ESC European Society of Cardiology

European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytab188

CASE REPORT
Other

Seventeen years of misdiagnosis in rare dyslipidaemia: a case report of sitosterolaemia in a young female

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Received 1 December 2020; first decision 23 December 2020; accepted 16 April 2021

Background Sitosterolaemia is a rare, autosomal recessive dyslipidaemia with increased absorption of dietary plant sterol and often presents with hypercholesterolaemia, xanthomas, and haematologic manifestations. If left untreated, sitosterolaemia can lead to high symptomatic burden and coronary artery disease (CAD).

Case summary We describe a case of a young female who initially presented at 4 years of age with classic manifestations of sitosterolaemia. She was misdiagnosed and treated for both juvenile arthritis and later familial hypercholesterolaemia until adulthood, when venous blood samples showed significantly elevated concentrations of plant sterols. DNA analyses showed that the patient was homozygous for a mutation in the ABCG5 gene, [c.1336C>T, p.(Arg446*)], which is known to be associated with sitosterolaemia.

Discussion Sitosterolaemia presents with multiple manifestations, which can initially be misinterpreted leading to prolonged misdiagnosis. Early diagnosis is key in order to relieve symptoms and prevent CAD.

Keywords Dyslipidaemias • Genetics • Hypercholesterolaemia • Case report • Sitosterolaemia

Learning points

- Sitosterolaemia is a rare dyslipidaemia that often presents with hypercholesterolaemia, xanthomas, and haematological disorders.
- Sitosterolaemia is an autosomal recessive disorder, thus parental consanguinity increases the risk significantly.
- Sitosterolaemia should be considered in hypercholesterolemic patients with poor effect of statin treatment, normocholesterolemic xanthomas, great effect of dietary changes on cholesterol levels and xanthomas, or unexplained haemolytic anaemia and macrothrombocytopenia.
- Ezetimibe and a diet low in plant sterols are recommended treatments of sitosterolaemia, and compliance to treatment is essential to reduce cholesterol levels.

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Handling Editor: Ching-Hui Sia
Peer-reviewers: Vasilios Giampatzis and Constantino Mancusi
Compliance Editor: Daniel Tardo
Supplementary Material Editor: Aiste Monika Jakstaite

Introduction

Sitosterolaemia is a rare, autosomal recessive dyslipidaemia. Patients often present with hypercholesterolaemia, xanthomas, and haematologic manifestations.[1] Current guidelines recommend testing for familial hypercholesterolaemia (FH) in children with a family history of elevated low-density lipoprotein (LDL) cholesterol, premature coronary artery disease (CAD), and/or positive genetic testing,[2] but there are no guideline recommendations on diagnostic evaluation of sitosterolaemia. There are no clinical trial data on management of sitosterolaemia, but a diet low in plant sterols and treatment with Ezetimibe are recommended.[3] However, recommendations are based on low level of evidence.[4,5] This report describes a young female with symptoms of sitosterolaemia, who was misdiagnosed during her childhood leading to a high symptomatic burden.

Timeline

Date	Medical information, treatment, or investigation
1999	Patient born
2003–2008	Several tumours related to joints surgically removed
2008	Pathological examination of joint-related tumour interpreted as granulomatous inflammation
2008	Diagnosis of juvenile idiopathic arthritis. Treatment with methotrexate initiated
2009	Progression of joint pain
2009	Blood cholesterol measurement for the first time. Total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol all significantly increased
2009	Previous biopsy from tumour was revised and found compatible with xanthoma
2009	Genetic testing negative for any known mutations in the LDL receptor and apolipoprotein B genes
2009	Diagnosis of familial hypercholesterolaemia. Initiation of treatment with Simvastatin 10 mg/day. No significant response
2010	Simvastatin increased to 20 mg/day with no significant response
2012	Change to Atorvastatin 80 mg/day
2012	Patient admitted to the hospital with acute liver failure. Ultrasound of the abdomen revealed an enlarged spleen. Side effects to the statin treatment was suspected and treatment was discontinued
2012	Treatment with Ezetimibe 10 mg/day initiated
2019	Patient referred to the haematology department with prolonged thrombocytopenia and reticulocytosis. Folic acid treatment for 3 months was initiated
2019	Patient referred to our department wishing to discontinue Ezetimibe. Total cholesterol was 6.1 mmol/L (236 mg/dL), HDL 2.2 mmol/L (85 mg/dL), and LDL was 2.8 mmol/L (108 mg/dL)
2019	Venous blood samples with significantly elevated concentrations of plant sterols, campesterole, and sitosterole
2019	DNA analyses. Patient homozygous for a mutation in the ABCG5 gene, [c.1336C>T, p.(Arg446*)], known to be associated with sitosterolaemia
2019	Ezetimibe 10 mg/day continued and dietary consulting initiated
2020	One-year follow-up. Increased total cholesterol and LDL. Patient admitted being inconsistent with treatment and diet

Case presentation

A 21-year-old woman was referred to the cardiology department by her general practitioner. Ten years prior she had been diagnosed with FH and was taking Ezetimibe 10 mg once a day. Her total cholesterol was 6.1 mmol/L (236 mg/dL), high-density lipoprotein (HDL) cholesterol was 2.2 mmol/L (85 mg/dL), and LDL cholesterol was 2.8 mmol/L (108 mg/dL). The patient wished to discontinue the medication. When she came to the outpatient clinic, she had not taken her Ezetimibe for 2 weeks. Her total cholesterol increased to 7.0 mmol/L (271 mg/dL) and LDL 4.0 mmol/L (155 mg/dL). The patient was a never smoker and had a normal body mass index. Her blood pressure was normal, and she had no signs of diabetes [haemoglobin A1c 23 mmol/mol (4.3%)]. Clinical examination revealed a xanthoma on the left hand (*Figure 1*). She had no complaints of chest pain or shortness of breath.

At age 4, the patient presented with an excrescence at the intergluteal cleft, which was surgically removed. At same age, she was admitted to the hospital with the suspicion of reactive arthritis. From age 4 to 10 years, she often had complaints of joint pain and presented with several joint-related tumours, some of which were surgically removed. One was sent for pathological examination and interpreted as granulomatous inflammation. She was then diagnosed with juvenile idiopathic arthritis at age 10 and treated with methotrexate for 1.5 years. Despite the treatment, her symptoms progressed. At that time, her blood cholesterol was measured for the first time. Total cholesterol was 9.8 mmol/L (379 mg/dL), HDL 7.8 mmol/L (302 mg/dL), and LDL 7.6 mmol/L (294 mg/dL). The previous biopsy was revised and found compatible with a xanthoma. She was diagnosed with clinical FH and had genetic testing done, which

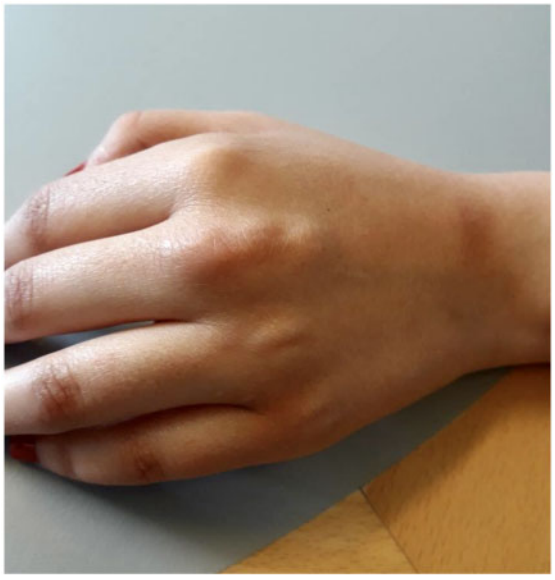

Figure 1 Xanthoma on third finger. At her first visit in the outpatient clinic, the patient presented with a xanthoma on the left hand.

was negative for any known mutations in the LDL receptor and apolipoprotein B genes. Her parents were cousins and neither of them had hypercholesterolaemia. Her mother's father suffered from stroke at age 58 and had a coronary artery bypass at age 65. His brother had acute myocardial infarction at 50 years of age. The patient's brother was apparently healthy (*Figure* 2). When she was diagnosed with FH, she changed her diet, which had some effect on her cholesterol levels and symptoms. Furthermore, she was started on Simvastatin 10 mg/day, which had little effect despite a later increase in dose to 20 mg/day and consequently a change to Atorvastatin 80 mg/day. Shortly after, she was admitted to the hospital with nausea and vomiting. She was icteric and had impaired liver function with alanine transaminase of ~1600 U/L. Ultrasound of the abdomen revealed an enlarged spleen (length of 13.7 cm). Side effects to the statin treatment were suspected and the treatment was discontinued. After the hospitalization, treatment with Ezetimibe 10 mg/day was initiated. Eventually, her liver function normalized completely.

After 5 years of mild thrombocytopenia on routine blood samples, the patient was referred to the haematology department with a platelet count of 139×10^9/L and reticulocytosis (reticulocyte count of 114×10^9/L). She had no symptoms of haematological disorders. On clinical examination there was no lymphadenopathy. Haemoglobin was normal (8.4 mmol/L), haptoglobin was slightly

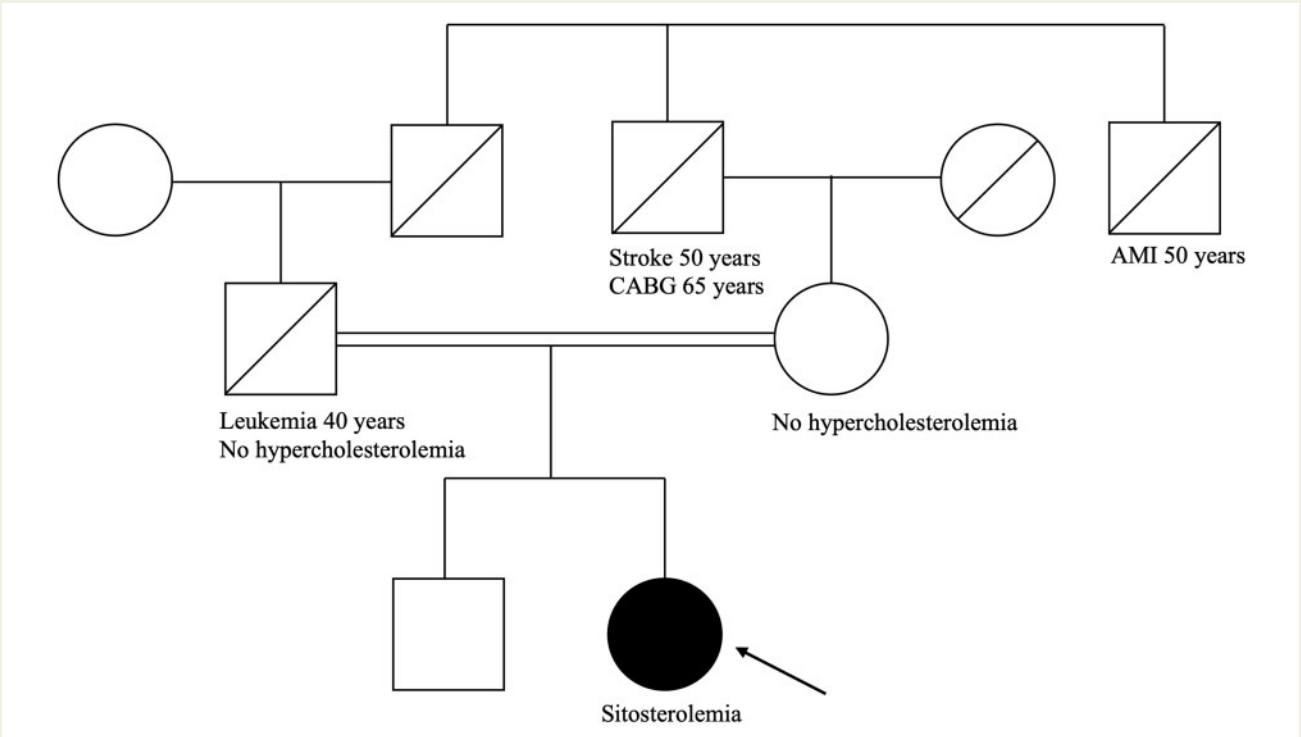

Figure 2 Pedigree. The patient was the only family member with sitosterolaemia, which is an autosomal recessive disorder. Her parents were cousins. Consanguinity is indicated by a double line. Males are represented by squares and females by circles. A clear symbol shows an unaffected individual, while a black symbol shows an affected individual. Deceased individuals are presented with a diagonal line. The arrow shows the proband. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting.

decreased (0.30 g/L), free haemoglobin was mildly increased (4 µmol/L), and direct antiglobulin test was negative. The cause of thrombocytopenia was not identified, and the patient was prescribed a folic acid treatment for 3 months, which had no effect on her platelet count (122×10^9/L after treatment).

At the cardiology outpatient clinic, blood samples were analysed for concentrations of plant sterols, campesterole, and sitosterole using a gas chromatographic/mass spectrometric method.[6] The concentration of campesterole was 170 µg/mL and sitosterole was 270 µg/mL. Normal values for both are <15 µg/mL.

DNA analyses showed that the patient was homozygous for a mutation in the ABCG5 gene [c.1336C>T, p.(Arg446*)], which is known to be associated with sitosterolaemia.[7]

The patient was referred to a dietary consultant and Ezetimibe 10 mg/day was again prescribed.

At the most recent follow-up, ~15 months after diagnosis, the patient had a total cholesterol level of 6.4 mmol/L (248 mg/dL) and LDL 4.0 mmol/L (155 mg/dL). The patient admitted being inconsistent with the medical therapy and having difficulties with diet adherence.

Discussion

This case report describes a 21-year-old female with manifestations of sitosterolaemia, including increased levels of total cholesterol, LDL and plant sterols, xanthomas, and thrombocytopenia. The patient was misdiagnosed with juvenile idiopathic arthritis and later FH until adulthood, when she was finally diagnosed with sitosterolaemia.

Sitosterolaemia is an autosomal recessive disorder characterized by increased plasma levels of plant sterols. It is associated with a mutation in either the ABCG5 or ABCG8 gene both encoding proteins, which help transport sterols to intestinal lumen or into bile.[7] This results in increased intestinal absorption and decreased biliary excretion of plant sterols leading to extreme plasma levels.[1] Patients often present with increased levels of total and LDL cholesterol, since cholesterol absorption can be increased as well.[1] However, cholesterol levels can be normal, as in the first cases of sitosterolaemia described in 1974.[8]

Differential diagnoses are other rare dyslipidaemias such as heterozygous FH, homozygous FH, autosomal recessive hypercholesterolaemia (LDLRAP1 mutations), lysosomal acid lipase deficiency, and cerebrotendinous xanthomatosis.

The major clinical manifestation of sitosterolaemia is xanthomas,[9] often tendinous or tuberous xanthomas formed on the extensor areas. However, intertriginous xanthomas have also been described.[10] Another known manifestation of sitosterolaemia is haemolytic anaemia and macrothrombocytopenia.[1] In several cases of sitosterolaemia, splenomegaly was present, sometimes leading to splenectomy.[11] In our case, the patient had acute liver dysfunction, which has previously been described in sitosterolaemia.[12]

Premature CAD has been described in young patients with sitosterolaemia, both in patients with hypercholesterolaemia[13] but also in normocholesterolemic patients.[14] However, there is no evidence regarding causality between sitosterolaemia and cardiovascular disease (CVD). A report of five sitosterolaemia patients with hypercholesterolaemia showed no signs of clinical or subclinical CVD and the authors suggested that premature CVD in sitosterolaemia is independent of circulating plant sterols.[15]

Non-invasive imaging techniques such as detection of coronary artery calcification with computed tomography and assessment of carotid or femoral plaque burden have been proven to predict cardiovascular events beyond traditional risk factors in asymptomatic individuals.[16,17] Guidelines suggest that such imaging techniques may be used in low- or moderate-risk patients in order to guide treatment strategy.[2] However, the benefits of screening asymptomatic patients, already receiving pharmacological treatment, are somewhat unclear. A possible benefit could be motivation to medication and lifestyle adherence, while there are some disadvantages such as radiation hazards and lack of long-term reassurance even if imaging shows no signs of atherosclerosis, especially in young individuals. In our case, we chose not to screen the patient with non-invasive imaging techniques since the results would most likely have no consequences for the current management.

Indications for plant sterol measurement in clinical practice could be hypercholesterolaemia with poor effect of statin treatment, normocholesterolemic xanthomas, unexpected effect of dietary changes, or unexplained haemolytic anaemia and macrothrombocytopenia.[1]

Hyperlipidaemia in sitosterolaemia responds well to reduction in dietary sterol intake,[9] while there is often a poor response to statin treatment.[1] The lack of improvement on statin treatment could have been a diagnostic clue in our case. Ezetimibe has been shown to reduce levels of total cholesterol and plant sterols in sitosterolaemia.[3] In some cases, treatment with Ezetimibe has significantly reduced xanthomas[4] and improved platelet count.[3] Thus, early initiation of treatment and compliance seem important in order to reduce symptoms and prevent CVD.

Conclusion

Sitosterolaemia is a rare form of dyslipidaemia characterized by increased levels of plant sterols. The condition often presents with hypercholesterolaemia, xanthomas, and haematologic manifestations and can initially be misinterpreted leading to prolonged misdiagnosis. Early diagnosis and prompt treatment with Ezetimibe and reduction in dietary sterol intake are essential to reduce cholesterol levels.

Lead author biography

Tanja Charlotte Frederiksen is an MD and PhD Student in Cardiology at Aarhus University Hospital. Her interest areas are genetic heart disease, electrophysiology, and personalized medicine.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

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