Homozygous Tangier disease with undetectable serum high density lipoprotein cholesterol levels and no clinical features

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Abstract

Introduction

Tangier disease is a very rare inherited disorder characterised by much reduced high-density lipoprotein levels, large yellow-orange tonsils and enlarged liver, spleen and lymph nodes. It is caused by mutations in the ATP-binding cassette transporter A1 gene. This paper reports a case of homozygous Tangier disease with undetectable serum high density lipoprotein cholesterol levels and no clinical features.

Case report

We report a study of a 40-year-old female who presented with undetectable high-density lipoprotein cholesterol but no clinical signs of Tangier disease. Her family history is significant for her father having premature cardiovascular disease and a moderately low high-density lipoprotein cholesterol and other relatives having low or undetectable high-density lipoprotein cholesterol levels.

The biochemical signs of this condition include serum HDL cholesterol concentration less than 0.12 mmol/L, apoA-I levels below 0.05 g/L, low total serum cholesterol below 3.9 mmol/L and normal or high serum triglycerides. The major clinical signs of Tangier disease are hyper-plastic orange-yellow tonsils, hepatosplenomegaly, neuropathy, corneal opacities, thrombocytopenia, anaemia and stomatocytosis. These clinical signs combine differently in each patient and we report a patient without physical signs identified by finding undetectable serum levels of HDL cholesterol.

Case report

A 40-year-old female was referred to the lipid clinic because of persistent undetectable serum HDL cholesterol (HDL-C) levels of <0.1 mmol/L. The other serum lipids had varied with total cholesterol of 2.9 to 2.3 mmol/L and triglycerides of 2.5 to 1.7 mmol/L. Serum apolipoprotein A1 was found to be undetectable at < 0.05 g/L (reference range: 1.25–2.15) and apolipoprotein B was within the normal adult reference range of 0.55 to 2.15 g/L at 0.95 g/L. Fasting plasma glucose was 4.7 mmol/L and renal, liver, thyroid function tests and a blood cell count were normal. On microscopy a blood film showed anisopikilocytosis with acanthocytes and elliptocytes.

A very low serum HDL-C was first recorded during her first pregnancy at age 23 years. At age 35 years, she underwent a bilateral oophorectomy and hysterectomy for endometriosis. She takes oestradiol 1 mg/day as hormone replacement therapy and tolterodine 4 mg/day, an antimus-carinic for urinary incontinence, and no over-the-counter medication or supplements. She stopped smoking 10 years ago, keeps to a healthy diet, takes exercise and only occasionally drinks alcohol.

Physical examination showed no discolouration of tonsils or pharynx, no enlargement of liver, spleen or lymph nodes, no peripheral neuropathy and no corneal opacities. She had a blood pressure of 113/67 mmHg and body mass index of 30 kg/square metre. Computed tomography studies showed mild calcification of the right coronary artery but no stenosis was found on angiography.

She was found to have family members with reduced HDL-C levels. Her brother aged 37 years has schizophrenia and a serum HDL-C <0.1 mmol/L. Her father, her 17-year-old daughter and 11-year-old son have low levels of HDL-C of 0.8 mmol/L, 1.0 mmol/L and 0.8 mmol/L respectively. Her father presented at age 40 years with a stroke and ischaemic heart disease.

Genetic analysis was undertaken in the medical genetics department, Oslo University Hospital, Norway. DNA sequencing of the translated exons with flanking intron sequences of the apolipoprotein A-I (apoA-I) and lecithin-cholesterol acyltransferase (LCAT) genes did not identify

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any mutation. DNA sequencing of the translated exons of the ATP-binding cassette transporter A1 (ABCA1) gene revealed that the patient is a true homozygote for mutation c.1758dupG in exon 14 in the ABCA1 gene. This mutation is a duplication that causes a frame shift, which leads to a premature stop codon being generated 43 codons downstream of the mutation (p.Arg587AlafsX43). This results in a non-functional protein and indicates a diagnosis of Tangier disease.

**Discussion**

Tangier disease is caused by mutations in the ABCA1 gene which encodes the membrane transporter ABCA1. The ABCA1 gene resides on chromosome 9q22-q31, contains 50 exons, and codes for a 2261-amino acid long membrane protein. In this case, the mutation was found to be a true homozygote for mutation in exon 14 in the ABCA1 gene. This is a duplication that causes a frame shift, leading to a premature stop codon being generated 43 codons downstream of the mutation, which in turn generates a non-functional protein. This transporter normally plays a key role in the first step of reverse cholesterol transport, through which the efflux of free cholesterol from non-hepatic peripheral tissues is transferred to HDL by the ATP-binding cassette transporter. Lipid-poor apoA-I acts as an acceptor, and the phospholipid component of HDL acts as a sink for the mobilised cholesterol and thereby plays a central role in both regulating cellular cholesterol homeostasis and forming HDL.

A non-functional ABCA1 impairs free cholesterol efflux from cells. This may lead to intracellular accumulation of esterified cholesterol, prevention of lipid-poor apoA-I particles converting into pre-β HDL and rapid catabolism of the poorly lipidated apoA-I primarily by the kidney. This rapid catabolism explains why this patient has very low levels of apoA-I despite a normal apoA-I gene.

There has been an on-going debate as to whether HDL deficiency in Tangier disease is caused by increased catabolism or by the decreased synthesis of apolipoproteins. A number of studies using radiolabeled HDL, apoA-I and apoA-II in Tangier disease affected patients have been performed and reveal a markedly increased catabolism of apoA-I, apoA-II and HDL. These studies support the metabolic basis of Tangier disease being a rapid catabolism of apoA-I and HDL. In our patient, a frame-shift mutation leads to the formation of non-functional ABCA1 proteins which in turn prevents the uptake of free cholesterol and leads to the loss of HDL particles.

Epidemiological studies demonstrate an inverse association between low levels of HDL cholesterol and increased risk of ischaemic heart disease, but population studies suggest that genetically low HDL cholesterol per se does not predict an increased risk of ischaemic heart disease. Reduced HDL is associated with cardiovascular disease by its function in regulating cholesterol efflux, modulation of the inflammatory response, antioxidiant activity and vasomotor regulation. Some believe that the main protective effect of HDL in preventing cardiovascular disease is by inhibiting the oxidative modifications of low density lipoprotein, an initial step in the atherosclerotic process. The literature on homozygous Tangier disease indicates a strong association with cardiovascular disease and premature onset of coronary artery disease.

To date, there is no specific treatment for Tangier disease. The hypothesis that elevation of HDL reduces the atherosclerotic burden and/or decreases ischaemic cardiovascular events in humans has unfortunately been impeded by a lack of drugs that selectively increase HDL. Most of the drugs designed to increase HDL levels, have not been shown to be effective in patients with Tangier disease. Our patient has no clinical evidence of cardiovascular disease but imaging studies of her coronary arteries show mild calcification without stenosis. As her father has low HDL cholesterol and presented with premature cardiovascular disease, it is likely that she too has a high risk for cardiovascular events. Even though her total cholesterol is low, she may benefit in the long term from low density lipoprotein cholesterol lowering therapy as well as weight reduction and a very low fat diet.

**Conclusion**

This case study illustrates how a patient with Tangier disease without clinical features may be identified by serum lipid profile screening and finding an undetectable HDL-C level. The diagnosis must be confirmed by genetic analysis of genes associated with low HDL-C. The degree of risk for cardiovascular disease may be estimated by studying the family history of lipid abnormalities and cardiovascular events.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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**References**