Low Levels of High Density Lipoprotein (HDL) and Corneal Opacity Caused by Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency

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Disclosure of interests

I, Mordechai Golomb, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
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Introduction:
Cholesterol transport and removal is achieved by the actions of the plasma enzyme LCAT (Lecithin Cholesterol Acyltransferase). LCAT bound to HDL esterifies cholesterol, facilitating its removal and providing cholesterol hemostasis.\(^1\)

The LCAT gene is 4.2 kilobases long and is localized to chromosome 16. Several mutations in this gene have been described, providing a commonly accepted classification: **Familial LCAT deficiency** (completely missing or lacking activity) **Fish Eye disease** (α-LCAT deficiency/partially lacking activity).\(^2\)

**Fish Eye Disease** (FED), first described in 1979\(^3\), is a rare recessive genetic disorder with less than 50 cases described worldwide thus far. Mutations in the LCAT gene cause lecithin-cholesterol acyltransferase (LCAT) deficiency, resulting clinically in corneal opacifications from cholesterol deposits (“boiled fish eye”) and dyslipidemia (low HDL).

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Methods:
Proband: A 64 year old male known to have Dyslipidemia for many years was recently evaluated for new visual impairment. Corneal opacifications raised suspicion of a metabolic disorder, specifically FED.

<table>
<thead>
<tr>
<th>Test</th>
<th>13/1/2015</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>454</td>
<td>30-150</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>88</td>
<td>80-200</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dl)</td>
<td>--</td>
<td>4-40</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dl)</td>
<td>65</td>
<td>100-200</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>56</td>
<td>40-125</td>
</tr>
<tr>
<td>Apolipoprotein C2 (mg/dl)</td>
<td>7</td>
<td>3-7</td>
</tr>
<tr>
<td>Apolipoprotein C3 (mg/dl)</td>
<td>17.9</td>
<td>9-19</td>
</tr>
</tbody>
</table>

Patient’s Lipid Profile.
Very low levels of HDL with normal LDL levels. The patient had normal Hg level and renal function.

Mutation Search and Analysis:
1. DNA was extracted from peripheral leukocytes using the “salt precipitation” technique.
2. Polymerase Chain Reaction (PCR) amplified the specific LCAT gene.
3. Complete Sanger nucleotide sequencing.
4. Mutation analysis performed by different well-established tools.
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Results:

PCR reaction:
Complete LCAT gene as observed by gel electrophoresis.

DNA sequencing:
Only one missense mutation substituting guanine (G) with adenine (A), resulting in the amino acid change - A117T.

Mutation Analysis:
SIFT analysis-tolerated mutation. Mutation Taster study- disease causing mutation, “possibly Norum Disease” (LCAT deficiency with anemia and renal dysfunction which our patient doesn’t have).
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Discussion and Conclusions:

We describe a case of a patient with a clinically suspected genetic disorder, reinforced by DNA sequencing and mutation analysis.

Further study is required to measure LCAT activity and cholesterol esterification rate thus elucidating the disease process and eliminating other possibilities such as Tangier disease, familial LCAT deficiency, and APO A-I deficiency.

This work provides a clear example of a **new era- the era of Precision Medicine**.

Proven mutations with adequate clinical correlation can provide patient tailored therapeutic options, such as gene therapy or enzymatic supplementation for our patient, and early diagnosis of other family members.

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