

- **Distinguishing from Best vitelliform dystrophy:**
- Lesions usually smaller lesions
- Usually appears in 4-5th decade
- Do not show disruption in layering of yellow pigment in dependent portion of lesion
- EOG usually nml
- Genetic testing
Fundus Pulverulentus Pattern Dystrophy

- Rare
- Characterized by coarse pigment mottling of RPE in macula
- Can be impossible to differentiate from AMD
Pattern Dystrophy

- Systemic associations:
  - Pseudoxanthoma elasticum
  - McArdle disease
  - Myotonic dystrophy
  - Crohn’s disease
  - Deafness
  - Maternally inherited diabetes
Pattern Dystrophy

- **Diagnosis:**
  - typical pattern findings
  - more pronounced on FA or FAF
  - +/- genetic testing

- **Management:**
  - Amsler grid monitor
  - anti-VEGF if CNV
  - smoking cessation
  - ?AREDS
Case 6

- 39 y/o white orthopedic surgeon
- Asymptomatic, was told “had eyes of an old man”

- BCVA 20/20 OD
- 20/20 OS
Diagnosis......

Familial (Dominant) Drusen
Familial (Dominant) Drusen

- Doyne was first to describe in British family
- Vogt described family from Swiss valley of Malattia Leventinese
- Same mutation on chromo 2p
- Inheritance: AD in some pedigrees, presumed genetically determined, inheritance pattern in most is not established**
- Genetics: EFEMP1 on chromo 2
  - An extracellular matrix protein expressed in the RPE leads to accumulates within and beneath RPE overlying drusen
Familial (Dominant) Drusen

- Asymptomatic
- Bilateral symmetric drusen
- Round yellow
- Onset: 20-30 years of age
- Numerous and varying size
- Lesions can coalesce, enlarge or disappear
- Extend beyond vascular arcade and nasal to optic nerve
Familial (Dominant) Drusen

- OCT: accumulation of lipofuscin at level of RPE
- FAF: increased and decreased AF
- FA: early blockage and late staining of drusen
Familial (Dominant) Drusen

- **Diagnosis:**
  - Presence of drusen at age 20-30s
  - Location of drusen: extend beyond arcade and nasal
  - Genetic testing not useful at this time

- **Management:**
  - No treatment, but typically good prognosis
  - AREDS MVI
  - Smoking cessation
Sorsby Macular Dystrophy (Pseudo-inflammatory Macular Dystrophy)
Sorsby Macular Dystrophy

- Inheritance: AD
- Prevalence: rare
- Genetics: linked to TIMP-3 gene on chromo 22q12
  - Abnormal turnover of extracellular matrix in/around Bruch’s membrane
Sorsby Macular Dystrophy

- Early sign is presence of numerous fine drusen-like deposits in 20s
- Development of bilateral CNV in 40s
- Leads to geographic atrophy w/ pronounced black pigment clumping around central atrophic zone “pseudo-inflammatory”
Sorsby Macular Dystrophy

- Color vision: may be abnl
- Visual fields: relative central and paracentral scotoma
- Peripheral field loss late
- FA: window defects, hyperfluorescence if CNV
- ERG/EOG: subnormal in advanced stage
- No treatment
- Poor prognosis VA HM
Sorsby Macular Dystrophy

- **Diagnosis:**
  - bilateral CNV in 40s
  - genetic testing for TIMP-3 gene mutation

- **Management:**
  - anti-VEGF for CNV
  - low vision aids
  - genetic counseling
North Carolina Macular Dystrophy (Lefler-Wadsworth-Sidbury Dystrophy)
North Carolina Macular Dystrophy (Lefler-Wadsworth-Sidbury Dystrophy)

- Prevalence: rare
- Inheritance: AD
- Genetics: MCDR1 gene on chromo 6q14-q16.2
North Carolina Macular Dystrophy
(Lefler-Wadsworth-Sidbury Dystrophy)

- Drusen appear early in 1st decade
- Progress to chorioretinal atrophy
- May resemble macular coloboma
- VA 20/200 or worse as progresses
North Carolina Macular Dystrophy (Lefler-Wadsworth-Sidbury Dystrophy)

- Color vision: nml
- Visual fields: central scotoma
- FA: window defects and late staining of drusen-like lesions
- OCT: CR excavations
- ERG: nml
- No treatment
North Carolina Macular Dystrophy (Lefler-Wadsworth-Sidbury Dystrophy)

**Diagnosis:**
- Family history
- Genetic testing for MCDR1 gene mutation

**Management:**
- Low vision aids
- Genetic counseling
Conclusion: Macular Dystrophies

- No cures
- Can cause vision loss at relatively young age

- Reassurance that most progress slowly and most retain some useful vision
- Monitor for CNV
- Low vision specialist
- Consider genetic counseling for some
  - valuable resource for you and your patients
  - can discuss the implications for other family members
  - guide patients to gene-specific clinical trials as they become available

- Hope for the future
Thank you