Sitosterolemia: A Rare Cause of Severe Hypercholesterolemia in Children

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ABSTRACT

Introduction: Severe hypercholesterolemia in children is commonly caused by familial hypercholesterolemia (FH); however, sitosterolemia, a rare autosomal recessive disorder, should be considered when FH genetic testing is negative.

Case Presentation: A 4-year-old boy presented with xanthomas on his knees. His total cholesterol was 561 mg/dL. Initially, homozygous FH was suspected, and rosuvastatin was started; however, genetic testing was negative. Subsequent genetic testing identified a homozygous *ABCG8* variant, consistent with sitosterolemia. Rosuvastatin was discontinued, and ezetimibe and dietary plant sterol restriction were initiated, resulting in significant improvement in cholesterol levels and resolution of xanthomas.

Discussion: Sitosterolemia results from impaired ABCG5/8 transporter function, leading to plant sterol accumulation, which can cause hypercholesterolemia, xanthomas, and hematologic abnormalities. Diagnosis is established by demonstrating elevated plant sterol levels or through genetic testing. Treatment involves dietary plant sterol restriction and ezetimibe.

Conclusions: Sitosterolemia, though rare, should be considered in severe hypercholesterolemia when FH genetic testing is negative. This case demonstrates a typical presentation and favorable response to treatment with ezetimibe and dietary modification.

INTRODUCTION

Severe hypercholesterolemia in children is usually defined as a low-density lipoprotein cholesterol (LDL-C) level of ≥ 190 mg/dL.[1] Severe hypercholesterolemia that persists despite a trial of lifestyle modifications is often due to a primary, inherited dyslipidemia, with familial hypercholesterolemia (FH) being most common. Sitosterolemia is another rare cause of severe hypercholesterolemia in children that should be considered if genetic testing for FH is negative. Here, we describe a case of sitosterolemia in a 4-year-old boy, characterized by xanthomas, severely elevated cholesterol, and elevated plant sterol levels in the blood.

CASE PRESENTATION

A 4-year-old boy with no significant past medical history was noted to have yellow cutaneous nodules on his knees at his well-child visit at age 4 years. His physical exam was otherwise normal, with no cardiac murmurs and no evidence of corneal arcus. He was referred to dermatology, and a punch biopsy of the right knee nodule (Figure 1) was performed. Histology of the biopsy showed a mixture of foamy histiocytes, lymphocytes, and other mononuclear cells, along with a few multinucleated giant cells. The differential diagnosis included xanthoma and juvenile xanthogranuloma.

A lipid panel showed severely elevated lipid levels, with an LDL-C of 406 mg/dL and a total cholesterol of 561 mg/dL. The family history was notable for consanguinity; the paternal grandfather and maternal grandfather are brothers. The paternal grandfather died at age 26 from a suspected myocardial infarction. The mother had a history of high cholesterol that was controlled with dietary modifications and is now normal. The father had not had his cholesterol measured.

Given the marked LDL-C elevation, the presence of xanthomas, and the family history, the highest clinical concern was for homozygous FH. The patient was started on the HMG-CoA reductase inhibitor rosuvastatin and was referred for genetic testing. An

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FH genetic testing panel was performed, including sequencing and deletion/duplication analysis of the 4 FH-associated genes (*LDLR*, *APOB*, *PCSK9*, and *LDLRAP-1*). While awaiting results, his rosuvastatin dose was increased without a significant effect on his LDL-C levels (Figure 2). During this time, he remained asymptomatic, and an echocardiogram showed no evidence of cardiac cholesterol deposition or valvular heart disease.

The FH genetic panel ultimately returned negative. Given the persistently elevated cholesterol and lack of significant response to rosuvastatin, an alternative genetic etiology was suspected. A broader genetic testing panel for hereditary dyslipidemia identified a homozygous pathogenic variant *ABCG8* (c.547del; p.Gln183Serfs*9 [NM_022437.2]), consistent with autosomal recessive sitosterolemia. Given this diagnosis, rosuvastatin was discontinued, and he was started on ezetimibe 10 mg daily.

The family underwent extensive dietary counseling to reduce plant sterols intake. A detailed diet history was obtained, and key foods high in plant sterols were identified. The patient was encouraged to avoid these foods, and alternatives were suggested. Foods particularly high in plant sterols and to be avoided in sitosterolemia include vegetable oils (eg, olive, corn, canola), nuts and seeds (eg, almonds, walnuts, cashews, sesame, sunflower), juice or soy milk fortified with plant sterols, kidney beans, lentils, and margarine. Plant sterols may also be present in foods or supplements marketed for heart health and also should be avoided. Most fruits and vegetables contain relatively low amounts of plant sterols; however, those with higher levels (eg, avocados) should also be avoided. Acceptable alternatives low in plant sterols include lean animal proteins (eg, chicken, turkey) and refined grains. Initiation of ezetimibe and dietary modification resulted in significant improvement in LDL-C and total cholesterol (see Figure 2) and resolution of the cutaneous xanthomas.

Cascade genetic testing of the patient's parents showed that both were heterozygous carriers of the variant. Given the autosomal recessive inheritance of *ABCG8*, his sister was at risk of being affected; however, she tested negative for the variant.

The patient remains clinically well and asymptomatic from a cardiovascular standpoint, with no recurrence of xanthomas. Complete blood cell counts occasionally have shown mild anemia (hemoglobin 10.8-11.6 g/dL), with normal platelet counts. Blood was sent for gas chromatography-mass spectrometry (GC-MS) after initiation of ezetimibe and diet changes, and plant sterol levels remained elevated (sitosterol, 12.81 mg/dL [normal ≤ 1.5 mg/dL]; campesterol, 7.77 mg/dL [normal ≤ 0.8 mg/dL]; stigmasterol, 0.6 mg/dL [normal ≤ 0.05 mg/dL]).

Figure 1. Right Knee Nodules

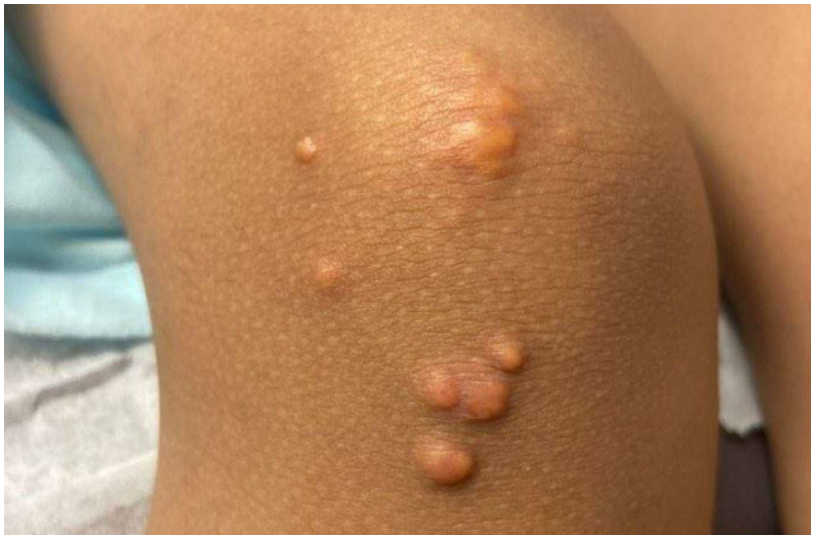
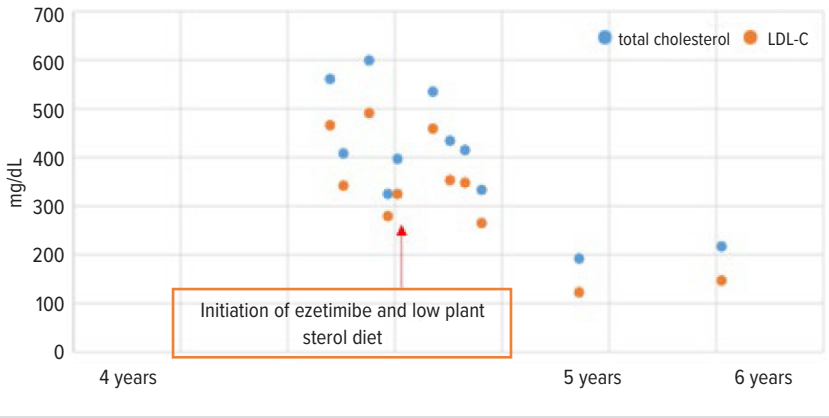


Figure 2. Patient Total Cholesterol and Low-Density Lipoprotein Cholesterol (LDL-C) Levels



DISCUSSION

Sitosterolemia is an extremely rare cause of severe hypercholesterolemia. The exact prevalence is unknown; however, fewer than 200 individuals have been reported in the literature, and the condition is likely underdiagnosed.[2]

The primary abnormality in sitosterolemia is the accumulation

of plant sterols. Plant sterols (most commonly sitosterol, campesterol, and stigmasterol) are structurally similar to animal cholesterol. However, unlike cholesterol, plant sterols are not used in human metabolism; therefore, plasma plant sterol levels are typically very low (<1 mg/dL).[2,3]

Sitosterolemia was first described by Bhattacharyya and Connor in 1974.[4] Subsequent studies have elucidated its molecular basis.[5-8] It is an autosomal recessive disorder caused by homozygous or compound heterozygous loss-of-function variants in *ABCG5* or *ABCG8*, which encode 2 proteins of the ATP-binding cassette family, which ultimately form a heterodimeric transport molecule primarily in the intestine and liver.[9]

Dietary cholesterol and plant sterols are transported from the intestinal lumen into enterocytes by the Nieman-Pick C1-like 1 (NPC1L1) protein. Most plant sterols are then excreted back into the intestinal lumen or biliary tract in the liver via the ABCG5/8 transporter. This transporter also excretes excess cholesterol. Although dietary intake of cholesterol and plant sterols is similar in Western diets, approximately 50% of cholesterol is absorbed into the bloodstream, compared with <5% of plant sterols.[2,3,9]

Accumulated plant sterols are transported in lipoproteins and may contribute to xanthoma formation, potentially at lower serum cholesterol levels than in FH.[10] Xanthomas can appear early in life and sitosterolemia with cutaneous findings has even been reported in breastfed infants.[11] Minor trauma may precipitate xanthoma development, particularly on extensor surfaces (eg, elbows and knees).

There is a heterogeneity in presenting serum cholesterol levels; however, most patients have at least mild elevation, and many have severe LDL-C elevation. Children with sitosterolemia may have higher serum cholesterol levels than adults, possibly due to age-related differences in LDL receptor expression or intrinsic cholesterol synthesis, although the mechanism remains unclear.[11,12] Patients are at risk for premature coronary artery disease,[13] and sudden death has been reported in a 5 year old with coronary ostial occlusion from aortic lipid deposits.[14] Valvular heart disease, particularly involving the aortic valve, may also occur.

There also may be significant hematologic effects in some patients. Circulating plant sterols appear to be toxic and damaging to red blood cells and platelets, and patients can develop hemolytic anemia and/or thrombocytopenia with stomatocytosis and macrothrombocytopenia, as well as splenomegaly.[15] These findings may rarely be the presenting symptom.[16] Routine complete blood cell count monitoring is recommended for all patients with sitosterolemia.

Patients may present with xanthomas, severe hypercholesterolemia, and/or hematologic abnormalities. Due to its rarity and similarity with more common disorders, sitosterolemia is often misdiagnosed. In addition to FH, cerebrotendinous xanthomatosis (CTX) should be considered and can be distinguished by the presence of gastrointestinal symptoms, cataracts, neurologic findings, and absence of hematologic findings.

In pediatric patients, sitosterolemia should be suspected in those with severe hypercholesterolemia unresponsive to standard therapy, those with associated hematologic abnormalities, and/or those with severe xanthomas. This case also underscores the importance of universal lipid screening in children, as recommended by the National Heart, Lung, and Blood Institute Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[17] These guidelines recommend screening once during ages 9 to 11 years and again during ages 17 to 21 years, with enhanced screening for high-risk individuals. As many children with inherited hypercholesterolemia disorders—including sitosterolemia—may present solely with dyslipidemia on laboratory testing, universal screening is essential for early diagnosis and detection.

The diagnosis of sitosterolemia can be made clinically based on phenotype and elevated plant sterols levels; however, GC-MS testing may not be widely available. Alternatively, the diagnosis can be confirmed with genetic testing. Although traditionally considered an autosomal recessive disorder, recent research suggests that heterozygous carriers may have increased coronary artery disease risk compared with the general population.[18]

Treatment focuses on limiting plant sterols in the diet as well as use of the NPC1L1 inhibitor ezetimibe. By blocking the NPC1L1 transporter, absorption of both dietary cholesterol and plant sterols is reduced. Small studies have demonstrated safety and efficacy in sitosterolemia, including in children.[19–21]

As noted above, foods high in plant sterols (eg, vegetable oils, nuts, seeds) should be avoided. Plant sterols found in health food products or supplements geared towards heart health also should be avoided. Naturally occurring plant sterols are not routinely listed on nutrition labels; however, they might be listed on products when plant sterols are added for a specific health benefit.

CONCLUSIONS

Sitosterolemia is a rare autosomal recessive disorder characterized by excess absorption and accumulation of plant sterols, with a phenotype that includes hypercholesterolemia, xanthomas, and hematologic abnormalities. Clinicians should consider this diagnosis in patients with severe hypercholesterolemia who are unresponsive to standard therapies, particularly in the presence of hematologic abnormalities or pediatric xanthomas.

Diagnosis can be established by measuring plant sterol levels in the blood and/or confirmed with genetic testing. Children with severe hypercholesterolemia should be referred to a pediatric lipid specialist. This case highlights the importance of considering alternative etiologies in patients who do not respond to standard lipid-lowering therapy.

Financial disclosures: None declared.

Funding/support: None declared.

Acknowledgements: As the patient is a minor, the patient's mother provided written consent for publication of this case.

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