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Case Report

# Sitosteloremia: Clinical Suspicion When Things Don´t Add Up

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## Abstract

Sitosteloremia is a rare disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol. We report a case of a healthy 10-year-old boy with hypercholesterolemia was treated with cholestyramine, but was suspended due to the poor tolerance, statins were initiated with increasing dose, without success. The laboratory study showed mutations in the ABCG5 gene and elevated serum sterol levels. With diagnosis of sitosteloremia, and treatment with low plant sterol diet and ezetimibe, for four months later, the serum cholesterol normalized. Misdiagnosis with familial hypercholesterolemia results in inappropriate therapy. Time matters, so early diagnosis and treatment of can prevent cardiovascular complications and improve the prognosis for patients.

***Keywords:*** *Sitosteloremia; Hypercholesterolemia; Misdiagnosis; Genetic; ABCG5*

## Abbreviations

STSL: Sitosteloremia; FH: Familial Hypercholesterolemia; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol

## Introduction

Sitosteloremia, also known as phytosterolemia (STSL, OMIM #210250), is a rare autosomal genetic disease (pathogenic variants in ABCG5 or ABCG8 gen). STSL is a disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol [1]. This condition was first described by Bhattacharyya and Connor in 1974 [2]. Epidemiology is unknown but growing evidence suggests underestimation of STSL incidence. STSL used to be considered an extremely rare disorder but recent studies indicate the possibility of a much higher prevalence in the general population [3].

STSL is caused by homozygous or compound heterozygous mutations in one of the two adenosine triphosphate binding cassette (ABC) genes, ABCG5 and ABCG8, located on human chromosome 2p21. These genes encode the heterodimer transporter ABCG5/G8, which is expressed in enterocytes, in the proximal small intestine, and hepatocytes, and function to rapidly excrete cholesterol, plant sterols and their saturated derivatives (stanols) from the body [4].

Plant sterols (sitosterol, campesterol, and stigmasterol) are sterol molecules naturally contained at low levels in plant foods such as fruits, vegetables, nuts and cereals [5].

Clinical features are heterogeneous, varying widely from asymptomatic to cutaneous/tendinous xanthomas, arthritis/arthralgias, or hematological abnormalities (anemia, stomatocytes, macrothrombocytopenia) [6]. Misdiagnosis with familial hypercholesterolemia results in inappropriate dietary intervention and treatment for a considerable period [7]. STSL is associated with an increased risk of premature atherosclerosis and sudden cardiac death [8,9].

Therefore, recognition of this condition requires a high level of suspicion, with confirmation upon genetic diagnosis or through measurement of plasma plant sterols. The first-line therapy for STSL is based on a plant sterol-restricted diet and the intestinal cholesterol absorption inhibitor ezetimibe [7,10].

## Case Report

A healthy 10-year-old Spanish boy was referred to our endocrinology department with hypercholesterolemia, total cholesterol (TC) 300 mg/dl, low-density lipoprotein cholesterol (LDL-C) 200 mg/dl, high-density lipoprotein cholesterol (HDL-C) 60 mg/dl.

Medical history: premature newborn (32 weeks´ gestation, birth weight of 1250g, height of 41 cm), short stature (constitutional delay of growth). Family history: father with mild hypercholesterolemia without treatment, but negative for premature coronary atherosclerosis in the family. Physical examination revealed body weight 23.7 kg (5p, -1.72 SD), height 132 cm (3p, -2.03 SD), body mass index (BMI) 13.6 kg/m$^2$ (6p, -1.56 SD), there were no xanthomas or arthritis. Initial blood test showed normal levels of triglycerides, glucose, creatinine, liver enzymes, white blood cells, hemoglobin (15.6 g/dl), platelets (177.000/mm$^3$), thyroxine (T4), thyroid stimulating hormone (TSH), apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB).

Initial treatment with cholestyramine was suspended due to the poor tolerance and pravastatin was initiated with increasing dose, without success. The same happened with atorvastatin with progressive blood tests of cholesterol worsening (total cholesterol 364 mg/dl, LDL-Cholesterol 290 mg/dl). So genetic analysis and blood test of plant sterols were performed: elevated serum sterol levels (beta-cholestanol: 35.2 mcmol/L, campesterol: 34.3 mcmol/L, sitosterol: 25.1 mmol/L), and presence in heterozygosity of two mutations in the ABCG5 gene (Table 1). Electrocardiogram, echocardiography, carotid artery intima-media thickness and cervical vascular ultrasound were normal. After definitive diagnosis of STSL, the patient was treated with low plant sterol diet and ezetimibe. After four months of treatment the serum cholesterol concentration normalized (TC 148 mg/dl, LDL-C 74/dl) (Table 2).

| Gene | Variants | Zygosity |
|---|---|---|
| ABCG5 | NC_000002.11: g.(?_440440254)_(44047240_44049935)del | Heterozygosity |
| ABCG5 | NM_022436.3: c.293C>Gp.(Ala98Gly) | Heterozygosity |

***Table 1:*** *Genetic testing.*

| | TC mg/dl | LDL-C mg/dl | HDL-C mg/dl | Treatment | Observations |
|---|---|---|---|---|---|
| March 2019 | 300 | 200 | 60 | Cholestyramine 4 g/day | Low-cholesterol diet, restricted animal sterols |
| June 2020 | Cholestyramine is discontinued due to intolerance and pravastatin 10 mg/day is started | | | | |
| Nov 2020 | 260 | 190 | 64 | ↑pravastatin 20 mg/day | Omega-3 Fatty Acids supplementation |
| January 2022 | 364 | 290 | 65 | Atorvastatin 20 mg/day | Increase in appropriate exercise |
| June 2023 | Diagnosis of STLS is made by serum plant sterols and genetic analysis.<br>Treatment: ezetimibe 10 mg/day, restriction of plant sterols | | | | |
| October 2023 | 148 | 74 | 66 | Ezetimibe 10 mg/day | Restricted plant sterols |
| TC = Total Cholesterol; LDL-C = Low-Density Lipoprotein Cholesterol; HDL-C = High-Density Lipoprotein Cholesterol | | | | | |

***Table 2:*** *Laboratory data and treatment.*

## Discussion

In our case, it was essential to check plasma plant sterol-concentration when hypercholesterolemia had a poor response to statins, and the definitive diagnosis of STSL with the genetic testing. Our patient didn´t suffer from xanthomas, and there were no hematological abnormalities, but STSL should also be suspected with the presence of cutaneous or tendon xanthomas, premature coronary artery disease, or unexplained macrothrombocytopenia and/or stomatocytic hemolysis [6].

Misdiagnosis STSL with FH results in inappropriate dietary therapy (promote vegetable fats) and treatment (especially statins) for a considerable period. Time matters, so early diagnosis and treatment of STSL can prevent cardiovascular complications and improve the prognosis for patients. Plant sterol-restriction diet and ezetimibe are an effective treatment for STSL and can be a controllable disease [5]. Patients with STSL usually do not respond to statins because HMG CoA reductase activity is already maximally inhibited [8].

Awareness about this condition, a rare, but commonly underdiagnosed and yet treatable cause of premature atherosclerotic disease, is imperative.

## Conclusion

STLS should be suspected and considered in children with hypercholesterolemia who do not respond to standard treatment. Raise awareness of STSL among pediatricians is important to be vigilant and to avoid misdiagnosis and inappropriate dietary therapy. Long-term follow-up is necessary in these patients.

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## Conflict of Interest

The authors declare no conflicts of interest.

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