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Familial Hypobetalipo- proteinemia-Induced Nonalcoholic Steatohepatitis

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Key Words

Familial hypobetalipoproteinemia · Nonalcoholic steatohepatitis · *APOB*

Abstract

Familial hypobetalipoproteinemia (FHBL) is a rare genetic disorder of lipid metabolism that is associated with abnormally low serum levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein B. It is an autosomal co-dominant disorder, and depending on zygosity, the clinical manifestations may vary from none to neurological, endocrine, hematological or liver dysfunction. Nonalcoholic fatty liver disease is common in persons with FHBL, however progression to nonalcoholic steatohepatitis is unusual. We describe here a patient with a novel *APOB* mutation, V703I, which appears to contribute to the severity of the FHBL phenotype. He had liver enzyme abnormalities, increased echogenicity of the liver consistent with steatosis, very low LDL cholesterol at 0.24 mmol/l (normal 1.8–3.5 mmol/l) and an extremely low apolipoprotein B level of 0.16 g/l (normal 0.6–1.2 g/l). *APOB* gene sequencing revealed him to be a compound heterozygote with two mutations (R463W and V703I). *APOB* R463W has previously been reported to cause FHBL. Genetic sequencing of his first-degree relatives identified the *APOB* V703I mutation in his normolipidemic brother and father and the *APOB* R463W mutation in his mother and sister, both of whom have very low LDL cholesterol levels. These results suggest that the *APOB* V703I mutation alone does not cause the FHBL phenotype. However, it is possible that it has a contributory role to a more aggressive phenotype in the presence of *APOB* R463W.

Introduction

Familial hypobetalipoproteinemia (FHBL) is a rare autosomal co-dominant genetic disorder of lipid metabolism. It is characterized by serum low-density lipoprotein (LDL) cholesterol or apolipoprotein B (apoB) levels ≤ 5 th percentile. The disorder was first described in 1979 by Steinberg et al. [1–3]. ApoB is the largest of the apolipoproteins and is important in the formation and secretion of very-low-density lipoprotein (VLDL) and chylomicrons. There are two forms of apoB found in serum, namely apoB-48 and apoB-100. These two isoforms are derived from differential splicing of RNA from a single *APOB* gene [4]. ApoB-48 is synthesized by enterocytes and is a key component of chylomicrons, while apoB-100 is synthesized by the liver and is the key protein component of VLDL and LDL particles; B-100 also contains the binding site for hepatocyte uptake [5]. The *APOB* gene is found on chromosome 2p24 and is unlinked to other apolipoprotein gene clusters [6].

Since the discovery of the first kindred with FHBL, many subsequent kindreds have been described, leading to the identification of numerous single nucleotide substitutions, gene deletions, splicing variations and linkage abnormalities in the *APOB* gene that can lead to defects in VLDL and chylomicron production and secretion. Persons with FHBL can be heterozygotes or homozygotes, with severity of the clinical phenotype related to the number of defective *APOB* alleles. Heterozygotes often have no clinical manifestations other than very low serum apoB-containing lipoprotein levels; these low levels of atherogenic lipoprotein particles may actually confer cardiovascular protection [7]. In contrast, FHBL homozygotes can have a range of clinical symptoms, including fat malabsorption, neurologic symptoms, red cell acanthocytosis, retinitis pigmentosa and/or nonalcoholic fatty liver disease. In fact, the clinical presentation of homozygous FHBL can be indistinguishable from that of abetalipoproteinemia (ABL) due to mutation in *MTTP*, which is the gene that encodes microsomal triglyceride transfer protein [8].

We describe here a case of nonalcoholic steatohepatitis (NASH) that led to the diagnosis of FHBL.

Case Report

A 44-year-old man was referred to the Vancouver General Hospital Division of Gastroenterology for advice regarding management of NASH. He was a shop owner, a life-long nonsmoker and drinking about half a bottle of wine a week. He was first noted to have elevated liver enzymes in 1996. At that time, he was told that AST (normal 5–35 U/l), ALT (normal 7–56 U/l) and GGT (normal 8–78 U/l) were all about 2-fold above the upper limits of normal. Hepatitis B and C serologies were negative. A liver biopsy was recommended, however the patient declined the procedure and elected to initiate a weight loss program with dietary modification and increased exercise for presumed NASH. About 3 years before presentation, he was found to have elevated transaminases on blood work done for an insurance application, with ALT 130 U/l and AST 111 U/l. These abnormalities were again attributed to NASH. After about 6 months of strict diet and exercise, as well as a 10-pound intentional weight loss, his liver enzymes normalized with ALT 44 U/l and AST 41 U/l. He reintroduced mild alcohol intake and reduced the amount of exercise, and 6 months later his liver enzymes were again elevated with ALT 94 U/l and AST 80 U/l. Other causes for elevated liver enzymes, including anti-nuclear antibody, ceruloplasmin and alpha-1 antitrypsin, were normal or negative. However, he was found to have an elevated ferritin at 737 $\mu\text{g/l}$ (normal 18–250 $\mu\text{g/l}$). Subsequent testing revealed him to be heterozygous for the C282Y mutation in the *HFE* gene for hemochromatosis. There was no other significant past medical history.

On examination, he was a stocky male with a body mass index of 32 kg/m². There were no extrahepatic signs of liver disease. Respiratory and cardiovascular examinations were normal. His abdomen was soft and nontender with no palpable organs or masses. Review of his blood tests from 3 years before revealed LDL cholesterol 0.24 mmol/l (normal 1.8–3.5 mmol/l), high-density lipoprotein cholesterol 1.29 mmol/l (normal 0.9–1.5 mmol/l) and triglyceride 0.37 mmol/l (normal 0.5–1.7 mmol/l). The serum apoB level was extremely low at 0.16 g/l (normal 0.6–1.2 mmol/l). A liver biopsy had been done in 2009 by the referring physician and had shown normal liver architecture. There was very mild portal and pericellular centrilobular fibrosis, mild focal mononuclear cell infiltration and moderate macrovesicular steatosis. There was no abnormal iron deposition and no Mallory hyaline.

Family history revealed that his sister (subject II-3 in [fig. 1](#)) also has elevated liver enzymes ([table 1](#)). She was obese, had type 2 diabetes and had recently been diagnosed with esophageal varices. She had been aware of a low LDL cholesterol level for several years. However, details of her liver disease were unknown. His mother (I-2) and several maternal relatives were known to have a very low cholesterol level. His mother's family was of Christian Lebanese origin. His father (I-1) had a normal cholesterol level. His father's family was from Great Britain.

Family history and laboratory results suggested the diagnosis of FHBL. ApoB immunoblotting on fasting plasma showed only a band at the expected apoB-100 position, arguing against truncation mutations. DNA was extracted from plasma samples from the patient and subsequently from all first-degree relatives and sent to the Cardiovascular Genetics Lab in London, Ontario. Direct automated sequencing revealed two different mutations in the *APOB* gene, namely R463W and V703I. These were found to be on opposite chromosomes, so the proband is a compound heterozygote. Family relationships, cholesterol levels and *APOB* mutation analysis are shown in figure 1 and table 1.

Our patient was advised to return to regular exercise and to maintain a healthy low-fat diet. He was also started on vitamin E and multivitamin supplementation. His weight decreased by about 5 kg over 6 months and his ALT normalized to 25 U/l.

Discussion

Rare monogenic disorders have been very informative for identifying key components of the metabolism of apoB-containing lipoproteins and triglycerides [9]. These disorders include ABL due to mutation of the *MTTP* gene, hypobetalipoproteinemia due to mutation of the *APOB* gene, familial combined hypolipidemia due to mutation of the *ANGPTL3* gene and PCSK9 deficiency due to mutations in the *PCSK9* gene [10, 11].

In addition to being important in metabolism, some of the gene products causing these disorders are now targets for new drugs designed to lower LDL cholesterol. For instance, mipomersen is an anti-sense RNA biologic that reduces LDL cholesterol by targeting the *APOB* gene, while lomitapide reduces LDL cholesterol by inhibiting microsomal triglyceride transfer protein [12, 13]. There are also numerous new biologic drugs in development that lower LDL cholesterol by targeting PCSK9 [14]. While these new drugs seem to be very effective at lowering LDL cholesterol, there is concern about potential long-term side effects, such as hepatosteatosis. Clinical evaluation of 'experiments of nature' such as FHBL patients who carry a germ-line mutation in *APOB* can provide clues of the potential long-term benefits and adverse reaction of pharmacologic therapies that target these key metabolic pathways.

ApoB truncation is due to *APOB* gene mutation, exon deletions and splicing variations. About 45 different truncated forms of apoB have been discovered to date, ranging from apoB-2 to apoB-90 [15–38]. The numbers represent estimated apoB mass

based on polyacrylamide gel electrophoresis, with apoB-100 being normal. Truncated apoB can form varying sizes and densities of lipoprotein particles depending on the length of truncation [39]. Truncated apoB particles have a lower production rate and higher clearance rate, resulting in low plasma levels of apoB [19, 40–42]. ApoB smaller than apoB-27.6 is undetectable in plasma due to rapid clearance [40]. In FHBL heterozygotes with apoB truncation, the average plasma concentration of apoB is around 25–30% of normal [43, 44].

FHBL due to *ANGPTL3* gene linked to chromosome 3p21 is associated with about a 50% reduction in apoB levels compared to normal individuals, as well as an elevated rate of catabolism of VLDL apoB [10, 45–47]. At least some individuals with this subtype of FHBL have gain-of-function mutations of PCSK9 [48]. This is a serine protease that destroys LDL receptors in the liver and thereby controls the level of LDL in plasma. Mutations that increase PCSK9 activity cause hypercholesterolemia, whereas mutations that inactivate PCSK9 have the opposite effect.

In FHBL, the genetic defect in triglyceride export can lead to increased intrahepatic triglyceride content. There have been several reports of nonalcoholic fatty liver disease in FHBL subjects as detected by ultrasound or liver biopsy [28, 49–52]. Schonfeld et al. [51] analyzed liver fat by magnetic resonance spectroscopy, body mass index, waist circumference and glucose tolerance of 21 individuals with FHBL due to apoB truncations compared with 14 controls. Despite similar mean values for obesity and insulin indexes, there was a 5-fold increase in liver fat in FHBL subjects. Similar studies with FHBL subjects due to chromosome 3p21 linkage or PCSK9 mutations revealed normal hepatic fat content, an important phenotypic difference between these mutations and apoB truncation [7, 46].

The proband in this report is a 44-year-old man with NASH secondary to FHBL. Genetic analysis revealed compound heterozygosity for two mutations, each of which results in amino acid substitution. As shown in figure 1, he inherited the R463W mutation from his mother (subject I-2). Heterozygosity for this mutation is associated with hypobetalipoproteinemia, while homozygosity has a more severe phenotype [53]. Interestingly, the R463W mutation was first reported in an extended Christian Lebanese family, which is also the ethnic background of our proband's mother. Our patient inherited a second nontruncating *APOB* mutation, V703I, from his father. This is a novel mutation, and analysis using the PolyPhen program predicts the effect of this amino acid substitution as 'possibly damaging' to apoB function. Although the two V703I heterozygotes in this kindred, subjects I-1 and II-1, had normal LDL cholesterol levels when the second allele encoded normal apoB-100, it is possible that this mutation, in the context of a defective form of apoB-100, such as the R463W mutation, contributes to increased intracellular degradation of apoB. This might act to compound the impairment of VLDL secretion in subject II-2 who had one copy of R463W, as evidenced by his lower LDL cholesterol level compared to the two R463W simple heterozygotes (subjects I-2 and II-3).

Although NASH is common in FHBL patients, the long-term effects of FHBL are still unclear [28, 49, 51, 54]. However, steatosis from FHBL can lead to end-stage liver disease. Interestingly, Harada et al. [54] reported a patient with recurrent NASH and cirrhosis due to FHBL post liver transplantation. This suggests that at least in some forms of FHBL, the intestinal defect may be sufficient to cause the phenotype.

Fortunately, our patient had only mild steatohepatitis. However, his sister (subject II-3) has developed esophageal varices, possibly due to liver cirrhosis from FHBL compounded by diabetes mellitus.

Diet and exercise continue to be the mainstay of treatment for patient with NASH induced by FHBL. As in our patient, exercise and weight loss led to improvement in liver enzyme tests. Fat malabsorption can be managed through diet modification by limiting intake of fats containing long-chain fatty acids as well as supplementing fat-soluble vitamins. Reports have suggested that the cellular membranes of patients with FHBL are relatively deficient in vitamin E; indeed severe vitamin E deficiency in both homozygous FHBL and ABL is responsible for the development of neurologic signs and symptoms [55, 56]. While the most common neurologic symptom is decreased or absent deep tendon reflexes, ataxia, proprioceptive deficits and pain have been described in both homozygous FHBL and ABL [57–59]. There are reports of success with vitamin E treatments for neurologic symptoms in FHBL and ABL [57, 60]. There is some evidence that combination therapy of vitamin A and E can slow the progression of retinal degeneration and may lead to restoration of vision if started early [61–63]. Our patient was started on vitamin E and multivitamin supplementation for primary prevention, as he does not currently have any neurological, hematological or ocular abnormalities.

Conclusion

FHBL is an uncommon autosomal co-dominant disorder of lipid metabolism that is often overlooked because low levels of LDL cholesterol may not attract the attention of health care providers. In the present case liver enzyme abnormalities were the first clue to diagnosis. The understanding of FHBL and liver disease is still in its preliminary stages. Patients with FHBL and NASH can progress to end-stage liver failure, therefore monitoring and risk reduction is important. Finally, patients with such rare disorders can provide insight into the possible long-term consequences of new LDL-lowering biologic therapies.

Table 1. Biochemical profile and *APOB* genotype of the proband, siblings and parents

Parameter	Father	Mother	Proband	Brother	Sister
Year of birth	1926	1940	1965	1966	1962
Lipids					
TC	4.28	3.74	1.81	3.99	2.55
LDL, mmol/l	2.52	1.57	0.68	2.33	0.93
HDL, mmol/l	1.14	1.82	0.97	1.17	1.19
TG	1.37	0.76	0.34	1.08	0.94
Apo-B100, g/l			0.16		
Transaminases					
AST, U/l			111		
ALT, U/l	21		130	25	20
GGT, U/l	<10		31	19	30
Ferritin, µg/l			737		
<i>APOB</i> mutation	V703I	R463W	V703I/R463W	V703I	R463W

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

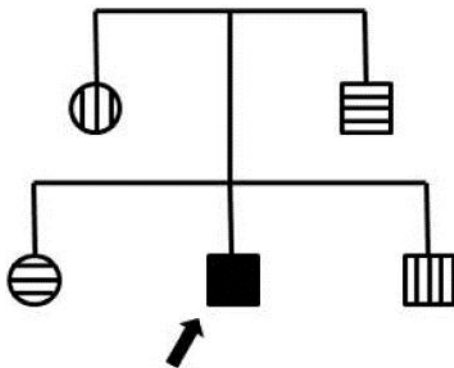


Fig. 1. Pedigree diagram. Circles = female gender; squares = male gender; black = compound heterozygote; horizontal lines = R463W heterozygote; vertical lines = V703I heterozygote. The arrow identifies the proband.

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