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Morning Case Report
Patient: AO

- CC: decreased VA
- 22-year-old Sudanese male presents to neuro-op clinic for evaluation by referral from Denver Health Medical Center. Has never been able to see well from both eyes but states that he thinks his vision is deteriorating in the last couple of months. Denies nyctalopia, eye pain, visual field defects only stating that his vision is blurry.
History Cont’d

• Ocular history:
  – Glaucoma suspect
  – Mild NPDR Both eyes s/p focal laser 6/2012 L for CSME

• PMH: Type 1 Diabetes, diagnosed at age 5

• Meds:
  – Travatan qhs
  – Insulin
  – Simvastatin
Family History

- Consanguineous parents
- Sister also is “blind” and has DMI. Pt states that she has severe neuro deficits.
- Father's uncle with hearing loss but no vision problems.
- Extensive DM family history (both type 1 and 2).
- Female cousin on maternal side - hearing issues, but no vision changes.
Exam

- Vision: 20/150, 20/200, PHNI
- Pupils 5 → 4.5, no APD
- IOP: 11/12
- Color plates: 0/15 both eyes
- Slight gaze-holding horizontal nystagmus
# Exam

<table>
<thead>
<tr>
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<th>Right</th>
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<tbody>
<tr>
<td>Lids/lashes</td>
<td>WNL</td>
<td>WNL</td>
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<tr>
<td>Conj/Sclera</td>
<td>Trace injection/melanosis</td>
<td>Trace injection/melanosis</td>
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<tr>
<td>Cornea</td>
<td>Clear</td>
<td>Clear</td>
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<tr>
<td>A/C</td>
<td>Deep and quiet</td>
<td>Deep and quiet</td>
</tr>
<tr>
<td>Iris</td>
<td>WNL</td>
<td>WNL</td>
</tr>
<tr>
<td>Lens</td>
<td>Clear</td>
<td>Clear</td>
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<tr>
<td>Vitreous</td>
<td>Normal</td>
<td>Normal</td>
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| Disk           | C/D: 0.85
Thinnest IT, mild
superior/inferior pallor

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| M/V/P          | MA’s along arcades                         | Macula: Focal laser scarring ST and IN to
macula, no obvious DME
MA’s along arcades and
numerous DBH 2/4
quadrants
Differential Diagnosis

• Hereditary Optic Atrophy
  – Leber’s hereditary optic neuropathy
  – Optic Atrophy type 1 (other names: Kjer’s type optic atrophy, Autosomal Dominant Optic Atrophy (ADOA))
  – Wolfram syndrome (DIDMOAD)
  – Optic Atrophy type 3 (other related: Behr’s syndrome)

• Glaucoma

• Infectious
  – Syphilis, HIV

• Nutritional Optic Neuropathy
  – ethanol, methanol, lead toxicity, B12 deficiency, etc.

• Compressive lesion
Work-up

• B12, RPR, HIV
• OPA1 mutation analysis, and if negative: Wolfram Syndrome-type1gene testing
• Consider MRI brain, MRA neck
Results

- B12: normal
- HIV/RPR: negative
- OPA1: negative
- WFS-1: homozygous pathogenic sequence variant
Wolfram Syndrome

- First described in 1938 by Wolfram with a case series involving 4 patients
- About 200 patients have been reported in the literature
- Autosomal Recessive
- Onset between ages 5 and 21
- Also known as DIDMOAD (see next slide)
- Decreased vision (usually < 20/400)
How it presents: DIDMOAD

- **DI**: Diabetes Insipidus
- **DM**: Diabetes Mellitus
- **OA**: Optic Atrophy
- **D**: Deafness
- In large study of 45 patients, DI in 71% of patients, 62% deafness, 58% renal tract abnormalities, 62% neurologic abnormalities (nystagmus included here). All four present in 54%.
- Other studies have shown DI and/or deafness present in 51% and all four present in 13%
- 60% affected by mental health issues such as depression, psychosis, etc.
- Primary hypogonadism, more prevalent in males
Figure 1: Natural history of Wolfram syndrome
DM = diabetes mellitus; OA = optic atrophy, DI = diabetes insipidus, D = deafness, Renal = renal-tract abnormalities, Ataxia = neurological abnormalities (one patient presented at 5 years).
WFS-1 gene

- Loss of function mutation throughout the gene, most commonly in exon 8.
- Encodes an endoplasmic reticulum (ER)-resident transmembrane protein that is involved in the regulation of the unfolded protein response (UPR), intracellular ion homeostasis, cyclic adenosine monophosphate production and regulation of insulin biosynthesis and secretion. Recently found to negatively regulate Sarcoendoplasmic reticulum ATPase and loss in function leads to accumulation of SERCA.
- Ca2+ influx and Beta cell death in the pancreas.
Expressivity differences

• Significant expressivity differences depending on mutation of gene and in what part (exon vs. intron, etc)

• Complete non-functioning gene vs. malfunctioning.
WFS-1 vs. WFS-2F

• WFS-1
  – WFS-1 gene, autosomal recessive inheritance
  – DIDMOAD features
  – Non-HLA-typed and non-autoimmune related DMI
• WFS-2
  – CISD2 gene, also encodes a ER transmembrane protein
  – More recently discovered, identified in 3 consanguineous families
  – DMI, optic atrophy, renal tract issues, but no DI
Relation to glaucoma?

- One case report of two siblings with juvenile-onset glaucoma with high IOP in addition to their wolfram syndrome optic atrophy presentation
Follow-up

- Sent to low vision with Dr. Hanson
- VA stable at this time
- Genetic counseling referral
- Coordinating care for sister to get genetic testing
References