An Unusual Pigmentary Retinopathy

Take Heart in the Diagnosis!

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Interesting Cases
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I have no financial interests in the topic presented.
11-year-old asymptomatic female presented with an unusual peripheral pigmentary retinopathy, symmetric and bilateral. Three years later, she underwent a cardiac transplant secondary to hypertrophic cardiomyopathy. Whole exome sequencing helped to link the retinal findings and the cardiac condition, confirming the diagnosis.
At presentation

HPI: 11 y.o. referred to the University of North Carolina (UNC) Ocular Genetics clinic from an outside ophthalmologist for further evaluation of peripheral retinal pigmentation and concern for retinitis pigmentosa (RP)
At presentation

- No history of nyctalopia, decreased peripheral vision, difficulty differentiating colors, light hypersensitivity, or hearing loss
- POH: myopia (glasses since the age of 6)
- PMH: uncomplicated NSVD, no history of birth defects, met all developmental milestones. She has mild cognitive delay (confirmed on Differential Ability Scales - DAS II testing)
At presentation

- **Meds:** none
- **ROS:** negative for cardiac or skeletal muscle complaints
- **SOCIAL HISTORY:** 5th grade. Lives with parents and older brother
- **FAMILY HISTORY:** Unknown, since patient was adopted in infancy. Only birth records were available.
Ocular examination

- $V_a$ (cc) 20/20\(^{-2}\) OD; 20/25\(^{-1}\) OS
- MRx:
  - OD -5.25 +2.5 @ 094
  - OS -5.25 +2.75 @ 080
- Pupils: No APD OU
- IOP ($T_a$): 18 OD, 15 OS
- Anterior segment WNL with no vitreous cell OU
- Fundus exam: linear peripheral pigmentation
Fundus Autofluorescence
Full-field Electroretinogram
Goldman Visual Field
Genetic testing

- Symptoms, exam, ancillary tests NOT consistent with RP
- With no known FH, dystrophy genetic panels had low diagnostic yield
- Since patient was asymptomatic, family declined genetic testing and opted for annual ophthalmic surveillance
Clinical course

• At age 12, patient developed nonspecific chest discomfort, initially diagnosed as gastroesophageal reflux disease (GERD)
• At age 14, she experienced acute congestive heart failure
• Within weeks, she underwent cardiac transplantation
“Hypertrophic cardiomyopathy with extensive replacement fibrosis and myocyte vacuolization, mixture of glycogen, granular dark-staining material and degenerative lipid and lamellar debris”

Genetics

• Cardiac genetics consultation at Carolinas Medical Center in Charlotte, NC
• Whole Exome analysis → *LAMP2* mutation: c.815T>G; p.Leu272Arg
• Constellation of mild cognitive delay, peripheral retinal pigmentation, acute congestive heart failure, the cardiac pathology report and the *LAMP2* mutation…
Danon Disease

- caused by deficiency of lysosome-associated membrane protein 2 (LAMP2), important for degradation of autophagic material
- Classic triad of cardiomyopathy, skeletal myopathy and intellectual disability
- X-linked Dominant -- males develop symptoms earlier and are more severely affected
### CLINICAL MANIFESTATIONS:

<table>
<thead>
<tr>
<th>Condition</th>
<th>M (%)</th>
<th>F (%)</th>
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<tbody>
<tr>
<td>Cardiomyopathy</td>
<td></td>
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<td>Normally hypertrophic</td>
<td>100</td>
<td>61-100</td>
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<tr>
<td>Electrical cardiac abnormalities</td>
<td></td>
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<tr>
<td>WPW most commonly (69% in M and 27% in F)</td>
<td>86-100</td>
<td>80-100</td>
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<tr>
<td>Myopathy</td>
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<td>From asymptomatic to wheelchair dependent</td>
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<tr>
<td>Mild proximal weakness (shoulder, neck, and legs) most common</td>
<td>80-90</td>
<td>33-50</td>
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<td>Intellectual disability (ID)</td>
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<td>Usually mild</td>
<td>70-100</td>
<td>6-47</td>
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<tr>
<td>Ocular disease (all forms)</td>
<td>69</td>
<td>64</td>
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Ocular manifestations

• Very few reports of ocular abnormalities in literature, first described in 2002
• LAMP2 mutation causes retinal pigment epithelial dysfunction leading to
  – peripheral pigmentary retinal dystrophy (PPRD)
  – “bull’s eye maculopathy”
  – cone-rod dystrophy
Genetics

- Point mutations, small deletions or insertions, and splicing mutations have all been identified on Xq24
- X-linked dominant with variable expressivity
  - Mosaicism is reported!
    - Likely contributes to the **significant** phenotypic variability seen, even within families
- Skewed X-inactivation (lyonization) in females

Our patient’s mutation:
LAMP2 c.815T>G; p.Leu272Arg

A missense mutation on exon 6

Pathogenesis simplified:

- LAMP2 = protein in membrane of lysosomes
- Disruption of lysosome fusion processes
- Autolysosome formation and function is perturbed
- Accumulation of damaged mitochondria, proteins and glycogen
- Cell damage

Pathogenesis in the eye

Mutation in LAMP-2 → RPE lysosome dysfunction → accumulation of deposits → RPE damage → degeneration of cone and rod photoreceptor cells

F/U - Patient is now 15 y.o.

- Doing well, 1 year s/p cardiac transplant
- ROS still negative for skeletal muscle weakness
- BCVA still 20/25 OU
- OCT - stable thinning of the outer retinal layers, stable CMT OU
- Retina - increase in linear pigmentation
Full-field Electroretinogram
Conclusion

• Case demonstrates importance of considering Danon disease in differential diagnosis of atypical peripheral pigmentary retinopathy, even in females

• Since retinopathy often presents before signs of cardiomyopathy, early identification and confirmatory genetic testing by retina specialists could improve prognosis
References


References


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