Hepatosteatosis with Hypobetalipoproteinemia

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Nonalcoholic fatty liver disease is increasingly recognized as a condition that may progress to chronic liver disease. Most cases of fatty liver are asymptomatic and often are detected during routine medical or laboratory examinations. There also are some rare genetic diseases such as abetalipoproteinemia and familial hypobetalipoproteinemia that may cause fatty liver disease. Both are inherited disorders of lipoprotein metabolism. Although abetalipoproteinemia and homozygous familial hypobetalipoproteinemia patients present with severe manifestations, heterozygotes are usually asymptomatic. In the last several years, case reports or studies indicating a relationship between hepatosteatosis and familial heterozygote hypobetalipoproteinemia (FHBL) have been reported. Here, we report three cases of FHBL with characteristic lipid profile, mildly elevated liver enzymes and hepatosteatosis confirmed by ultrasonography.

Key words: hypobetalipoproteinemia ■ apolipoprotein-B ■ hepatosteatosis ■ fatty liver

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INTRODUCTION

Fatty liver is defined as an accumulation of lipids in the liver that exceeds 5% of the liver weight or at visualization with >5% of hepatocytes containing fatty droplets at light microscopic examination.[1] It usually is associated with obesity, type-2 diabetes mellitus, hyperlipidemia, insulin resistance, hypertension, alcoholic hepatitis, autoimmune hepatitis, viral hepatitis and exposure to certain drugs or toxins.[2] Ultrasonography can detect the presence of fatty liver by means of increased echogenicity and sound attenuation with a sensitivity of 89% and a specificity of 93%.[3]

In the absence of common associations, some rare genetic disorders should be considered when fatty liver is suspected. These include abetalipoproteinemia and familial hypobetalipoproteinemia, both inherited disorders of lipoprotein metabolism that cause low cholesterol levels.[4] Familial hypobetalipoproteinemia is caused by an autosomal codominant mutation in the gene for apolipoprotein B (apo-B) and is characterized by very low apo-B concentrations in plasma and/or low levels of LDL cholesterol. Homozygous apo-B deficiency can present with fat malabsorption, fatty liver and progressive neurologic degenerative diseases, and retinitis pigmentosa; and acanthocytosis develops at a young age. Heterozygotes, however, are almost always asymptomatic. In several studies, it has been linked with fatty liver and elevated liver enzymes.[5-7]

Here, we present three adult patients with incidentally found fatty liver and low cholesterol levels in whom the diagnosis of familial heterozygous hypobetalipoproteinemia was made on the basis of characteristic lipid profiles.

CASE 1

A 44-year-old man with no other known diseases was referred our clinic because of low cholesterol levels and elevated liver transaminases. There was no drug or hepatotoxic chemical exposure. He rarely drank alcohol. On physical examination, his blood pressure was 130/80 mmHg and his body mass index (BMI) 24.7 kg/m^2. He told us his sister also had low cholesterol levels. Routine laboratory tests, including complete blood count, erythrocyte sedimentation rate, electrolytes, blood urea nitrogen, creatinine and thyroid function tests, were all within normal ranges (Table 1). He had low cholesterol, LDL and apolipoprotein-B levels, but elevated liver enzymes. His viral hepatitis markers were negative. Abdominal ultrasonography showed hepatosteatosis and hepatomegaly. With this lipid profile and increased liver enzymes with fat accumulation, the patient was diagnosed as familial heterozygous hypobetalipoproteinemia with hepatosteatosis.

CASE 2

A 34-year-old man referred to our clinic for thyroid nodule was found to have elevated aminotransferases. His physical examination was within normal limits, except for a BMI of 33.3 kg/m^2. Routine laboratory tests revealed elevated liver enzymes. Additional laboratory tests were all in normal ranges and negative for either

acute or chronic viral hepatitis. His lipid profile also was consistent with familial heterozygous hypobetalipoproteinemia. In abdominal ultrasonography, liver parenchyma was found to be diffusely hyperechogenic due to hepatosteatosis. We learned that his father was found to have cholesterol of 72 mg/dl, triglyceride 34 mg/dl, HDL 47 mg/dl, LDL 23 mg/dl and VLDL 6 mg/dl. This patient was believed to have familial heterozygous hypobetalipoproteinemia leading to hepatosteatosis. Obesity, however, may also have some additive effect on clinical presentation.

CASE 3

A 35-year-old male was found to have low LDL levels of 33 mg/dl during a routine examination. He had no history of acute or chronic disease. His blood pressure and BMI were 110/75 mmHg and 23.5 kg/m^2, respectively. He also had mild hepatomegaly. On laboratory evaluations, blood glucose was normal and liver enzymes were above normal ranges (Table 1). Like cases 1 and 2, he also had low cholesterol and LDL levels. Hepatosteatosis was confirmed by ultrasonography. After other secondary causes of hypobetalipoproteinemia were excluded, he was clinically diagnosed as heterozygous hypobetalipoproteinemia.

DISCUSSION

Apolipoprotein B is the major structural protein component of the triglyceride-rich very-low-density lipoproteins (VLDL) secreted from the liver and the chylomicrons secreted from the intestine.[8] The normal protein secreted from the liver as part of LDL particles is apo-B 100, which is the largest apolipoprotein, made of 4,536 amino acids. There are >30 mutations leading to abnormal truncations, some as short as apo-B 2 and others as long as apo-B 89. Short truncations of apo-B transport smaller numbers of triglyceride molecules than longer ones. Decreased levels of apo-B-containing lipoprotein in the plasma cause low plasma cholesterol and triglyceride levels.[4] Low rates of hepatic production of normal lipid and the impaired capacities of truncated forms to transport triglycerides from the liver, however, cause accumulation of triglycerides and other lipid components in the liver. Major clinical variants of these genetic defects are abetalipoproteinemia, familial homozygous hypobetalipoproteinemia and heterozygous hypobetalipoproteinemia.

Familial heterozygous hypobetalipoproteinemia affects approximately one in 500 people.[7] It is diagnosed by a characteristic lipid profile in the absence of malabsorption or a disease known to cause secondary hypobetalipoproteinemia.[5] Heterozygosity does not appear to be deleterious, resulting only in plasma levels of total cholesterol ranging from 40–180 mg/dl, average ~90 mg/dl. Levels of LDL are about 25–45 mg/dl or <50% of normal ranges. Apo-B levels are extremely low. In the homozygote state, cholesterol levels are usually less than half of normal, often 20–45 mg/dl and triglycerides only a few milligrams per deciliter.[4,7] Heterozygote individuals are usually asymptomatic. Rarely, fat malabsorption and mild neuromuscular manifestations have been reported. However, there is growing evidence that the hepatobiliary system is involved in familial heterozygous hypobetalipoproteinemia. In 1994, Wishingrad described an asymptomatic women with fatty liver and decreased levels of apolipoproteins.[7] Then the first report of fatty liver in familial heterozygous hypobetalipoproteinemia with a documented frameshift mutation in an apo-B gene was published in

Table 1. Some individual and laboratory characteristics of patients with normal values of our laboratory given in parenthesis

	Case 1	Case 2	Case 3
Age/sex	44/male	34/male	35/male
Body mass index (kg/m^2)	24.7	33.3	23.5
Blood pressure (mmHg)	130/80	120/80	110/75
Fasting plasma glucose (mg/dl)	101	97	86
Postprandial plasma glucose (mg/dl)	93	90	92
Total cholesterol (<200 mg/dl)	104	70	32
Triglyceride (<200 mg/dl)	103	36	158
LDL-cholesterol (<130 mg/dl)	46	21	43
HDL-cholesterol (35–150 mg/dl)	37	41	32
VLDL-cholesterol (<40 mg/dl)	20	7	32
Apolipoprotein-B (55–135 mg/dl)	46	31	28
ALT (5–40 U/L)	86	102	104
AST (8–33 U/L)	37	43	76
GGT (5–40 U/L)	33	38	41
ALP (91–258 U/L)	225	141	154
Bilirubin (0.1–1.2 mg/dl)	0.62	2.4	0.23
Family member with hypobetalipoproteinemia	Sister?	Father	No information

1996. In this report, the accumulation of lipids in the hepatocytes was believed to result from reduced ability of the truncated apo-B (apo-B 38.95) to recruit intracellular lipids in the assembly of lipoprotein particles.[6]

In human and animal studies, this truncation or other truncated forms of apolipoprotein B was found to be related to fatty liver.[9,10] Chen et al. generated genetically engineered mice carrying a truncated apo-B (apo-B-38.9/apo-B-100 mice) that display the familial heterozygous hypobetalipoproteinemia lipoprotein phenotype and show a fatty liver due to the reduced ability of apo-B-38.9 to transport triglycerides.[8] Tarugi showed that presence of a truncated form of apo-B (apo-B-54.5) acts as a predisposing factor for the development of fatty liver.[10]

The diagnosis of familial heterozygous hypobetalipoproteinemia in our three patients was based on the characteristic lipid profile in the absence of a secondary cause. All were clinically asymptomatic with low cholesterol, LDL cholesterol, apo-B levels and mildly elevated liver enzymes. Hepatosteatosis was detected by ultrasonography. None of the patients had apparent causes such as diabetes mellitus, hyperlipidemia, hypertension, excessive alcohol intake or drug use that could explain elevated liver enzymes and hepatosteatosis. They also had no signs and symptoms of malnutrition or malignancy in which lipid fractions may be decreased. As other causes of hepatosteatosis were ruled out, the primary factor leading to hepatosteatosis in all cases was believed to be familial heterozygous hypobetalipoproteinemia, although obesity may have contributed to the abnormal liver enzymes and hepatosteatosis in case 2. It is not clear why heterozygotes develop hepatosteatosis, but the presence of truncated apo-B—although much lower than homozygotes—and the low rate of production of apo-B 100 may contribute to fatty liver in these patients.[6] One of the criteria of diagnosing this disorder is detection of a similar pattern in a first-degree relative. Case 2 was the only patient in whom we have had the opportunity to evaluate a first-degree relative. His father also had low levels of cholesterol and LDL cholesterol. Case 1 reported that his sister also had a similar lipid profile, but we were unable to confirm that.

It is unfortunate that we were not able to show hepatosteatosis histologically because this is the gold standard for diagnosis. It can be argued that it is necessary to perform liver biopsy when all other causes are excluded by history, and laboratory tests when lipid profile is consistent with a benign disease like familial heterozygous hypobetalipoproteinemia.

Patients with abetalipoproteinemia and familial homozygous hypobetalipoproteinemia should be treated orally with large doses of vitamin E to prevent the development of neurologic complications. For heterozygotes, no specific treatment is indicated, but administration of moderate doses of vitamin E is recommended as neurologic involvement may occur rarely.[9] We gave no medication to our patients and, unfortunately, we have no follow-up data. Familial heterozygous hypobetalipoproteinemia is believed to be associated with normal longevity. The prognosis for liver involvement appears to be excellent; however, periodical clinical and laboratory examination may be recommended until further studies are performed. Heterozygotes also should have genetic counseling.

In conclusion, we suggest that familial hypobetalipoproteinemia should be considered one of the rare causes of hepatosteatosis, and a lipid profile should be assessed while evaluating a patient with hepatosteatosis.

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