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Case Report

Pediatric Sitosterolemia: A Case Report and Literature Review

Nelly Silva[1]*, Margarita Vega[1], Daniela Ramírez[1], Victoria Leal[2] and Awadalla Shokery[2]

[1]Fellow in Pediatric Endocrinology at Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

[2]Pediatric Endocrinologist, Professor at Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

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***Corresponding author:** Nelly Silva, MD. Fellow in Pediatric Endocrinology, Bogotá, Colombia

A B S T R A C T

Sitosterolemia is a rare autosomal recessive disorder caused by pathogenic variants in ABCG5 or ABCG8, leading to increased intestinal absorption and reduced biliary excretion of plant sterols. We report a 13-year-old boy with severe hypercholesterolemia and poor response to high-dose atorvastatin. Targeted sequencing identified a pathogenic truncating ABCG8 variant (c.1974C>G; p.Tyr658*) and a second ABCG8 variant of uncertain significance (c.1570G>C; p.Gly524Arg). Plasma β-sitosterol was markedly elevated (35 mg/dL; reference 1.7-3 mg/dL), confirming the diagnosis. Atorvastatin was discontinued and treatment with ezetimibe 10 mg/day plus a phytosterol-restricted diet produced a rapid and substantial lipid improvement, with total cholesterol 124.5 mg/dL and LDL-cholesterol 59.9 mg/dL on follow-up, accompanied by clinical improvement.

Keywords: Sitosterolemia; ABCG8; Pediatric dyslipidemia; Familial hypercholesterolemia mimic; Plant sterols; β-sitosterol; Ezetimibe

Introduction

Sitosterolemia (OMIM #210250), also known as phytosterolemia, is an autosomal recessive lipid disorder caused by biallelic pathogenic variants in ABCG5 or ABCG8. These genes encode sterol transporters that limit intestinal absorption and promote biliary excretion of sterols. Loss of function results in markedly increased circulating plant sterols (predominantly sitosterol and campesterol), variable hypercholesterolemia, tendon or cutaneous xanthomas and, in some patients, premature atherosclerotic disease and hematologic abnormalities[1-3]. Diagnosis is challenging because the phenotype overlaps with heterozygous or homozygous familial hypercholesterolemia (FH). A key clinical clue is a limited lipid response to statins and potential worsening after dietary advice that increases intake of plant sterols (e.g., nuts, seeds, avocado, vegetable oils and fortified products). Optimal management focuses on reducing intestinal sterol absorption-most commonly with ezetimibe-together with dietary restriction of phytosterol-rich foods[1,4,5]. We describe a pediatric case initially treated as FH, later confirmed as sitosterolemia by plasma sterol measurement and genetic testing, with a marked biochemical response to ezetimibe.

Case Presentation

A 13-year-old male was referred for evaluation of persistent hypercholesterolemia despite treatment with atorvastatin (10–30 mg/day) over approximately two years. The patient was

asymptomatic, with no known personal history of cardiovascular disease. Family history of premature cardiovascular disease or severe hypercholesterolemia was not reported. Physical examination did not reveal xanthomas. Baseline lipid profile prior to referral showed LDL-cholesterol (LDL-C) of 313.4 mg/dL. Given the working diagnosis of FH, dietary counseling emphasized plant-based fats and fiber (including frequent use of olive oil, avocado and nuts). Four months later, the lipid profile showed a paradoxical deterioration, with LDL-C rising to 412.8 mg/dL; triglycerides were 88 mg/dL. Liver enzymes and thyroid function tests were within normal limits. The poor response to highdose statin therapy and the worsening after increasing plant-based fat intake prompted evaluation for sitosterolemia. Targeted next-generation sequencing identified two ABCG8 variants in heterozygosity: a truncating pathogenic variant c.1974C>G (p.Tyr658*) and a missense variant of uncertain significance (VUS), c.1570G>C (p.Gly524Arg). Phase was not established at the time of writing; parental segregation testing was recommended1,3. Plasma β-sitosterol was markedly elevated at 35 mg/dL (reference range 1.7–3 mg/dL), supporting the diagnosis. Atorvastatin was discontinued and ezetimibe 10 mg/day was initiated, together with dietary restriction of phytosterol-rich foods. On follow-up, the patient demonstrated substantial improvement of the lipid profile with clinical improvement: total cholesterol 124.5 mg/dL, LDL-C 59.9 mg/dL and triglycerides 92.4 mg/dL[5].

Discussion

Sitosterolemia is considered rare, yet it is likely underdiagnosed, particularly among children labeled as FH based solely on lipid levels. Clinical manifestations are heterogeneous and may include xanthomas, premature atherosclerosis and hematologic findings such as hemolytic anemia or macrothrombocytopenia; however, some patients present only with hypercholesterolemia[1-3]. In this case, two features were especially informative: (1) minimal benefit from prolonged statin therapy and (2) deterioration after increasing dietary plant-based fats, which can be phytosterol-rich. These clues motivated confirmatory testing with plasma sterol measurement and genetic analysis. In pediatric cohorts, plasma cholesterol and LDL-C can be markedly elevated and cardiovascular involvement-including carotid changes-has been reported, supporting the importance of early recognition and treatment[3,6]. Molecular confirmation is central. The ABCG8 truncating variant identified (p.Tyr658*) is consistent with loss of transporter function. The second variant was reported as a VUS; segregation studies can help clarify whether the variants are in trans and strengthen diagnostic certainty. Regardless, the markedly elevated β-sitosterol level and the clinical/biochemical response to ezetimibe support the diagnosis[1,6]. Ezetimibe is the preferred pharmacologic therapy because it inhibits intestinal sterol absorption via NPC1L1, lowering both cholesterol and plant sterols. In a randomized placebo-controlled study in sitosterolemia, ezetimibe produced significant reductions in plasma sitosterol and campesterol concentrations[5]. Dietary management remains essential, focusing on reducing phytosterol intake (notably from vegetable oils, nuts, seeds, avocado and fortified foods), while maintaining overall nutritional adequacy. Early diagnosis and targeted treatment can normalize lipid levels and may reduce the risk of early atherosclerosis[1,3].

Conclusion

Sitosterolemia should be considered in children with severe hypercholesterolemia who show limited statin response and paradoxical worsening after plant-fat-rich dietary interventions. Measuring plasma plant sterols and confirming ABCG5/ABCG8 variants enable accurate diagnosis. Timely initiation of ezetimibe and a phytosterol-restricted diet can lead to rapid and substantial biochemical improvement.

Declarations

Ethics approval and consent to participate

Written informed consent for participation and publication was obtained from the patient's legal guardians. Institutional review board approval was not required for a single anonymized case report, in accordance with local policies.

Consent for publication

Consent for publication of anonymized clinical information was obtained from the patient's legal guardians.

Availability of data and materials

Not applicable. No datasets were generated or analyzed beyond the clinical record.

Conflicts of interest

The authors declare no conflicts of interest.

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Authors' contributions

AS and VL contributed to clinical evaluation and manuscript drafting. NS supervised the clinical workup and critically revised the manuscript. DR and MV contributed to literature review and manuscript editing. All authors read and approved the final manuscript.

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