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CASE REPORT

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Phenotypic Variability in Atherosclerosis Burden in an Old-Order Amish Family With Homozygous Sitosterolemia

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ABSTRACT

Sitosterolemia is a rare atherogenic sterol storage disease with variability in its presentation requiring a high degree of clinical suspicion. We present 8 cases of sitosterolemia from an Amish kindred that, despite a background of decreased genetic and lifestyle variability, still had markedly variable presentations. (**Level of Difficulty: Advanced.**)

Sitosterolemia is an autosomal recessive sterol storage disorder. It is caused by mutations in 2 adenosine trisphosphate-binding cassette (*ABC*) genes (*ABCG5* or *ABCG8*), which are transporters that limit uptake of dietary sterols, thus avoiding excess accumulation. Affected individuals have plasma plant sterol concentrations that are 30 to 100 times elevated and can have elevated low-density lipoprotein cholesterol (LDL-C). Clinical manifestations include xanthomas, hemolytic anemia, macrothrombocytopenia, and premature atherosclerosis. Although <100 cases of sitosterolemia have been reported, this disease is believed to be substantially underdiagnosed. Sitosterolemia can be phenotypically similar to heterozygous or homozygous familial hypercholesterolemia (1,2); however, hematologic abnormalities rarely appear in isolation (3). Atherosclerosis associated with sitosterolemia is inconsistent (4-7) and can range from severe, with xanthomas in infants (8), to asymptomatic in adults with persistent hypercholesterolemia (4-6,9).

LEARNING OBJECTIVES

- Sitosterolemia is a rare autosomal recessive sterol storage disorder that can be misdiagnosed as familial hypercholesterolemia.
- Sitosterolemia's heterogeneous presentation can include xanthomas, premature atherosclerosis, hemolytic anemia, and macrothrombocytopenia.
- Sitosterolemia should be considered when xanthomas are present, extremely premature atherosclerosis is noted, or if a patient with hypercholesterolemia fails to respond as expected to a statin medication.

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We report clinical, laboratory, and carotid ultrasound data from 8 members of an old-order Amish family who were homozygous for mutations in *ABCG8 G1720A*.

CASE 1

HISTORY OF PRESENTATION. An 8-year-old Amish girl presented with failure to thrive, learning difficulties, and 4 months of nausea, vomiting, dizziness, and joint pain. Her family noted "lumps" on her knees and lower extremity edema. Her weakness was so severe that her siblings pulled her to school in a wagon. Her mother reported that the girl learned more slowly than her 10 siblings and needed to repeat first grade. Her family history was significant for multiple paternal relatives with myocardial infarctions. On examination, a 1-cm subcutaneous mass was noted overlying the right anterior knee. She had 1- to 2-mm yellowish nodules on the skin over her right Achilles tendon, right shin, and elbows. Her weight was 18.1 kg, and her height was 116.8 cm (both below the third percentile).

DIFFERENTIAL DIAGNOSIS. Inborn error of metabolism, homozygous familial hypercholesterolemia, sitosterolemia, and cerebrotendinous xanthomatosis are all differential diagnoses to consider in this patient.

INVESTIGATIONS. Results of a biopsy of one of the patient's skin nodules revealed a xanthoma. Her fasting lipid panel showed the following: total cholesterol, 474 mg/dl (normal, <170 mg/dl); high-density lipoprotein cholesterol, 41 mg/dl (normal, >45 mg/dl); triglycerides, 118 mg/dl (normal, <75 mg/dl); and LDL-C, 409 mg/dl (normal, <110 mg/dl). She was presumptively diagnosed with homozygous familial hypercholesterolemia, but the result of targeted mutation testing for a pathogenic sequence variant commonly found in the Amish population (*APOB G10580A*) was normal. Consequently, the patient's serum sitosterol and campesterol levels were measured (Table 1), and targeted testing for *ABCG8 G1720A* revealed homozygosity for the mutation. She was diagnosed with sitosterolemia. Her mean common carotid artery intima-medial thickness (IMT) was above the 75th percentile for age, and plaques were visualized.

MANAGEMENT. Management of the patient included dietary avoidance of sterols and ezetimibe 10 mg daily. A bile acid-binding resin was added later.

FOLLOW-UP. After 2 years, the patient had a >80% decrease in sitosterol and campesterol levels. Linear growth improved. She gained weight, had resolution of abdominal and joint pain, and she now can walk to school.

CASES 2 TO 8

HISTORY OF PRESENTATION. Approximately 6 weeks after presentation of Case 1, a 23-year-old Amish man presented with progressive exercise intolerance since age 12 years. He reported yellow nodules on his Achilles tendons, plantar surfaces of his feet, elbows, and buttocks. He said his first cousin's 8-year-old daughter and his father have similar nodules. He had a 3/6 systolic murmur at the right upper sternal border and tendon xanthomas. He had bilateral carotid and femoral artery bruits.

DIFFERENTIAL DIAGNOSIS. Homozygous or heterozygous familial hypercholesterolemia, sitosterolemia,

ABBREVIATIONS AND ACRONYMS

ABC = adenosine triphosphate–binding cassette

IMT = intima-medial thickness

LDL-C = low-density lipoprotein cholesterol

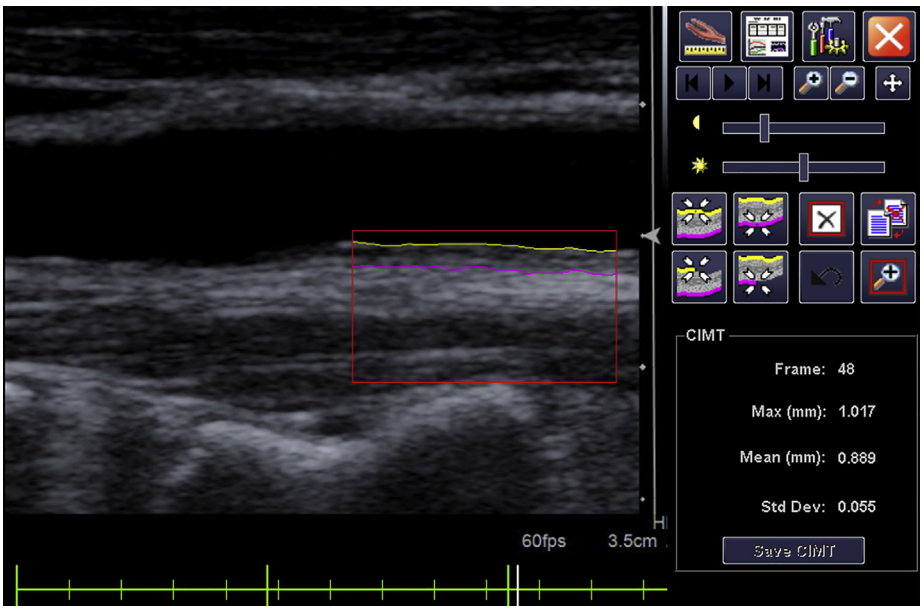
TABLE 1 Laboratory, Vascular, and Clinical Findings in 8 Patients With Sitosterolemia

				Initial Laboratory Studies			Vascular Imaging		Clinical Findings	
Case #	Relationship to Proband	Age, yrs	Sex	Sitosterol (mg/dl)	Campesterol (mg/dl)	Total Cholesterol (mg/dl)	CCA IMT (mm)	Plaque Count	Symptoms	Xanthomas
1	First cousin once removed	8	Female	409.2	147.2	474	0.462*	2	Present	Present
2	Proband	23	Male	217.7	109.1	393	0.715*	9	Present	Present
3	Father	50	Male	150.0	67.9	253	1.0835*	4	Present	Absent
4	Brother	26	Male	141.4	68.8	215	0.503	0	Absent	Absent
5	Sister	20	Female	139.8	44.4	NA†	0.466*	0	Absent	Absent
6	Sister	15	Female	223.1	92.4	321	0.455	0	Absent	Absent
7‡	Sister	13	Female	226.8	110.2	146	0.387	7	Present	Present
8	Sister	11	Female	148.2	77.2	292	0.482	0	Absent	Absent

The reference range for sitosterol was 0 to 5 mg/dl, and the reference range for campesterol was 0 to 7 mg/dl. *Common carotid artery (CCA) intima-medial thickness (IMT) above the 75% percentile for age, race, and sex. †Not measured because the patient was pregnant at the time of diagnosis. ‡Initial total cholesterol measured during ezetimibe therapy (sitosterol and campesterol values measured before ezetimibe).

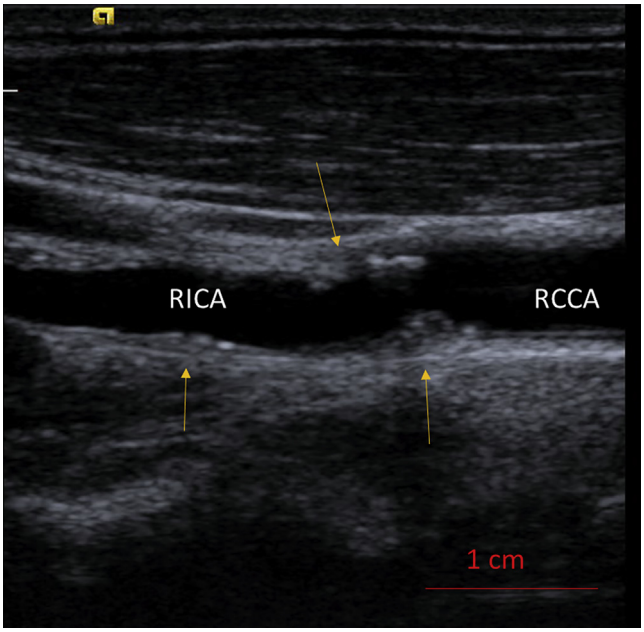
NA = not available.

FIGURE 1 Example of Increased Carotid Intima-Medial Thickness



The **red box** is the measured region of interest; the **yellow line** is the blood-intima interface; and the **purple line** is the media-adventitia interface.

FIGURE 2 Example of Carotid Artery Atherosclerotic Plaques



Plaques are detected on the far wall of the right common carotid artery (RCCA) **(arrow)**, near the wall of the carotid bifurcation **(arrow)**, and the far wall of the right internal carotid artery (RICA) **(arrow)**.

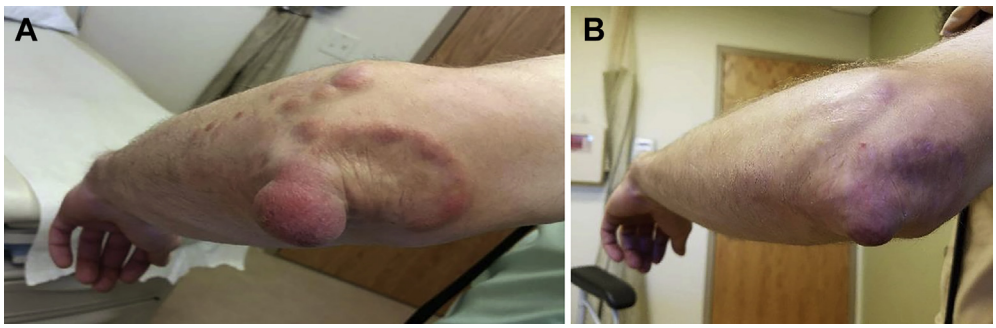
Erdheim-Chester disease, and cerebrotendinous xanthomatosis are differential diagnoses to consider here.

INVESTIGATIONS. An echocardiography showed a trileaflet but thickened aortic valve with mild insufficiency and no stenosis. ABCG8 G1720A testing revealed homozygosity for the mutation. The patient's father and 5 of his 10 siblings were then tested and were homozygous for the mutation. The remaining 5 siblings and his mother were heterozygous carriers (Table 1). Only 3 of 7 individuals in this family had clinical symptoms of easy fatigability or dyspnea on exertion. Of the 3, each had markedly increased carotid IMT and carotid plaques (Figures 1 and 2), and 2 had tendon xanthomas (Figure 3). No asymptomatic individuals had xanthomas. No family members had diabetes mellitus or hypertension, were overweight, or used tobacco.

MANAGEMENT. Patient management included dietary avoidance of sterols and ezetimibe 10 mg daily. Bile acid-binding resins were added later.

FOLLOW-UP. All symptomatic individuals had improved exercise tolerance and xanthoma regression. Xanthomas of Case 2 are shown in Figure 3. Further investigation identified 2 paternal aunts with premature atherosclerosis who were treated similarly.

FIGURE 3 Xanthomas on Extensor Elbow Surface in Patient With Sitosterolemia



(A) Xanthomas in Case 2 before treatment. Multiple elbow and forearm extensor surface xanthomas at diagnosis. **(B)** Xanthomas in Case 2 after 2.5 years of treatment. Significant regression was noted after 2.5 years of treatment with ezetimibe and a bile acid-binding resin.

DISCUSSION

Sitosterolemia is a rare sterol storage disorder with significant phenotypic variability. Despite having very similar diets, levels of physical activity, and identical mutations in *ABCG8* on a background of high consanguinity, these patients had marked phenotypic variability in symptoms and measures of arterial injury. Some of this variability may be due to aging: 2 of the 3 oldest individuals had increased carotid IMT and carotid plaques. However, age does not sufficiently explain all the variation, as much younger members of the family had symptoms, xanthomas, and carotid plaques, and some older affected members had no findings.

Sitosterolemia is diagnosed by measuring serum sitosterol, campesterol, and stigmasterol levels and identifying elevations 30 to 100 times normal. Some individuals may have elevated serum cholesterol levels, but some common laboratory assays cannot differentiate cholesterol from plant sterols and will incorrectly report high sterol levels as cholesterol. To our knowledge, carotid IMT has not been measured previously in a sitosterolemia cohort. Increased wall thickness represents arterial injury due to risk factor exposure and denotes increased future cardiovascular disease in a wide range of disease pathologies (10).

Ezetimibe is the treatment of choice because it inhibits absorption of sterols from the gut; statins do not lower blood sterol levels. If a statin fails to achieve expected LDL-C reduction, sitosterolemia should be considered. Genetic testing can identify a pathogenic mutation in *ABCG5* or *ABCG8*.

CONCLUSIONS

Homozygous sitosterolemia can have marked phenotypical variability even in a setting of limited genetic and environmental variability. Due to its rarity and phenotypic heterogeneity, diagnosis requires a high degree of clinical suspicion.

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