Severe Mixed Hyperlipidemia, Heterozygous APOE p.V254E, Pancreatitis, Diabetes Mellitus, and Plantar Xanthomas

Brian Cheung¹, Barry Tedder¹, Ernst J. Schaefer², and Robert A. Hegele³

¹Saint Bernards Medical Center, Jonesboro, AR. ²Boston Heart Diagnostics, Framingham, MA. ³University of Western Ontario, London, ON.

Introduction

• Severe mixed hyperlipidemia is a condition characterized by elevated triglycerides and cholesterol. It can be affected by genetic factors, such as mutations in apo E, which is a protein that is central in lipid metabolism.

• Mature apo E is a 299 amino acid polypeptide that is a component of triglyceride-rich lipoproteins and mediates their catabolism through hepatic receptors, including the LDL receptor, LDLR related protein and VLDL receptor.

• Genetic variation in the APOE gene includes common polymorphisms (E4, E3, and E2 isoforms) and rare missense variants; both types of variation have been shown to predispose to dyslipidemia.

• Environmental factors, such as uncontrolled diabetes mellitus and obesity, may also affect the phenotypic expression in individuals who carry APOE variants.

• We present a case of a patient with longstanding severe hypertriglyceridemia and hypercholesterolemia, who also had pancreatitis, diabetes, and plantar xanthomas. She was found to be heterozygous for the rare APOE p.V254E missense variant.

References

Disclosures: funding was provided by Boston Heart Diagnostics, Framingham, MA and The Dyslipidemia Foundation, Natick, MA.
Methods

- Chart review, medical history and physical examination
- Lipase and amylase levels
- Lipid and lipoprotein testing
- CT abdomen and pelvis
- *APOE* genotyping
- Next generation DNA sequencing was performed using the LipidSeq targeted panel on the Illumina MiSeq platform, which included analysis of the *LPL, APOC2, APOA5, LMF1, GPIHBP1, GCKR, CREB3L3, GPD1, APOE, APOC3, LDLR, APOB*, and *PCSK9* gene loci
The Patient

- A 56-year-old obese Caucasian woman presented with a one day history of nausea, non-bilious/non-bloody emesis, periumbilical pain, and abdominal distension.
- She complained of chronic abdominal pain lasting months.
- PMHx of mild carotid disease, abdominal aorta non-obstructive atherosclerotic disease, and subclavian and coronary artery calcifications, CKD
- FMHx of brother with CAD with CABG in his 40s and history of HLD, but unknown classification
- Vital signs stable. BMI 36.6 with truncal obesity.
- No arcus senilis appreciated. Dry mucus membranes. Tenderness in the right scapular region, firm abdomen, tenderness to light palpation in the umbilicus and right upper and lower abdominal quadrants. Right Achilles tendon xanthomas and multiple large chronic non-tender non-pruritic bilateral plantar xanthomas on the soles of her feet with no palmar or tuberoeruptive xanthomas.
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Results

- Serum glucose levels peaked at 430mg/dL
- Hemoglobin A1c was 9.9%
- Lipase was greater than 10,000 U/L
- CT abdomen and pelvis without contrast indicated peripancreatic fat stranding around the head, body, and tail of the pancreas and the duodenum.
- Cholesterol/Apo B ratio was 2.20
- Triglyceride/Apo B ratio was 5.52
- Heterozygous coding mutation in APOE where valine is substituted with glutamic acid at the 254 codon position, causing a missense; the background APOE genotype was E3/3
- Polygenic Triglyceride Risk Score of 14/28, which is the 50th percentile
- Genetic testing indicated no mutations in LPL, APOC2, APOA5, LMF1, GPIHB1, GCKR, CREB3L3, GPD1, APOC3, LDLR, APOB, and PCSK9 gene loci

### Table 1: Laboratory Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (6 months prior admission)</th>
<th>Day of admission</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 20</th>
<th>Outpatient (3 weeks after admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>&gt;1575</td>
<td>&gt;1575</td>
<td>1237</td>
<td>324</td>
<td>263</td>
<td>393</td>
<td>509</td>
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<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>299</td>
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<td>246</td>
<td>225</td>
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<tr>
<td>LDL-C (mg/dL)</td>
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<td>ApoB (mg/dL)</td>
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<td>LP(a) (mg/dL)</td>
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### Discussion

### References

### Treatment

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<tr>
<th>Diet</th>
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Treatment

• The patient’s pancreatitis was treated with IV fluids and bowel rest.
• The patient was started on 80 mg atorvastatin and 10 mg ezetimibe, which both improve LDL receptor functionality and help with VLDL and LDL clearance. 145 mg fenofibrate increased HDL and lowered LDL, triglycerides, and apo B. 4 g fish oil was started to lower triglycerides and raise HDL.
• 40 mg insulin glargine and 15 mg pioglitazone were started. Pioglitazone was specifically chosen to help lower triglycerides. The improved control of diabetes reduced the impact of her genetic APOE defect by improving lipoprotein lipase functionality.
• The patient was able to lose 15 lbs with a low fat, reduced sugar diet and regulated meal plans.
• On follow up, the patient complained of exertional angina. Due to high Apo B containing lipoproteins, diabetes, obesity, probable obstructive sleep apnea, chronic kidney disease, and hypertension she has high cardiovascular risk.
Discussion

- Differential diagnosis included combined hyperlipidemia, mixed dyslipidemia and dysbetalipoproteinemia. The rare heterozygous APOE mutation is consistent with dominant predisposition to dysbetalipoproteinemia however, elevation in apo B would be atypical. Plantar xanthomas are seen in dysbetalipoproteinemia, but not in mixed hyperlipidemia. Conversely, pancreatitis is typically seen in mixed hyperlipidemia but not dysbetalipoproteinemia.

- The initial differential included familial hyperlipidemia in the setting of severe insulin resistance, as the patient had elevated apo B and LDL cholesterol, and plantar and tendon xanthomas. Pancreatitis is consistent with chylomicronemia at some point in the patient’s clinical course. The severe insulin resistance may be contributing to decreased LPL activity, resulting in elevated TG. This patient has features resembling dysbetalipoproteinemia, as patients can have plantar and tendon xanthomas and mutations in APOE. It is characterized by triglycerides/Apo B ratio of less than 10 (5.52 in this patient). However, the cholesterol/Apo B ratio is typically greater than 6.2, and it is only 2.2 in this patient, which is inconsistent with dysbetalipoproteinemia. Mixed hyperlipidemia can present with pancreatitis and has APOE mutations, which is the most likely diagnosis.

- Genetic testing revealed a normal APOE E3/3 genotype; the E2/2 genotype is the classical predisposing genotype for dysbetalipoproteinemia. Here, DNA sequencing was required to find the rare APOE p.V254E missense variant. This defect is likely contributing may affect the structure of apo E, although it occurs towards the C-terminus of the protein and outside the receptor binding domain. It may contribute to poor clearance of VLDL and VLDL remnant particles from the liver. This is due to reduced ability of Apo E on the VLDL particle to bind to the LDL receptor, which Apo E typically has a 20 times higher affinity to the LDL receptor than Apo B. The abnormal Apo E function interferes with lipolysis of VLDL by lipoprotein lipase. When combined with diabetes and LPL dysfunction due to insulin resistance, the poor clearance by the LDL receptor is even more exacerbated as seen in our patient.
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Acknowledgements

• We would like to thank the National Lipid Association for awarding Dr. Brian Cheung M.D. the Young Investigator award.

Disclosures

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Graph 1: Laboratory Results

- **Baseline (6 months prior to admission)**
- **Day of admission**
- **Day 4**
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- **Day 12**
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- **Outpatient (3 weeks after admission)**

- **Started Atorvastatin, Fish oil, Fenofibrate**
- **Started Ezetimibe**
- **Started Pioglitazone**

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**Laboratory Measurements (mg/dl):**
- **Triglycerides**
- **Total Cholesterol**
- **LDL-C (mg/dL)**
- **VLDL-C**
- **ApoB**