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Case Report

A case of sitosterolemia misdiagnosed as familial hypercholesterolemia: A 4-year follow-up

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Familial hypercholesterolemia (FH) is a common inherited disease that exhibits significantly increased levels of low-density lipoprotein cholesterol (LDL-C), skin or tendon xanthomas, corneal arcus, and premature coronary heart disease (CHD).[1] The prevalence of heterozygous FH is nearly 1 of 300 worldwide, and the prevalence of homozygous FH (HoFH) is 1 of 160,000 to 1 of 300,000.[1] The Dutch Lipid Clinic Network diagnostic (DLCN) criteria

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are the most commonly recommended criteria for diagnosing FH patients.[1] In addition to FH, sitosterolemia should be considered in children who present with xanthoma. The estimated incidence of this rare autosomal recessive disorder is approximately 1 in a million.[2] We report a 16-month-old child with suspected HoFH and LDL-C levels that were reduced from 14.69 to 3.24 mmol/L after dietary control without lipid-lowering therapy. Quantitation of plant sterol levels by gas chromatography and targeted exon sequencing for genetic testing were used to confirm the diagnosis of sitosterolemia.

Case presentation

A 16-month-old child from Shandong, China, was first admitted to our atherosclerosis clinic in June 2013 with multiple xanthomas that were 1.0 to 3.0 cm in diameter at the elbow, knee, and hip. The level of his total cholesterol (TC) was 20.47 mmol/L, and the LDL-C concentration was 14.69 mmol/L. The medical history revealed that the baby was breast fed with commercial formula before 13 months. The food supplement was added at 6 months. The child was only fed commercial formula with the food supplement between 13 and 16 months. The child was diagnosed clinically with FH based on the DLCN criteria. The mother exhibited a slightly higher TC (5.6 mmol/L) and LDL-C levels (3.4 mmol/L). His father exhibited normal TC (4.25 mmol/L) and LDL-C levels (2.59 mmol/L). Echocardiography and carotid ultrasound revealed that his father had plaque in the left external carotid artery (5.7 × 2.1 mm), but his other arteries were normal. Statin drugs were not administered because the child was young, and the only suggested treatment was a low-fat/low-cholesterol diet. Notably, his cholesterol levels were significantly reduced (TC 4.95 and LDL-C 3.24 mmol/L) 8 months later.

Diagnosis of HoFH was suspected for the following reasons: (1) LDL-C was dramatically reduced (from 14.69 to 3.24 mmol/L) only through diet control (Fig. 1); (2) his parents' LDL-C levels were not high, which may be reflective of a recessive inheritance pattern. Therefore, sitosterolemia was considered.

Gas chromatography was used to analyze the plant sterol levels in vivo at the patient's 24-month checkup. The plant sterol levels were 30 times higher than those of normal children (sitosterol 308.87 mg/L, campesterol 90.53 mg/L, stigmasterol 43.72 mg/L, cholesterol 15.58 mg/L). His parents' plant sterol levels were normal. The proband's 2 whole-blood tests revealed mild anemia. The proband was mildly anemic with a hemoglobin level of 101 g/L. A Giemsa-stained blood smear revealed a very small amount of stomatocytes (Fig. 2). Using a targeted exon sequencing chip designed by our laboratory,[3] only mutations in the ABCG8 gene were found. DNA Sanger sequencing confirmed 2 ABCG8 heterozygous mutations in the proband (c.490C>T, p.R164X, and c.1707-1709delTTC) derived from his mother and father (Fig. 3). These 2 mutations of ABCG8 were reported in other populations,[4] but they were not reported in to occur simultaneously in a Chinese population. The patient's sitosterolemia was confirmed.

Dietary restriction successfully controlled the LDL-C levels of the proband from 14.69 mmol/L to nearly 5 mmol/L between 16 and 55 months (Fig. 1). However, small doses of cholesterol-absorption inhibitors (ezetimibe 5 mg/d p.o.) were administered when he was 4.5 years old because the plant sterol levels were higher than normal. Ezetimibe therapy significantly decreased the plant sterol levels after 1 month (Table 1). However, his cholesterol remained at a high level (TC 8.24 and LDL-C 5.65 mmol/L) at 56 months of age. These results may have occurred for 2 reasons: first, the ABCG8 gene mutation also affects cholesterol

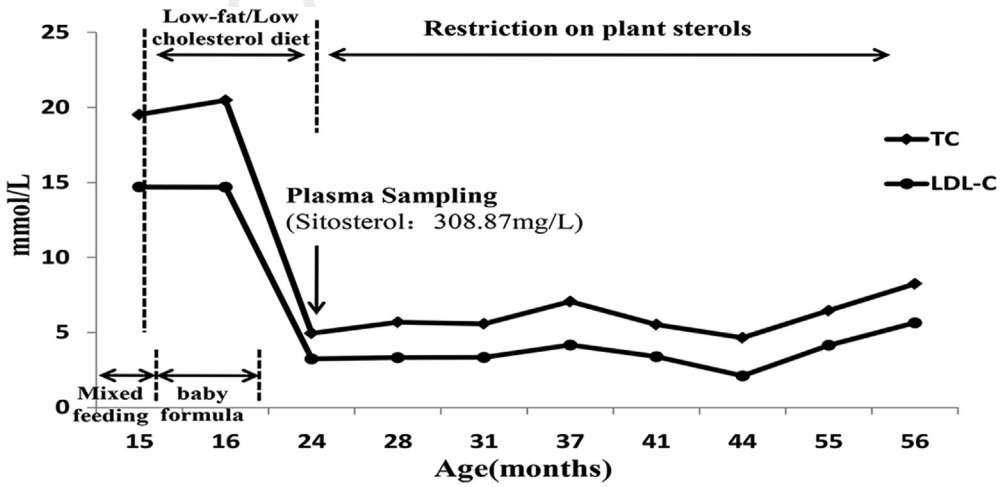

Figure 1 Trends of total cholesterol and low-density lipoprotein cholesterol levels in probands. Breastfeeding to 15 months of age. A low-saturated fat/low-cholesterol diet was introduced at 16 months of age and maintained throughout the entire period. Plant sterol analysis was performed when the patient was aged 24 months, after which plant sterol restriction was introduced. The patient was given ezetimibe orally at 55 months of age.