

Sitosterolemia with Extensive Xanthomas in Two Siblings in India: A Case Report

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Abstract: Sitosterolemia is a rare, autosomal recessive inherited sterol storage disease associated with high tissue and serum plant sterol concentrations. First described in 1974 in two sisters by Bhattacharyya and Connor. Patients presents with extensive tendon and tuberous xanthomas but normal plasma cholesterol levels with elevated plant sterol levels. The high plant sterol levels were shown to be due to the increased absorption and delayed removal of plant sterols from the body. Sitosterolemia has been shown to result from mutations in the genes for 2 proteins (ABCG5 or ABCG8). Markedly increased serum concentration of plant sterols, such as sitosterol and campesterol, cause premature atherosclerosis and massive xanthomas. Known treatments for Sitosterolemia, includes a low-sterol diet, bile-salt binding resins, ileal bypass surgery and low density lipoprotein (LDL) apheresis. Recently, Ezetimibe, an inhibitor of intestinal cholesterol absorption, has been used. Ezetimibe also reduces the gastrointestinal absorption of plant sterols, thereby also lowering the serum concentrations of plant sterols. We present a case report of 2 siblings presented in our hospital with extensive tendon xanthomas. Patients are under treatment with bile salt binding resins & Ezetimibe.

Keywords: ABCG5, ABCG8, Ezetimibe, Sitosterolemia, Xanthomas,

I. Introduction

Sitosterolemia is a rare, autosomal recessive inherited plant storage disease¹ characterized by tendon and tuberous (i.e., planar) xanthomas that can occur in childhood and in unusual locations (heels, knees, elbows and buttocks). First described in 2 sisters, 40 years ago by Bhattacharyya and Connor². Only 45 patients with Sitosterolemia have been reported worldwide until date in medical literature³. It is known to be caused by mutation in ABCG5 or ABCG8 genes. It is characterized by disruption of the normal homeostatic mechanisms that regulate dietary cholesterol absorption and prevent the accumulation of non-cholesterol sterols². Phytosterols are almost undetectable in plasma from normal individuals¹. Excess cholesterol and plant sterols are re-secreted into the intestinal lumen for excretion by ABCG5 & ABCG8. Mutation in these transporters impairs plant sterol excretion, resulting in accumulation of plant sterols in the plasma and tissues^{4,5}. As a rare entity, various treatment modalities like bile acid binding resins and ileal bypass surgery have been tried and are effective treatments for sitosterolemic patients, whereas statins are ineffective. A newer therapy, Ezetimibe has been used showing most promising reduction effect on serum sitosterol levels^{6,7}. We here present a case report of 2 such siblings presented in our hospital with extensive tendinous xanthomas.

II. Case Report

Two siblings of age 11 year male (Fig 1, 2) and 6 year female (Fig 3, 4); presented in our hospital's surgery OPD with complaints of multiple swelling over various joints and joint pain. 11 year male presented with swelling over elbows, knee joints, buttocks and various other joints of body. Swelling first appeared at the age of 5 years. Swelling increased in number and size. They are subcutaneous swelling, non-tender, grey to yellowish in color, firm in consistency, varies in size from 5mm to 5cm; with largest swelling measuring approximately 4cm x 5cm. Further examination reveals thickening of Achilles tendon. Examination of 6 year female shows similar types of swelling over various joints with first appearance of swelling at similar age of 5 years. Patient's parents and 2 elder siblings were having no similar lesions and complaints. There was a history of similar lesions in grandfather from paternal side with history of death due to heart attack at the age of 45 years. Maternal side of patient was found to be normal.



(Fig 1 & Fig 2 showing xanthomas in male child)



(Fig 3 & Fig 4 showing early xanthomas in female child)

Biopsy of swelling was taken. Patient's complete blood picture & lipid profile were sent. There values are—

Investigations –

	CASE 1	CASE 2
Hb (g/dL)	9.6	10.1
WBC (X10 ⁹ /L)	7.3	6.4
RBC (X10 ¹² /L)	4.4	3.9
Platelet (X10 ⁹ /L)	162	154
Total cholesterol (mg/dL)	148	136
LDL (mg/dL)	36	24
HDL (mg/dL)	42	55
Triglycerides (mg/dL)	81	76

Plant Sterols Levels –

	Case 1	Case 2
Campesterol (µg/dL)	16.1	12.3
Sitosterol (mg/dL)	33	38
Sitostenol (mg/dL)	14.5	12.6
Cholestanol (mg/dL)	2.1	1.8

Biopsy reveals large foamy histiocytes having foamy vacuolated cytoplasm and centrally placed nucleus present in lobules, separated by septa s/o Xanthoma.

As the patient's lipid profile was almost normal. On the basis of family disease pattern and lipid profile status other diagnosis for xanthomas were sought. Other sterols levels were measured & their level was noted.

As the plant sterol levels were found to be raised, diagnosis of sitosterolemia was made.

Patient was initially treated with dietary modifications & Ezetimibe. Currently patient is on therapy with Ezetimibe 10mg daily.

Sitosterolemia has to be differentiated from other causes of xanthomas like familial hypercholesterolemia which is an autosomal dominant disorder so has to be phenotypically expressed in one of the parents, characterized by elevated LDL-C and normal triglycerides by DSA and HELP aphaeresis system. And cerebrotendinous xanthomas which are characterized by infantile onset diarrhea, child onset cataract while in adults with

paraparesis dysarthria & progressive neurological deterioration. Laboratory examination in beta sitosterolemia shows elevated level of beta-sitosterol (upto 60 times), campesterol & sitostenol (upto 6 times), while in cerebrotendinous xantho-granuloma shows increased cholestanol (upto 6 times).

III. Discussion

Sitosterolemia or phytosterolemia is a rare plantstorage with 45 patients reported worldwide³. First case of sitosterolemia was described by Bhattacharyya and Connor in 1974 in two female siblings².

Inheritance of sitosterolemia was autosomal recessive¹, characterized by tuberous and tendinous xanthomas, premature atherosclerosis, and arthralgia. Mainly while in some cases as hemolysis, macrothrombocytopenia, stomatocytosis, hypersplenism, xanthelasma, archaic cornea. Sterol transporter neimann pick C1L1 has role in preferential absorption of cholesterol over plant sterols. The absorbed plant sterol further excreted out by the ABCG5 & ABCG8 transporter⁵. Etiopathogenesis of sitosterolemia was found to be complete loss of function of 2 genes located at STSL locus over human chromosome 2P21 encoding for adenosine triphosphate binding cassette transporter i.e. ABCG5 & ABCG8 transporter^{1,9,10}. These half transporter are heterodimers; either one of them is defective in patients of sitosterolemia, never both. They are present over intestinal mucosal cell and hepatocytes. They are responsible for plant sterol extrusion from intestinal cells and hepatocytes. Their dysfunction leads to storage of plant sterols in plasma and tissues (15-63%)¹¹⁻¹³.

Work of Glueck et al first supported correlation between elevated plant sterol level and coronary heart disease¹⁴, later supported by Framingham offspring study¹⁵ and Procainamide study¹⁶.

Management of sitosterolemia was to be aimed with dietary measurement i.e. restriction of excess phytosterol containing food ex - vegetable oils, margarine, nuts, chocolates, shell fish & treatment with bile acid sequestrants (Colestipol & cholestyramine). Although some reports have shown that diet therapy is often unsuccessful as it is difficult to comply with and has also shown to produce adversely contradictory increases in plasma plant sterol levels^{17, 18}. Statins (HMG CoA Reductase Inhibitor), sitostanol have little usefulness in these patients. For the local treatment of lesions laser ablation and chemical ablation with trichloroacetic acid was found to be helpful. Partial ileal bypass surgery has led to considerable reduction of total plasma level of sterols. Plasma apheresis was tried in few cases but its role has not been established by any clinical trial till date. Most promising results were found with Ezetimibe, a novel drug, selective inhibitor of NPC1L1 intestinal sterol transporter has been shown to block the transport of dietary sterols and to progressively reduce the levels of preferably plant sterols also helpful in limiting complications of sitosterolemia such as thrombocytopenia and hemolysis²¹.

In our cases, elder sibling arrived at our hospital with extensive tendinous xanthomas. Biopsy was taken which was suggestive of Xanthomas. Further detailed history was sought, revealing a younger sibling also affected with similar complaints. Complete blood picture & complete lipid profile were carried out; results were normal. Plant sterol levels were carried out revealing abnormal levels. Diagnosis of Sitosterolemia was made. Patients were initially kept on dietary modifications for 2 months followed by Ezetimibe therapy. Currently, patients are on Ezetimibe therapy for 2 months and under regular follow up.

IV. Conclusion

Xanthomas are usually associated with lipid metabolism disorder & simply not a cosmetic lesions as they can signify serious cardiovascular & metabolic diseases. The definite management for Sitosterolemia has not been established. Ezetimibe a treatment agent has worked effectively. Additionally patients should be under regular follow up for cardiovascular & hematological complications.

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