Hepatosteatosis may reveal heterozygous familial hypobetalipoproteinemia

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ABSTRACT: We report an interesting case of heterozygous familial hypobetalipoproteinemia (FHBL) in a 22-year-old asymptomatic man with mild hepatosteatosis and hypocholesterolemia. This diagnosis was made based mainly on his characteristic lipid profile in the absence of a secondary cause and family history. Liver function tests were all within normal ranges. Other primary and secondary causes of hypobetalipoproteinemia and hepatosteatosis were excluded. Fasting lipid profile and liver ultrasonography of relatives revealed the presence of unknown heterozygous FHBL in his father, paternal grandfather, and youngest sister.

Key words: Abetalipoproteinemia, fatty liver, hepatosteatosis, hypobetalipoproteinemia, hypocholesterolemia.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) may range from simple hepatic steatosis (fat accumulation in hepatocytes) without significant concomitant inflammation or fibrosis to steatohepatitis with varying degrees of inflammation and fibrosis.1 By definition, NAFLD occurs in patients with little or no history of alcohol consumption. The most commonly reported risk factors associated with NAFLD are central obesity, type 2 diabetes mellitus (DM), dyslipidemia (mainly hypertriglyceridermia), metabolic syndrome, viral hepatitis, and exposure to certain drugs (such as amiodarone, methotrexate, corticosteroids, estrogens) or toxins.2,3 Other factors associated with NAFLD are metabolic (hypothyroidism, galactosemia, glycogen storage diseases, homocystinuria, tyrosemia) or nutritional (severe malnutrition, total parenteral nutrition, starvation diet) abnormalities, genetic disorders of lipoprotein metabolism [a. abetalipoproteinemia (ABL) caused by mutations in the microsomal triglyceride transfer protein (MTP) gene, and b. familial hypobetalipoproteinemia (FHBL) caused by a mutation in the apolipoprotein (apo) B gene], or other health problems (autoimmune hepatitis, Wilson’s disease, celiac sprue).2–4

Herein, we describe a case of heterozygous FHBL in a 22-year-old man with NAFLD and hypocholesterolemia.
2. Case report

A 22-year-old, asymptomatic male, was found to have hepatosteatosis in an abdominal ultrasound scan performed due to a mild right upper quadrant abdominal pain. He had no history of acute or chronic disease, alcohol consumption or drug use. On physical examination, his blood pressure was 120/70 mmHg and his body mass index (BMI) 23 kg/m². Laboratory tests including complete blood count, blood smear, erythrocyte sedimentation rate, C-reactive protein, coagulation panel (prothrombin time, partial thromboplastin time), renal, thyroid, and liver function tests (LFTs) (table 1) were all within normal ranges. Stool studies for ova, parasites, and white blood cells, in order to exclude some causes of fat malabsorption, were negative. Fasting lipid profile revealed hypocholesterolemia with low apolipoprotein (apo) B levels (table 1). Hepatosteatosis was confirmed by new ultrasound scan. Serological tests (including those for hepatitis B and C viruses), indirect immunofluorescence tests for antimitochondrial antibodies, antinuclear, anti-smooth muscle cell and anti-liver-kidney microsomal of type 1 antibodies were negative. Serum copper, ceruloplasmin, alpha 1-antitrypsin, vitamin E and iron studies (iron concentration, transferrin saturation, ferritin) were within reference values. His cardiorespiratory, neurological, and ophthalmic examinations were normal. Fasting lipid profile determination and abdominal ultrasonography showed hypocholesterolemia with fatty liver in his father, paternal grandfather, and youngest sister, while these were normal in his mother. As secondary causes of hypobetalipoproteinemia were excluded, our patient was diagnosed as heterozygote for FHBL. Liver biopsy and molecular study were not performed. Genetic counselling and the need for periodic monitoring and a diet with low to moderate amounts of fat and energy and restricted use of alcohol, were recommended to our patient.

3. Discussion

FHBL is a rare autosomal dominant disorder of lipoprotein metabolism characterized by low plasma concentrations of apoB.4–6 The prevalence in the general population varies from 0.1% to 1.9%.6 FHBL subjects are characterized by low levels of apoB containing proatherogenic lipoproteins from birth onwards.6 More than 50 mutations in the apoB gene leading to FHBL have been reported, most of which encode for a truncated apoB molecule.5–7 However, a large proportion of FHBL subjects have no apoB gene mutations or are carriers of rare amino acid substitutions in apoB with unknown effect.8–10 Heterozygotes for FHBL have apoB concentrations approximately one third of normal, are almost always asymptomatic and diagnosed accidentally. Homozygotes may have barely detectable apoB, NAFLD, and clinical manifestations resulting from deficiency of fat-soluble vitamin E (e.g. atypical retinitis pigmentosa and progressive neuromuscular abnormalities).4,5,7,9 Heterozygous FHBL affects approximately 1 in 500 people.11

In our case, the differential diagnosis included primary and secondary causes of hypcholesterolemia with low apoB levels and hepatic steatosis. Homozygous ABL and homozygous FHBL were excluded based on his clinical presentation, laboratory examinations, and family history.3 ABL is a rare autosomal recessive disease due to a variety of genetic defects in MTP resulting in defective processing of the apoB-containing lipoproteins. Homozygotes have extremely low plasma TC (<50 mg/L) and TG levels, and fat-soluble vitamins (A, D, E, K) deficiencies, with a characteristic marked decrease in vitamin E.12,13 On the contrary, heterozygotes for ABL have normal cholesterol levels. Homozygous ABL phenotypic expression is essentially the same as that for homozygous FHBL; the malabsorption of dietary fat and liposoluble vitamins produce severe sequelae in infancy and childhood, such as “failure to thrive”, anemia, acanthocytosis, ataxia, and retinitis pigmentosa.4,5,12,13 In contrast, heterozygotes for ABL or FHBL are generally asymptomatic. Differential diagnosis between homozygous ABL and homozygous or heterozygous FHBL can be based on parental lipid profile. Heterozygotes for FHBL (which is a dominant condition) have half the normal levels of the apoB-containing lipoproteins with TC ranging from 40–180 mg/dL, while heterozygous parents of ABL homozygotes (which is a recessive disorder) exhibit normal plasma cholesterol. Compound heterozygotes (as patients with mutations of the apoB

<table>
<thead>
<tr>
<th>Table 1. Subject biochemical results.</th>
<th>Values</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>34 U/L</td>
<td>5–40 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>29 U/L</td>
<td>5–40 U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>26 U/L</td>
<td>10–75 U/L</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>0.9 mg/dL</td>
<td>0.5–1.8 mg/dL</td>
</tr>
<tr>
<td>TC</td>
<td>102 mg/dL</td>
<td>&lt;200 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>38 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>23 mg/dL</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>apoB</td>
<td>29 mg/dL</td>
<td>46–164 mg/dL</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: γ-glutamyl transpeptidase, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, apoB: apolipoprotein B
gene at 2 different sites) may present with signs and symptoms of neurologic involvement.\(^{12}\)

Secondary causes of low apoB or/and low cholesterol levels, such as strict vegetarian diet, severe liver diseases (as autoimmune hepatitis, alcoholism, hepatits B and C, chronic cholestatic liver disease, etc), intestinal fat malabsorption (as chronic pancreatitis, celiac sprue, etc), malnutrition, malignancy, hyperthyroidism and medications affecting lipid metabolism,\(^{4,5,11,14}\) were also excluded. Mipomersen, an apoB-100 synthesis inhibitor, has been shown to decrease apoB containing lipoproteins in patients at increased risk of cardiovascular disease who are not at target or are intolerant of statins. Although the short-term efficacy and safety of mipomersen has been established, concern exists regarding the long-term potential for hepatic steatosis.\(^{15}\)

The mild fatty liver infiltration in a patient with normal BMI and negative history of DM, hepatitis or alcohol consumption urged his further evaluation. The presence of fatty liver in our case was detected only by ultrasonography. Liver biopsy was considered unnecessary, because of LFTs normal values and biopsy-related risks (e.g. excessive hemorrhage, infection or even death). In contrast to homozygous FHBL and ABL, elevated serum transaminases with hepatomegaly due to NAFLD are unusual in heterozygotes for FHBL.\(^{5,12,13}\) In 1994, Wishingrad described an asymptomatic woman with fatty liver and decreased levels of apolipoproteins.\(^{16}\) The first report of fatty liver in heterozygous FHBL with a documented frame shift mutation in an apoB gene was published in 1996.\(^{17}\) In this report, the accumulation of lipids in the hepatocytes was believed to result from reduced ability of the truncated apoB 38.95 to export lipids from hepatocytes into the blood stream.\(^{17}\) Since then several cases reports of heterozygous FHBL with fatty liver have been reported.\(^{3,7,9,11,18–22}\) FHBL individuals with a variety of truncated apoB proteins have liver fat content three times higher than unaffected controls.\(^{3,24}\) Although it is not clear why heterozygotes develop NAFLD, the presence of truncated apoB –much lower than homozygotes– and the low rate of production of apoB 100 may contribute to fatty liver in these patients.\(^{5,8,11,17,23}\) FHBL individuals appear more susceptible to the effects of adiposity and insulin resistance.\(^{9,24}\) The long-term impact of fatty liver in FHBL is unknown. As the progression of fatty liver to non-alcoholic steatohepatitis (NASH) and cirrhosis is possible,\(^{1,2}\) it is prudent to recommend a diet with low to moderate amounts of fat and energy and limited use of alcohol, in these individuals. Although the LFTs were normal and the AST/ALT ratio (as a marker for the risk of disease progression) was <1, in our patient,\(^{26}\) the absence of liver enzyme elevations does not completely preclude advanced fibrosis or cirrhosis in these subjects.\(^{1}\) Therefore, a liver biopsy may be required in our patient in the future. Moreover, a number of tools are currently available or in development for the non-invasive assessment of hepatic fibrosis in NAFLD (cross-sectional imaging studies, liver stiffness, direct and indirect serum bio-markers, etc).\(^{27,28}\)

Our patient was diagnosed as heterozygote for FHBL based mainly on his clinical picture, characteristic lipid profile (in the absence of a secondary cause) and family history. The investigation of a mutation in the apoB gene was not necessary for the diagnosis.\(^{11,20}\) No specific medication was administered as his neurological examination was normal and heterozygotes for FHBL in his family had not shown any sign of neurological disorder. Modest doses of vitamin E (alpha tocopherol) are recommended to protect FHBL heterozygotes from neurological complications.\(^{11}\) Also, vitamin E could be beneficial for these patients with hepatosteatosis.\(^{29}\) Vitamin E administration protects cell membranes from attack by free radicals and prevents red blood cells from hemolysis. Although the long-term effects of heterozygous FHBL for health and longevity are unknown, a screening clinical and laboratory examination of an homozygote’s asymptomatic kindred may be useful.

In conclusion, physicians should be aware of this rare disorder of lipoprotein metabolism in asymptomatic patients with hepatic steatosis; a lipid profile should be assessed while evaluating a patient with hepatosteatosis.

References

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