Sitosterolaemia presenting with consistent skin xanthomas in a pair of monozygotic twins who responded to ezetimibe treatment

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Sitosterolaemia (STSL), also known as phytoesterolaemia, was first described by Bhattacharyya and Connor in 1974. It is a rare autosomal recessive disorder caused by homozygous or compound heterozygous variants in ABCG5 or ABCG8, both of which play important roles in the selective excretion of plant sterols from the liver and intestine, leading to a failure to excrete plant sterols.

Clinical features of STSL usually include tendinous and/or cutaneous xanthomas, premature coronary atherosclerosis, arthritis, haematological abnormalities such as haemolytic anaemia, iron deficiency anaemia and macrothrombocytopenia. Herein, we report details of monozygotic twins who had STSL presenting with skin xanthomas.

Eight-year-old monozygotic twin girls were referred to the outpatient clinic for evaluation of skin lesions that had developed the year before. Interestingly, the twins had similar lesions in identical locations. They were otherwise healthy and born to nonconsanguineous parents. Physical examination revealed several well-defined yellowish-brown nodules and papules on their elbows, knees and buttocks (Figure 1a).

Laboratory results showed marked hypercholesterolaemia with serum total cholesterol (TC) levels of 9.27 mmol L\(^{-1}\) and 10.15 mmol L\(^{-1}\) (normal range <4.40 mmol L\(^{-1}\)) and low-density lipoprotein cholesterol (LDL-C) levels of 7.52 mmol L\(^{-1}\) and 7.91 mmol L\(^{-1}\) (normal range <3.12 mmol L\(^{-1}\)) for twin ‘A’ and twin ‘B’, respectively.

Histological findings revealed atrophy of the epidermis, and a large number of foam cells throughout the dermis with multiple Touton giant cells (Figure 2a). Whole exome sequencing and Sanger sequencing were performed on the family members using genomic DNA from peripheral blood. Compound heterozygous variants, i.e. maternal c.904+1G>A and paternal c.1166G>A (p.Arg389His) in ABCG5 (GenBank reference sequence: NM_022436.3) were identified in the twins (Figure 2b). Both of the detected variants have been reported previously in patients with STSL.

As a diagnosis of STSL was suspected, peripheral blood smear examination of the twins was further performed, revealing macrothrombocytes and stomatocytosis (Figure 2c), consistent with the features of STSL. Thus, lipid-lowering therapy including a restrictive plant-sterol diet control and oral ezetimibe with a dose of 10 mg every 48 h were started.

After 4 months of treatment with ezetimibe, the TC and LDL-C level decreased dramatically (twin A: TC level: 4.67 mmol L\(^{-1}\) and LDL-C levels: 2.70 mmol L\(^{-1}\) and twin B: TC level: 4.59 mmol L\(^{-1}\) and LDL-C levels: 2.81 mmol L\(^{-1}\)) and partial resorption of the skin lesions was observed (Figure 1b).

Clinical presentation of STSL is variable, making early diagnosis challenging. Furthermore, conventional lipid tests cannot distinguish cholesterol from phytosterols. Although elevated plasma phytoester is diagnostic, it is not a routine test and not available in most low- and middle-income countries. Thus, it is difficult to diagnose STSL and treat it in the early stages.

Persistent high cholesterol levels can cause premature coronary artery disease, which is usually severe and accounts for most deaths in people with STSL. Therefore, early diagnosis and treatment are very important for patients with STSL. Recently, homozygous or compound heterozygous variants in ABCG5 or ABCG8 that can encode the sterol efflux transporter sterolin 1 and sterolin 2, respectively, which pumps sterols out to the intestinal lumen or into bile, have been identified as the cause of STSL. Although genetic testing is a reliable diagnostic tool for STSL, it is sometimes time-consuming and expensive. Alternatively, as haematological manifestations of stomatocytosis/macrothrombocytopenia can be the only clinical sign of STSL, peripheral blood smear examination is simple, faster and more convenient to diagnose STSL.

Breastfed infants with STSL can present with extremely high cholesterol levels with xanthomatosis because of the high cholesterol content of breast milk, but with a normal sitosterol/cholesterol ratio. The plant-sterol level increases and the cholesterol level somewhat decreases as the infant starts eating fruits and vegetables.

Treatment of STSL includes restriction of intake of plant sterols and blocking the absorption of sterols. Patients with STSL should avoid plant-sterol-rich foods, such as corn oil, sesame seeds, peanuts, soybeans, rapeseed oil, sesame oil, rice oil, margarine, avocado, chocolate and shellfish. In addition to plant sterols, they also need to avoid cholesterol-rich foods, including animal liver and eggs.
Ezetimibe and bile-acid sequestrant resins have been established as standard therapies to reduce the absorption of plant sterols from the intestine and increase their secretion from the liver.\textsuperscript{4} It is of note that patients who are hypercholesterolaemic with \textit{ABCG5} or \textit{ABCG8} variants exhibit satisfactory responses to ezetimibe to lower LDL cholesterol.\textsuperscript{2} Patients with STSL usually do not respond to statins. Therefore, it is essential to consider STSL and to assay plasma phytosterols for patients with early-onset xanthomas and hypercholesterolaemia with poor response to statins.\textsuperscript{2} The twins showed remarkable improvement with a restricted diet and ezetimibe treatment, and further follow-up was continued to monitor the patients’ growth indicators and potential adverse drug reactions.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Data sharing is not applicable to this article as no new data was created or analysed in this study.

Ethics statement

Ethical approval: the study was approved by the Medical Ethics Committee of Dermatology Hospital of Southern Medical University. Informed consent: all patients gave written, informed consent for participation and publication of their case details and images.

References

1 Bhattacharyya AK, Connor WE. Beta-sitosterolemia and xanthomatosis. A newly described lipid storage disease in two sisters. \textit{J Clin Invest} 1974; \textbf{53}:1033–43.

CPD questions

Learning objective

To demonstrate knowledge about the clinical and genetic features of sitosterolaemia (STSL).

Question 1

Which of the following is not a clinical feature of STSL?

(a) Xanthomas.
(b) Premature coronary atherosclerosis.
(c) Haematological abnormalities.
(d) Arthritis.
(e) Hypertrophic scars.
Figure 2  (a) Histological picture shows atrophy of the epidermis, and a large amount of foam cells throughout the dermis with multiple Touton giant cells [haematoxylin and eosin staining, original magnification: (left) × 100 and (right) × 200]. The arrow indicates the Touton giant cell. (b) Sanger sequencing confirmed the two heterozygous variants in ABCG5 in twin A. (c) Peripheral blood smear examinations revealed macrothrombocytes and stomatocytosis (arrow, original magnification × 1000).

Question 2

Which of the following are the causative genes for STSL?

(a) ABCG3 and ABCG7.
(b) ABCG5 and ABCG8.
(c) ABCG2 and ABCG6.
(d) ABCG3 and ABCG9.
(e) ABCG4 and ABCG7.

Instructions for answering questions

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