CLINICAL VIGNETTE

Rare Case of Familial Hypobetalipoproteinemia

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Case Presentation

A 27-year-old male with a past medical history of asthma presented to internal medicine for an annual exam. He was doing well with no significant complaints. Vital signs were temperature 36.2 ° C, blood pressure 127/77, heart rate 67, respiratory rate 14, SpO2 98%, height 6'3", weight 158 lbs. Physical exam was unremarkable. Lab work was notable for total cholesterol of 88 mg/dL, LDL cholesterol 13 mg/dL, HDL cholesterol 72 mg/dL, and triglycerides of 15 mg/dL. The remainder of his labs were unremarkable including complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, and hemoglobin A1C. Given low LDL and concern for Familial Hypobetalipoproteinemia (FHBL), the patient was referred to genetics.

Further genetic family history was obtained. The patient's father was healthy and a balanced translocation carrier involving chromosomes 2 and 9. The patient's paternal first cousin was born with an unbalanced chromosomal disorder which caused significant intellectual disability, G-tube dependence, and early death at age 18. Analysis of *APOB, ANGPTL3, and PCSK9* genes along with a karyotype were performed. Evaluation revealed one heterozygous likely pathogenic variant in the APOB gene consistent with a diagnosis of heterozygous *APOB* Familial Hypobetalipoproteinemia (*APOB*-FHBL). The patient received counseling on the diagnosis and recommendations for ongoing surveillance.

Discussion

Heterozygous *APOB*-FHBL occurs in 1 in 3000 individuals in the general population.[1] Pathogenic variants are inherited in an autosomal recessive manner. Patients may go undiagnosed until adulthood as they are usually asymptomatic.

The diagnosis of *APOB*-FHBL should be considered in patients with a total cholesterol less than 115 mg/dL, LDL cholesterol less than 50 mg/dL, triglycerides less than 45 mg/dL, low plasma apo B level, slightly elevated liver enzymes and/or liver ultrasound with hepatic steatosis in the absence of risk factors, or who have first degree relatives with hypocholesterolemia.[1] The diagnosis is made via genetic testing.

Patients who are heterozygous APOB-FHBL may have mild liver dysfunction due to hepatic steatosis, however 5%-10% can develop severe nonalcoholic steatohepatitis and rarely cirrhosis.[1] The increased risk of hepatic steatosis is thought to be related to impaired secretion of VLDL-TG from the liver, leading to accumulation of VLDL-TG in the liver.[2] In addition, fat malabsorption can lead to vitamin deficiency, steatorrhea or failure to thrive may occur.

Individuals with heterozygous *APOB*-FHBL typically do not require treatment, although routine surveillance is required to monitor for potential complications. Dilated fundoscopy is recommended given the association of low serum LDL and retinal issues including atypical hyperpigmentation and retinal degeneration. Patients should undergo lipid and liver function testing every 1 to 2 years, while liver ultrasound is also recommended every 3 years starting at the age of 10 in patients with elevated transaminases given increased risk of hepatic steatosis.[1] Given the risk for fat malabsorption, levels of fat soluble vitamins including Vitamins A, D, E, and K should be obtained, and patients should be maintained on a high dose oral fat-soluble vitamin supplement. As with other causes of hepatic steatosis, adhering to a low-fat diet, exercising regularly, limiting alcohol consumption, and maintaining a healthy weight can decrease risk of complications. Prenatal genetic testing is important in these individuals and their partners as patients who are heterozygous for *APOB*-FHBL have a 50 percent chance of passing the variant to their offspring.[1]

A potential benefit of heterozygote APOB-FHBL is lower cardiovascular risk. *Peloso* et al reported patients with APOB-FHBL were at 72% lower risk of coronary artery disease when compared to noncarriers of the heterozygous mutation.[3] In *Sankatsing* et al, carotid intima-media thickness in the FHBL group was lower compared to the control group despite higher risk factors such as smoking and diabetes in the former group compared to the latter.[2]

Conclusion

As individuals with heterozygous *APOB*-FHBL are usually asymptomatic, practitioners should have a high degree of suspicion when encountering patients with low total cholesterol, low LDL, low triglycerides, and transaminitis due to hepatic steatosis. Diagnosis is important given the need for surveillance of potential complications including hepatic dysfunction, fat malabsorption and related issues, and retinal pathology.

REFERENCES

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