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Case Report

# Hypolipidemia due to Familial Hypobetalipoproteinemia in Adolescents

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ABSTRACT

*Background/Objective:* Individuals with heterozygous familial hypobetalipoproteinemia (h-FHBL) due to loss-of-function mutation in the apolipoprotein B gene are typically asymptomatic with mild liver dysfunction, which is often detected incidentally. About 5% to 10% of those with h-FHBL develop steatohepatitis which occasionally progress to cirrhosis especially in the presence of alcohol use, excess calorie consumption, or liver injury. We report 3 patients with hypobetalipoproteinemia, 2 with confirmed h-FHBL, and 1 with suspected h-FHBL.

*Case Report:* Three asymptomatic adolescents presented with low lipid levels detected on screening laboratory studies. Patient 1, a 13 $^{6}/_{12}$-year-old male and patient 2, a 15 $^{9}/_{12}$-year-old female, were siblings. Patient 3 was a 12 $^{6}/_{12}$-year-old female. All had total cholesterol ranging from 61 to 87 mg/dL, low-density lipoprotein cholesterol 10 to 28 mg/dL, and triglycerides 19 to 36 mg/dL. Aspartate transaminase and alanine transaminase levels were normal in patients 1 and 3 and were elevated in patient 2. Liver ultrasounds of patients 2 and 3 showed hepatic steatosis. Molecular testing identified pathogenic variant of apolipoprotein B gene in patients 1 and 2, c.133C>T(p.Arg.45Ter) confirming the diagnosis of h-FHBL.

*Discussion:* More studies are needed in children with h-FHBL and other forms of hypobetalipoproteinemia to improve awareness of these disorders and to develop guidelines for monitoring and risk reduction in affected patients.

*Conclusion:* Health care providers should be aware that persistent hypolipidemia may indicate h-FHBL, which can be a risk factor for liver dysfunction. Youth with h-FHBL should be counseled about lifestyle modifications and screened for the development of metabolic dysfunction–associated steatotic liver disease.



## Introduction

Hypobetalipoproteinemia characterized by low plasma lipoproteins can be due to primary (genetic/familial) or secondary causes.[1,2] Secondary causes of hypobetalipoproteinemia include anemia, chronic illness, hepatitis C infection, malignancy, and hyperthyroidism.[1] Familial hypobetalipoproteinemias (FHBL) are monogenic disorders which are further classified into: (1) class I FHBL disorders due to **s**ecretion **d**efects (FHBL-SD) in apolipoprotein B (APO B) containing lipoproteins and (2) class II FHBL disorders due to **e**nhanced **c**atabolism (FHBL-EC) of lipoproteins.[2] FHBL-SD disorders are further subdivided to include: 1) FHBL-SD1 (abetalipoproteinemia), an autosomal recessive disorder due to biallelic loss-of-function variant of microsomal triglyceride transfer protein gene, 2) FHBL-SD2 (FHBL) due to autosomal semidominant mutation in *APOB* gene with biallelic (homozygous FHBL) and monoallelic (heterozygous familial hypobetalipoproteinemia [h-FHBL]) forms, and 3) FHBL-SD3 (chylomicron retention disease), an autosomal recessive disorder due to biallelic loss of function in the *SARB1* (secretion associated Ras related GTPase 1B) gene. FHBL-EC

*Abbreviations:* ALT, alanine transaminase; APO B, apolipoprotein B; AST, aspartate transaminase; FH, family history; FHBL, familial hypobetalipoproteinemia; FHBL-EC, FHBL disorders due to enhanced catabolism; FHBL-SD, FHBL disorders due to secretion defects; h-FHBL, heterozygous familial hypobetalipoproteinemia; LDL-C, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction–associated steatotic liver disease; PCSK9, proprotein convertase subtilisin/kexin type 9; SAR B1, secretion associated Ras related GTPase 1B; TC, total cholesterol; VLDL, very low-density lipoprotein.

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disorders are further subdivided into: 1) FHBL-EC1, an autosomal semidominant disorder due to loss-of-function variants in the *ANGPTL3* (angiopoietin-like protein 3) gene and 2) FHBL-EC2, an autosomal semidominant disorder due to loss-of-function variants in the *PCSK9* (proprotein convertase subtilisin/kexin type 9) gene.[2]

Compared to other FHBL-SD disorders that are characterized by fat malabsorption, hepatic steatosis, failure to thrive in infancy and early ophthalmologic and neurologic abnormalities, individuals with h-FHBL are often asymptomatic with mild liver dysfunction.[2] The prevalence of h-FHBL is estimated to be 1:1000 to 1:3000.[3] These patients can have elevations in liver transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]) and low total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels that are often detected incidentally.[2,4] In some patients with h-FHBL, liver dysfunction can progress from hepatic steatosis to steatohepatitis and cirrhosis in the presence of other risk factors for liver disease, such as alcohol use, obesity, or liver injury.[4] We describe 3 adolescents with hypobetalipoproteinemia: siblings with confirmed h-FHBL and an unrelated patient with suspected h-FHBL. One of the adolescents had elevated liver enzymes and 2 of them had hepatic steatosis identified by ultrasound liver.

### Highlights

- We describe 3 youth with heterozygous familial hypobetalipoproteinemia (h-FHBL).
- Asymptomatic patients with persistent hypolipidemia should be evaluated for h-FHBL.
- Patients with h-FHBL should be screened for liver dysfunction.

### Clinical Relevance

Health care providers should be aware that persistent hypolipidemia may indicate heterozygous familial hypobetalipoproteinemia (h-FHBL), which can be a risk factor for liver dysfunction. Youth with h-FHBL should be counseled about lifestyle modifications and screened and monitored for the development of metabolic dysfunction–associated steatotic liver disease.

## Case Report

Three asymptomatic adolescents without a history of consanguinity presented with low levels of TC, LDL-C, and triglycerides, with normal high-density lipoprotein cholesterol. All had fasting lipid panels obtained as part of laboratory studies for the evaluation of overweight/obesity (Table 1). Patients 1 and 2 were siblings; their mother reported that she had similarly low lipid concentrations. Patient 3 was an adolescent girl and information on family history (FH) of lipid disorders was not available. All had normal growth and development. None had a history of anemia, abnormal thyroid function, chronic illnesses, or malignancy and none were taking chronic medication. FHs were negative for metabolic

**Table 1**
Clinical and Laboratory Parameters of Patients at Diagnosis

| Clinical parameters (ref range) | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age at diagnosis | 13 y 10 mo. | 15 y 9 mo. | 12 y 6 mo. |
| Sex | Male | Female | Female |
| Ethnicity | Hispanic | Hispanic | Cape Verdean |
| Weight in kg (percentile) | 69.5 (94%ile) | 68.7 (89%ile) | 103.3 (99.88%ile) |
| BMI kg/m$^2$ (percentile) | 23.82 (90%ile) | 27.84 (94%ile) | 39.9 (99.96%ile) |
| Symptoms | None | None | None |
| Indication for testing | Screening labs for overweight | Screening labs for overweight | Screening labs for obesity |
| Total cholesterol (110-169 mg/dL) | 86 | 77 | 61 |
| LDL-C, measured by quantitative enzymatic assay (70-109 mg/dL) | 10 | 10 | 28 |
| LDL-C estimated using the Martin/Hopkins method[5] (mg/dL) | 8.6 | 4.3 | 17.7 |
| HDL-C (45-70 mg/dL) | 72 | 67 | 33 |
| Triglycerides(30-89 mg/dL) | 19 | 20 | 36 |
| Non-HDL cholesterol (70-119 mg/dL) | 14 | 10 | 28 |
| AST | 24 (13-38 IU/L) | 48 (14-37 IU/L) | 19 (14-37 IU/L) |
| ALT | 25 (8-36 IU/L) | 64 (8-29 IU/L) | 20 (8-29 IU/L) |
| Hemoglobin (11.4-15.4 g/dL) | 14 | 12.2 | 13 |
| TSH (0.35-5.5 uIU/mL) | 2.6 | 1.103 | 2.667 |
| HBsAG | Nonreactive | … | … |
| HCV antibody | Nonreactive | … | … |
| HAV IgM antibody | Nonreactive | … | … |
| HBV core IgM antibody | Nonreactive | … | … |
| Ultrasound liver | Normal | Hepatic steatosis | Hepatic steatosis |
| Molecular testing | Heterozygous pathogenic variant in the *APOB* gene APOB c.133 C>T(p.Arg45Ter) stop_gain | Heterozygous pathogenic variant in the *APOB* gene APOB c.133 C>T(p.Arg45Ter) stop_gain | … |
| Family history | Mother and sister (patient 2) with h-FHBL | Mother and brother (patient 1) with h-FHBL | Not available |

Abbreviations: ALT = alanine transaminase; APOB = apolipoprotein B; AST = aspartate transaminase; BMI = body mass index; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; h-FHBL = heterozygous familial hypobetalipoproteinemia; IgM = immunoglobulin M; LDL-C = low-density lipoprotein cholesterol; TSH = thyroid stimulating hormone.

dysfunction–associated steatotic liver disease (MASLD) or cirrhosis. Examination revealed acanthosis nigricans in patients 2 and 3, elevated blood pressure in patient 1(127/78 mm of Hg) and hypertension in patient 3(148/78 mm Hg). None had hepatomegaly. AST and ALT were elevated in patient 2 (Table 1). Patient 3 was diagnosed with type 2 diabetes based upon a hemoglobin A1c of 7% with negative pancreatic autoantibodies. Patients 1 and 2 were referred to pediatric gastroenterology and hepatic steatosis was identified on ultrasound liver in patient 2. Liver ultrasound, done as part of the work up for obesity in patient 3, showed hepatic steatosis. Patients 1 and 2 had low fat-soluble vitamin concentrations: vitamin D 16.8 ng/mL and 12.7 ng/mL respectively (reference range 30-100[6]), vitamin E (alpha tocopherol) 4.7 mg/L and 4.5 mg/dL (reference range 5.5-18[7]), and vitamin A (serum retinol) 14.56 μg/dL and 8.96 μg/dL (reference range 26-70[8]). Molecular testing demonstrated a loss-of-function mutation of *APOB* gene (c.133C>T [p.Arg.45Ter]) in patients 1 and 2 (and their mother) confirming a diagnosis of h-FHBL. Patient 3 has not had genetic testing performed or testing of vitamin concentrations to date; plans are to obtain these in the future.

## Discussion

We describe 2 asymptomatic adolescent siblings who, along with their mother, were diagnosed with h-FHBL, and a third unrelated, asymptomatic adolescent with hypobetalipoproteinemia suggestive of h-FHBL.

Lipoproteins that transport lipids in circulation are crucial for the absorption, transport, and delivery of fat-soluble vitamins to peripheral tissues. Enterocytes secrete chylomicrons that transport dietary fat and fat-soluble vitamins while hepatocytes produce very low-density lipoproteins (VLDL) that transport endogenous lipids to extrahepatic tissues. Assembly of these particles depends on APO B that functions as a scaffold for lipoprotein integrity. The *APOB* gene is transcribed and translated into APO B100 in the liver and into APO B48 via ribonucleic acid editing in enterocytes.[2]

Loss-of-function mutation in the *APOB* gene can result in FHBL-SD2.[2] Frameshift or nonsense mutation or splicing variant of the *APOB* gene results in the synthesis of truncated forms of APO B protein, mostly liver derived APO B100 isoforms and rarely intestine derived APO B48 isoforms.[2,9] The mode of inheritance of FHBL-SD2 is often described as autosomal semidominant or codominant meaning that phenotype of individuals with h-FHBL (1 normal allele and 1 variant allele) is intermediate between those with 2 normal alleles and those with biallelic pathogenic variants (homozygous FHBL). Also, the severity of h-FHBL is inversely proportional to length of the variant APO B protein formed: the longer the peptide, the milder the phenotype.[2,9] Patients 1 and 2 (and their mother) carried a mutation of *APOB* gene (c.133C>T[p.Arg.45Ter]) that caused premature termination of the protein, resulting in a truncated protein. Genetic diagnosis was not available for patient 3, though her clinical picture of low TC, LDL-C, and triglycerides without symptoms and in the absence of secondary causes of hypobetalipoproteinemia and hepatic steatosis are suggestive of h-FHBL.

In contrast to other FHBL-SD disorders which involve development of fat malabsorption, steatorrhea, failure to thrive in infancy, and neurologic and ophthalmologic abnormalities, individuals with h-FHBL are usually asymptomatic.[2,4,9] FH may reveal asymptomatic hepatic steatosis and/or hypolipoproteinemia in first degree relatives. However, lack of positive FH does not rule out a diagnosis of h-FHBL.[4]

Laboratory findings of individuals with h-FHBL include plasma TC, LDL-C, and APO B levels below the fifth percentile for age and sex, and triglycerides <45 mg/dL.[10] TC levels are typically in the range of 106.3 ± 24 mg/dL and LDL-C 40.6 ± 16.6 mg/dL in patients with h-FHBL.[2] Deficient VLDL export and limited enterocyte synthesis of chylomicrons lead to reduced triglyceride levels. Since LDL-C is a catabolic product of VLDL, LDL-C levels are low.[10,11] Decreased secretion of APO B results in reduced hepatic VLDL export, which can lead to hepatic steatosis in individuals with h-FHBL explaining the elevated AST and ALT often detected in these patients.[2,4] Compared to the general population, individuals with h-FHBL have a 3- to 5-fold increase in hepatic fat content.[4]

Other laboratory parameters that help to distinguish h-FHBL from homozygous FHBL, FHBL-SD1, and FHBL-SD3 include acanthocytes and creatinine kinase. Acanthocytes, which are abnormally shaped red blood cells due to changes in the lipid composition and fluidity of the red cell membrane, are a salient feature in patients with FHBL-SD1 and homozygous FHBL. Elevation in creatinine kinase is noted in patients with FHBL-SD3. None of these features have been reported in h-FHBL.[2] Molecular genetic testing showing a heterozygous pathogenic variant in *APOB* gene confirms the diagnosis as h-FHBL.[4]

About 5% to 10% of patients with h-FHBL develop steatohepatitis, which can progress to fibrosis and cirrhosis especially in the presence of risk factors for liver disease including alcohol use, excess calorie consumption, and liver injury.[3] At the same time, lifelong reductions in serum LDL-C levels are protective against atherosclerotic cardiovascular disease in individuals with h-FHBL.[2,4,12]

A study by Mouzaki et al observed that h-FHBL is common among patients with MASLD. In this study of 740 children with overweight/obesity with presumed or confirmed MASLD, hypobetalipoproteinemia suggestive of h-FHBL was found in ~8% of patients. The patients with clinical findings of hypobetalipoproteinemia had significantly lower body mass index, truncal adiposity, and triglyceride levels and were less likely to require metformin for type 2 diabetes compared to those without hypobetalipoproteinemia. Despite the favorable anthropometry and metabolic profiles, these patients had increased steatosis severity.[11]

No dietary restrictions or specific treatments are commonly needed for those with h-FHBL. Supplementation may be considered with low fat-soluble vitamin levels at doses close to the recommended daily allowances.[9] Current recommendations are to monitor individuals with h-FHBL with annual lipid profiles and hepatic panels. Liver ultrasound is recommended every 3 years starting at 10 years of age in those with elevated liver transaminases.[4] Patient 3 had normal liver enzymes, and her liver ultrasound showed hepatic steatosis, indicating that transaminases may not be elevated in those with hepatic steatosis. More longitudinal studies are needed in children with h-FHBL and other forms of hypobetalipoproteinemia to improve awareness of these disorders and to develop guidelines for monitoring and risk reduction in affected patients.

## Conclusion

Owing to the risk of hypercholesterolemia in the development of cardiovascular disease, low lipids are often regarded as insignificant. However, consistent finding of extremely low lipids may indicate a lipid disorder which may be associated with other complications. Asymptomatic patients with persistent hypolipidemia should be evaluated for h-FHBL; those with h-FHBL should be counseled about lifestyle modifications to reduce risk of liver disease and screened for the development of MASLD.

## Disclosure

The authors have no conflicts of interest to disclose.

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