Eye Disease in Cobalamin C Deficiency

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No Disclosures
Objectives

• How the pediatric ophthalmologist evaluates vision / retina in young patients

• Understand what we know about the structure of the eye/retina in Cobalamin C deficiency and also the function

• Review of literature

• Low vision

• Your questions, answered
Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.
Pediatric eye exam
Nystagmus
- What does this mean?
- When does it develop?
- Will it ever go away?

Strabismus
Pediatric eye exam

- Slit lamp exam
- Cataract (lens opacity)
- Dilated exam
- Retina
- Optic Nerve
What I see
More complex testing
Optic Nerve in Cobal C

- Sometimes normal
- Often pale
- **Part of the eye but also part of the brain.**
- Optic nerve atrophy:
  - Can be seen in Cobalamin disorders (G) and many other disorders.
  - Very common and very NON specific – can have a LARGE range of visual function with optic nerve atrophy.
  - We can measure this with OCT… more to come on this.
The Retina in Cobal C Defect

- This is more interesting to me because:
  - It’s appearance is very characteristic. Few other diseases have retinas that look like this
  - It’s variable – not every patient has this
  - I’m hopeful that the clues to understanding what is happening early in the retina will lead to improved treatments and one day a cure.
Normal right retina
Normal left retina
While some of my patients have normal retinas, most do not
Advanced disease
Patient 1

- Compound heterozygosity for an *MMACHC* (p.Y205X) mutation and an intragenic deletion
24 months old
Patient 2

Patient 3

- homozygous for c.271dupA allele (p.Arg91LysfsX14)

[Images of retina with and without lesions]
Patient 4

- Two heterozygous pathogenic variants in MMACHC:
  - c.271dupA (p.R91Kfs*14)
  - c.440G>A (p.G147D)

- Normal exam, now 8 months old
Let’s look closer at the retina
High Definition OCT at 5-micron Resolution
Patient 1
4 months old

8 months old
Patient 2
6 months old 12 months old
What’s in the literature?
2014
• 12 patients
• Average age of exam 10 years old
# Long-term Visual Outcome of Methylmalonic Aciduria and Homocystinuria, Cobalamin C Type

Robert Gizezki, MD, Marie-Claude Robert, MD, Liliane Gomez-Lopez, MD, Jaqueline Orquin, MD, Jean-Claude Decarie, MD, Grant A. Mitchell, MD, Marie-Sylvie Roy, PhD, Luis H. Ospina, MD

## Table 1. Clinical Visual Outcomes in Cobalamin C Disease

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age at Initial Examination</th>
<th>Follow-up (yrs)</th>
<th>Initial Best-Corrected Visual Acuity (Right Eye—Left Eye)</th>
<th>Last Best-Corrected Visual Acuity (Right Eye—Left Eye)</th>
<th>Maculopathy</th>
<th>Nystagmus</th>
<th>Optic atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>2 mos</td>
<td>14</td>
<td>FF—FF</td>
<td>15/200—15/200</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1 mo</td>
<td>10</td>
<td>LP—LP</td>
<td>20/80—20/80</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>5 mos</td>
<td>23</td>
<td>Fx—Fx</td>
<td>20/800—20/800</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>6 mos</td>
<td>2</td>
<td>Fx—Fx</td>
<td>20/1.50—20/1.50</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>5 mos</td>
<td>11</td>
<td>LP—LP</td>
<td>20/100—20/100</td>
<td>—</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>9 mos</td>
<td>13</td>
<td>FF—FF</td>
<td>20/25—20/25</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2 mos</td>
<td>7</td>
<td>FF—FF</td>
<td>FF—FF</td>
<td></td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>6 mos</td>
<td>10</td>
<td>LP—LP</td>
<td>3/200—3/200</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>5 yrs</td>
<td>12</td>
<td>LP—LP</td>
<td>20/100—20/100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>19 mos</td>
<td>5</td>
<td>Fx—Fx</td>
<td>20/25—20/25</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>6 yrs</td>
<td>0</td>
<td>20/20—20/20</td>
<td>20/20—20/20</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>4 mos</td>
<td>3</td>
<td>FF—FF</td>
<td>20/150—20/150</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>

F = female; Fx = fixates; FF = fixates and follows; LP = light perception; M = male; + = yes; − = no.
MACULOPATHY: 8/12 patients
Nystagmus: 8/12 patients
Optic nerve atrophy: 6/12 patients

VISION: Visual function was age appropriate in 3/12 patients.

None of these 3 patients had nystagmus, maculopathy OR optic atrophy
- Review of the current literature – 55 early onset and 38 with late onset disease
- Added 7 more of our cases
- Overall: 62 patients with early onset CblC
About half of the patients had enough information documented to study. Of those:

- 5% had normal vision
- 10% were mildly visually impaired (20/30-20/40)
- 5% moderate visual impairment (20/50-20/80)
- 21% with moderate to severe impairment (20/100-20/800)
- 31% severely impaired (worse than 20/800)
Framework for standardizing exams so we can understand natural history better.

- 6 months – baseline testing
- 12 months – repeat testing
- 18 months - office
- 24 months – repeat testing
By far the most comprehensive study – NIH

25 patients
- 72% macular degeneration
- 64% nystagmus
- 52% strabismus
- 68% optic nerve atrophy
Ophthalmic Manifestations and Long-Term Visual Outcomes in Patients with Cobalamin C Deficiency

Brian P. Brooks, MD, PhD, Amy H. Thompson, PhD, Jennifer L. Sloan, MS, PhD, Irini Manoli, MD, PhD, Nuria Carrillo-Carrasco, MD, Wadih M. Zein, MD, Charles P. Venditti, MD, PhD

Key
Shading = genotype
DupA homozyg = solid
DupA heterzyg = half shaded
Non-DupA = open
Shape = onset
Infant onset = circle
Later onset = triangle

Age at visit. years

Non-quantifiable Acuities

BCVA or VA, LogMAR

Visual Acuity, Snellen

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Retinal Structure in Cobalamin C Disease: Mechanistic and Therapeutic Implications

Tomas S. Aleman¹, Frank Brodie¹, Christopher Garvin², Dina Y. Gewaily¹, Can H. Ficicioglu³, Monte D. Mills², Brian J. Forbes², Albert M. Maguire¹,² and Stefanie L. Davidson²
11 patients

OCT

ALL with early onset disease had maculopathy and poor vision
Answers to some questions
Unanswered questions

- Why do some patients have disease and others don’t?
- Can we do gene therapy? (not yet…..)
What you CAN do

- **Vision therapy** – NO!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
  - http://www.aapos.org/terms/conditions/108

- **Vision rehabilitation** – YES.
  - This is maximizing what you have.
  - Teachers for the visually impaired
  - Anchor center for the Blind
What you CAN do

- Treating refractive error, strabismus.
- Seeing an ophthalmologist who is interested in this disease so we can work as a team
- www.aapos.org
Thanks

- my patients
- CHC
- James Weisfeld-Adams, MD

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