CASE DESCRIPTION

A 54-year-old asymptomatic man with a 5-year history of type 2 diabetes mellitus (T2DM) was found to have an extremely low serum cholesterol concentration. He had no history of major childhood illness, malabsorption, or any cardiovascular or neurologic dysfunction. He had smoked for 30 years and was not using alcohol or any lipid-lowering drugs. Additionally, he was not a vegetarian. His family history included stroke (father died at age 52 years) and chronic kidney disease (57-year-old brother). His eldest son had died of a suspected myocardial infarction at the age of 21 years. The patient had a blood pressure of 120/80 mmHg, a heart rate of 78 beats/min, and a body mass index of 32 kg/m². The results of a physical examination were normal. Hepatic steatosis and mild hepatomegaly were observed via abdominal ultrasonography. A transthoracic echocardiogram was normal, and the results of a treadmill exercise test (Bruce protocol) were negative.

Laboratory studies were performed. Serum concentrations of liver enzymes, results of thyroid function tests, and values of hematology parameters were all normal, as were those for serum bilirubin, creatinine, urea nitrogen, uric acid, and calcium. The fasting serum glucose concentration was increased [155 mg/dL (8.6 mmol/L); reference interval, 60–110 mg/dL (3.33–6.11 mmol/L)], and the patient’s hemoglobin A₁c value was 7% (reference interval, 4%–6%). The laboratory results for serum lipids, lipoproteins, apolipoproteins, proteins, immunoglobulins, and fat-soluble vitamins and provitamins are shown in Table 1. Of note, the serum concentrations of total cholesterol (TC), triglycerides, LDL cholesterol (LDL-C), and apolipoprotein B (apo B) were all markedly decreased. The serum concentrations of total protein and globulin were both high. The results of serologic tests for hepatitis A, B, and C viruses and HIV were negative.

DISCUSSION

OVERVIEW OF HYPOBETALIPOPROTEINEMIA

Hypobetalipoproteinemia (HBL) is defined by plasma concentrations of TC, LDL-C, or apo B that are lower than the fifth percentile. Primary HBL includes a group of genetic disorders: abetalipoproteinemia (ABL), chylomicron retention disease (CMRD), and familial HBL (FHBL). ABL, a condition usually diagnosed early in life, features steatorrhea, oral fat intolerance, acanthocytosis, retinitis pigmentosa, and neurologic abnormalities. The plasma lipid profile of ABL patients is characterized by extremely low plasma TC, VLDL, and LDL concentrations, and an almost complete absence of apo B. CMRD is characterized by the absence of apo B-48 in plasma. Steatorrhea, malnutrition, and growth retardation are the main clinical manifestations of CMRD. Because hepatic apo B synthesis is maintained, LDLs are present in the plasma. FHBL is a codominant disorder with a frequency...
in the heterozygous form of 1 in 500 to 1 in 1000. FHBL heterozygotes are often symptom free but may also present with nonalcoholic fatty liver disease and a mild increase in the serum concentrations of liver enzymes. FHBL homozygotes may experience severe fat malabsorption and show severe clinical and biochemical manifestations similar to those of ABL. Interestingly, plasma apo B concentrations are lower than expected for the deficiency of only 1 gene, as was the case here. Approximately 50% of FHBL patients are carriers of pathogenic mutations in the APOB [apolipoprotein B (including Ag(x) antigen)] gene. Most APOB mutations cause the formation of truncated apo B forms, which have reduced capacity to export lipids from the hepatocytes as lipoprotein constituents. Truncated apo B forms with a size smaller than apo B-30 are not detectable in plasma because they are rapidly cleared. Detectable truncated forms appear to be more frequent in patients with moderate HBL, because long truncated apo B molecules maintain a residual lipid-binding capacity to form lipoprotein particles. Truncated apo B molecules shorter than apo B-70.5 are cleared from the plasma mostly by the kidney, whereas truncated apo B molecules with a size $\geq 70\%$ of that of apo B-100 are removed by the liver (1, 2).

HBL can also be caused by several nongenetic factors, such as a strict vegetarian diet, malnutrition, drugs, and disease-related conditions. These factors are regarded as secondary causes of HBL. Because the liver plays a key role in the metabolism of most plasma lipoproteins and apolipoproteins, alterations in plasma lipid patterns can be observed in conditions characterized by hepatic cellular damage, such as infections by hepatitis B and C viruses, cirrhosis, or hepatocellular carcinoma. Chronic parenchymal liver diseases (including hepatocellular carcinoma) lead to a decrease in plasma cholesterol by impairing the synthesis and metabolism of cholesterol. Moreover, increased consumption of cholesterol by tumor cells plays a role in reducing serum cholesterol in hepatocellular carcinoma (3). Advanced stages of HIV infection are characterized by reduced TC, HDL-C, and LDL-C concentrations and increased triglyceride concentrations in the plasma (4). Enhanced cholesterol excretion and an increased LDL turnover are believed to be responsible for the hypcholesterolemia seen in hypothyroidism (5). Malnutrition and inflammation are thought to be responsible for the hypcholesterolemia observed in chronic hemodialysis patients (6).

FURTHER ANALYSIS OF LOW LDL-C AND apo B Secondary hyperlipoproteinemia with increased VLDL-C concentrations and decreased HDL-C concentrations usually accompany T2DM. Noteworthy

| Table 1. Selected patient laboratory results with corresponding reference intervals. |
|--------------------------------|-----------------|-----------------|
| Variable                    | Result          | Reference interval |
| Lipids, lipoproteins, and apolipoproteins |                  |                  |
| TC, mg/dL (mmol/L)          | 70 (1.81)       | $<200$ (5.18) |
| TG, mg/dL (mmol/L)          | 22 (0.25)       | $<150$ (1.69) |
| LDL-C, mg/dL (mmol/L)       | 10 (0.26)       | $<100$ (2.59) |
| HDL-C, mg/dL (mmol/L)       | 56 (1.45)       | $\geq 60$ (1.55) |
| apo A-1, mg/dL (g/L)        | 106 (1.06)      | 104–202 (1.04–2.02) |
| apo B, mg/dL (g/L)          | $<20$ (<0.2)    | 66–133 (0.66–1.33) |
| Serum proteins and immunoglobulins |                |                  |
| Total Protein, g/dL (g/L)   | 8.6 (86)        | 6.4–8.3 (64–83) |
| Albumin, g/dL (g/L)         | 4.2 (42)        | 3.5–5.2 (35–52) |
| Globulin, g/dL (g/L)        | 4.4 (44)        | 2.5–3.5 (25–35) |
| $\beta_2$-Microglobulin, mg/L (nmol/L) | 1.5 (127) | 0.96–2.16 (81–183) |
| IgA, mg/dL (g/L)            | 2300 (23)       | 57–543 (0.57–5.43) |
| IgG, mg/dL (g/L)            | 696 (6.96)      | 700–1600 (7.00–16.00) |
| IgM, mg/dL (g/L)            | $<25$ (<0.25)   | 40–230 (0.4–2.3) |
| Fat-soluble vitamins and provitamins |            |                  |
| Vitamin E, mg/dL ($\mu$mol/L) | 0.52 (12.1)  | 0.60–1.80 (13.9–41.8) |
| $\beta$-Carotene, $\mu$g/dL ($\mu$mol/L) | 7.2 (0.13)   | 10–80 (0.19–1.50) |

* TG, triglycerides.  
* Desirable value is indicated in parentheses.  
* Optimal value is indicated in parentheses.
was that despite the presence of T2DM, our patient had very low lipid concentrations in the serum. When the patient was questioned further, he remembered that he had previously had low cholesterol concentrations (data not available). To rule out interference in the measurement, we analyzed the reaction kinetics of the lipid parameters that had been measured with the Roche Modular system and commercial kits. The reaction curves were normal, and the patient’s data met all the biochemical criteria for an HBL diagnosis.

In the differential diagnosis, secondary causes of HBL were excluded first. The patient was not a vegetarian and not using any lipid-lowering drugs. Furthermore, he had no signs, symptoms, or laboratory findings of any disease that could be associated with secondary HBL. Therefore, the patient’s disease was diagnosed phenotypically as primary HBL.

ABL, CMRD, and homozygous FHBL are associated with a severe clinical phenotype, notably in children and young adults (2). Our patient, however, showed no evidence of malabsorption, retinitis pigmentosa, or neurologic disease, and there was no evidence of acanthocytes. The mild clinical phenotype strongly suggested the clinical diagnosis of heterozygous FHBL. Given that the patient’s family history included a sudden death of a son at a young age and that heterozygous FHBL carriers of short truncated forms might be at risk of developing more-severe liver disease in the presence of other factors that can cause liver injury, we confirmed our diagnosis through molecular diagnosis by identifying the mutation in the APOB gene. Sequence analysis of the APOB gene showed the presence of a single-nucleotide substitution in exon 26 (c.7692C>T) in the heterozygous state. This substitution converts the arginine codon at position 2495 into a termination codon (p.R2495X), leading to the formation of a truncated apo B containing 2494 amino acid residues (instead of the 4536 residues in the full-length apo B protein). This truncated apo B, designated apo B-55 according to the accepted nomenclature, had previously been described in FHBL (7, 8).

FHBL, T2DM, AND CARDIOVASCULAR DISEASE
Cardiovascular disease is a well-known severe complication of T2DM. Prospective results from the Bruneck Study showed that T2DM is a strong independent predictor of advanced carotid atherosclerosis (9). The use of the thickness of the carotid intima-media as a surrogate marker of cardiovascular disease has been applied in several trials that have investigated T2DM patients. Although our patient had several cardiovascular risk factors, he did not manifest any macrovascular complications. Additionally, his carotid intima-media thickness (0.53–0.58 mm) was normal and without atherosclerotic plaques. These findings suggest a protective effect of low LDL-C in FHBL and are consistent with those of Pulai et al., who found no macrovascular complications in two apo B-55 carriers with T2DM (8).

INVESTIGATION OF INCREASED TOTAL SERUM PROTEIN
The patient’s increased serum concentrations of total protein and globulins prompted further evaluation. An immunoglobulin quantification showed a greatly increased IgA concentration, a markedly decreased IgM concentration, and a borderline-low IgG concentration (Table 1). Serum protein electrophoresis revealed a monoclonal spike of 1.57 g/dL (15.7 g/L) in the β region. This monoclonal band was characterized via serum immunofixation electrophoresis as an IgAκ band. Protein electrophoresis and immunofixation electrophoresis of the urine did not reveal the presence of a monoclonal protein. Plasma cells were slightly increased (by 5%–6%) in the bone marrow (reference interval, 0.2%–2.2%). The radiologic skeletal survey revealed no osteolytic lesions. Because the patient showed no clinical manifestations related to the monoclonal gammopathy, such as hypercalcemia, anemia, renal insufficiency, or bone lesions, he was diagnosed with monoclonal gammopathy of undetermined significance (MGUS). MGUS is an asymptomatic premalignant disorder that is identified through routine blood tests, usually in people ≥50 years of age. MGUS

POUNDS TO REMEMBER
- HBL is defined by plasma TC, LDL-C, or apo B concentrations that are lower than the fifth percentile. HBL may be caused by mutations in several genes (primary HBL) and by several nongenetic factors, such as a strict vegetarian diet, malnutrition, drugs, and disease-related conditions (secondary HBL).
- FHBL is an autosomal codominant disorder that may be caused by mutations in the gene encoding apo B that lead to the formation of truncated apo B species.
- FHBL heterozygotes are often symptom free but may also present with nonalcoholic fatty liver disease and a mild increase in serum concentrations of liver enzymes.
- The presence of FHBL can be protective against the progression of atherosclerosis, owing to reduced lifetime exposure to atherogenic apo B-containing lipoproteins.
- MGUS is an asymptomatic premalignant disorder defined by a serum monoclonal protein concentration ≤3.0 g/dL (≤30 g/L) and by ≤10% plasma cells in the bone marrow without evidence of multiple myeloma or other related malignant disorder.

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is defined by a serum monoclonal protein concentration ≤3.0 g/dL (≤30 g/L) and by ≤10% plasma cells in the bone marrow without evidence of multiple myeloma or other related malignant disorder (10).

We therefore identified FHBL and MGUS independently of each other in an asymptomatic diabetic patient who was referred for further evaluation of his extremely low serum cholesterol concentration. The patient was sent to the endocrinology and gastroenterology departments for follow-up of the T2DM and fatty liver, respectively. Furthermore, the hematology department started to monitor the patient, because patients with MGUS are at increased risk for progression to multiple myeloma.

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References


Commentary

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In this case of hypobetalipoproteinemia (HBL), differential diagnoses for genetic and secondary HBL are provided. Several additional issues can be noted.

This patient also had an IgA paraproteinemia, which can influence cholesterol concentrations. Monoclonal paraproteinemia can hinder lipoprotein clearance, thereby increasing circulating cholesterol while artifically lowering cholesterol measurements (1). This patient’s cholesterol concentrations were lower than those typically observed with heterozygous genetic HBL, raising the question of paraprotein interference or another unidentified heterozygous mutation influencing apolipoprotein B (apo B) concentrations. Perhaps another familial variant was in play in the death of the proband’s son at age 21 years.

Familial hypocholesterolemia has received recent attention with the identification of mutations in the ANGPTL32 (angioptein-like 3) and PCSK9 (proprotein convertase subtilisin/kexin type 9) genes as novel causes of low cholesterol concentrations (2). Like HBL-associated apo B variants, ANGPTL3 and PCSK9 mutations appear well tolerated and potentially atheroprotective, features that are generating therapeutic interest in these targets. Similarly, inhibiting APOB transcription via the use of antisense oligonucleotides is in late-stage therapeutic development. Ongoing attempts to lower apo B concentrations despite the success of statins and other cholesterol-lowering medications (e.g., ezetimibe, bile acid sequestrants, niacin) reflect many clinical issues: statin intolerance, high baseline cholesterol concentrations, the lowering of LDL goals, and the increasing identification of familial hypercholesterolemia and its treatment challenges.

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1 Human genes: ANGPTL3, angiopoietin-like 3; PCSK9, proprotein convertase subtilisin/kexin type 9.