Aortic Atherosclerosis and Liver Disease in a 13-Year-Old Boy

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Initial Presentation

• An eleven year old male was referred to our lipid clinic for evaluation of a marked hyperlipidemia, hepatic transaminase elevation and hepatomegaly.

• Clinical Chemistry Assessment

| TC: 336 | ALT: 120 | TSH: 2.66 |
| TG: 239 | AST: 78  | FBS: 95   |
| LDL-C: 272 | Total Bili: 0.7 | HgA1C: 4.8% |
| HDL-C: 16  | Direct Bili: 0.1 | UA: Normal |
| Apo B: 225 | Creatinine: 0.5 |

• Physical Exam:  
  Height: 49 inches  
  Weight: 67 pounds  
  BMI: 19.6 kg/m²  
  BP: 106/61 mmHg

• Significant Exam Findings:
  • PODC  
  • Hepatomegaly  
  • short stature  
  • tuberous xanthomas
Family Medical History

- Normal paternal family Hx of either ASCVD or HLD
- Mild HTG
- Overweight

- 43
  - HLD
  - HLD ➔ Liver enzymes

- 17
  - HLD
  - HLD ➔ Liver enzymes

- 14
  - HLD
  - HLD ➔ Liver enzymes

- 11
  - HLD
  - HLD ➔ Liver enzymes

- 9
  - HLD
  - HLD ➔ Liver enzymes

- 38
  - MI @36
  - CABG @37
  - Smoker
  - Normal Lipids
  - Bariatric surgery @37

- 68
  - MI @36
  - CABG @37
  - Smoker
  - Normal Lipids
  - Thyroid Cancer (resection)

- 65
  - Normal Lipids
  - HTN
  - HLD
  - Obesity

- 45
Differential Diagnosis

• Rule out Familial Combined Hyperlipidemia and heterozygous Familial Hypercholesterolemia

• Rule out secondary cause of hyperlipidemia (hypothyroidism, diabetes mellitus, CKD, nephrotic syndrome, obesity)

• Differential diagnosis:
  – Familial Dysbetalipoproteinemia (Type III)
  – Lysosomal Acid Lipase Deficiency
Results of LAL Activity

- EDTA tubes containing whole blood were sent to Mayo Medical Laboratories for assessment of LAL activity

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<thead>
<tr>
<th></th>
<th>DT</th>
<th>CT</th>
<th>BT</th>
<th>AT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAL activity, pmol/hr/spot</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>&gt; 21.0</td>
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- Interpretation: results are indicative of LAL-D.
### Results of DNA Sequencing of LIPA Gene

<table>
<thead>
<tr>
<th></th>
<th>Siblings</th>
<th>Parents</th>
<th>Maternal Grandparents</th>
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<tbody>
<tr>
<td></td>
<td>DT</td>
<td>CT</td>
<td>BT</td>
</tr>
<tr>
<td><strong>Allele 1</strong></td>
<td>c.894G&gt;A</td>
<td>c.894G&gt;A</td>
<td>c.428+1g&gt;a</td>
</tr>
<tr>
<td><strong>Allele 2</strong></td>
<td>c.428+1g&gt;a</td>
<td>normal</td>
<td>normal</td>
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</table>

**c.894G>A**: common splice mutation accounting for about 60% of all LIPA mutations. It is a substitution mutation; a guanine is replaced with an adenine at last position (894) at the 3′ end of exon 8.

**c.428+1g>a**: A unique mutation. A splice junction mutation that substitutes a guanine with an adenine at the first nucleotide site at the 5′ end of intron 3. Considered a Wolman mutation since it results in the production of a truncated (inactive enzyme).
Treatment

• All siblings placed on a low-fat (<7% of total calories from saturated fat), balanced approach to nutrition at a daily calorie intake to support and maintain a healthy body weight.

• All siblings enrolled in a Phase III clinical trial for enzyme replacement therapy (1mg/kg, IV).

• Transitioned to commercial product (Kanuma) on 12/22/15.