A Non-classical Presentation of Tangier Disease with Three *ABCA1* Mutations

Muhammad Ali Pervaiz • Gerald Gau • Allan S. Jaffe • Amy K. Saenger •
Linnea Baudhuin • Jay Ellison

Received: 12 April 2011 / Revised: 31 May 2011 / Accepted: 14 July 2011 / Published online: 28 September 2011
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Abstract Tangier disease is a very rare autosomal recessive inherited disorder characterized by markedly reduced high-density lipoprotein (HDL) levels, characteristic large, yellow–orange tonsils, and enlarged liver, spleen and lymph nodes. It is caused by mutations in the *ABCA1* gene. There is no specific treatment, and medications traditionally used to increase HDL are ineffective. A number of patients with non-classical Tangier disease have been described in the literature, who presented with low HDL levels, corneal lesions, hepatosplenomegaly, and thrombocytopenia. We report here about a 45-year-old female with a past medical history of early coronary artery disease, myocardial infarction, multiple episodes of angina, immeasurable HDL, and a history of idiopathic thrombocytopenia purpura. She had a tonsillectomy performed previously, but did not remember if the tonsils were of

any unusual color. There was no history of peripheral neuropathy. Her family history is significant for her father and mother having Alzheimer disease and hypertension, respectively. On physical examination she did not have any hepatosplenomegaly or corneal opacities. She was found to have three mutations in the *ABCA1* gene. These were designated A1046D (c.3137C>A) in exon 22; Y1532C (c.4595A>G) in exon 34, and W1699C (c.5097G>T) in exon 37. All three have been reported to be deleterious in functional studies. The patient has immeasurable HDL, which leads us to assume that two mutations are on one allele and one mutation on the other. We suspect that this condition is under-diagnosed, and as more patients are reported in the literature, the phenotype of Tangier disease will be elucidated further.

Communicated by: Robert Steiner.

Competing interests: None declared.

M. Ali Pervaiz (✉)
Biochemical Genetics Laboratory, Mayo Clinic, 200 First Street
SW, Rochester, MN, USA
e-mail: pervaiz.muhammad@mayo.edu

M. Ali Pervaiz
e-mail: dr.alipervaiz@yahoo.com

G. Gau
Department of Medicine, Mayo Clinic, Rochester, MN, USA

A.S. Jaffe • A.K. Saenger • L. Baudhuin
Cardiovascular Laboratory Medicine, Mayo Clinic, Rochester,
MN, USA

J. Ellison
Reflects work done while affiliated with Department of Medical
Genetics, Mayo Clinic, Rochester, MN

Introduction

Tangier disease (OMIM 205400) is a rare autosomal recessive inherited disease characterized by markedly reduced high-density lipoprotein (HDL) levels (Schaefer et al. 2010). This leads to accumulation of cholesterol esters in macrophages and other reticuloendothelial tissues. The deposition of cholesterol esters leads to the characteristic large, yellow–orange tonsils, corneal opacities, peripheral neuropathy, and enlarged liver, spleen and lymph nodes. It is caused by mutations in the *ABCA1* gene (HGNC: 29) encoding an ATP-binding cassette transporter. The protein mediates efflux of unesterified cholesterol and phospholipids from cells and their transfer to lipid poor Apo-AI particles. These are then converted to nascent HDL. There is no specific treatment and medications traditionally used to increase HDL are ineffective. A number of cases of non-classical Tangier disease have been described in the

literature (Bertolini et al. 2001; Ishii et al. 2002; Pichit et al. 2010; Hooper et al. 2009). These patients had low total plasma cholesterol and HDL cholesterol levels, premature coronary artery disease, corneal lesions and hepatosplenomegaly, and one of them had thrombocytopenia. None of the other features of Tangier disease, including enlarged tonsils, anemia, and peripheral neuropathy, were present. We report a patient with some similar features.

Case Report

Our patient is a 45-year-old female with a past medical history of early coronary artery disease, myocardial infarction, diffuse atherosclerosis, multiple episodes of angina, total cholesterol of 60 mg/dL, triglycerides of 103 mg/dL, calculated LDL of 34 mg/dL, immeasurable HDL, and a history of idiopathic thrombocytopenia purpura, with her lowest platelet levels being 50×10^9 per liter. Additional cardiac risk factors were tested including serum C-reactive protein (5.6 mg/L; normal ≤ 3.0), cardiac fibrinogen (348 mg/dL; normal < 340), total homocysteine (11 $\mu\text{mol/L}$; normal ≤ 13) and lipoprotein (a) mass (16 mg/dL; normal ≤ 30). NMR Spectroscopy of lipoprotein particles detected total LDL particle concentration of 1,809 H nmol/L (optimal $< 1,000$; near or above optimal: 1,000–1,299; borderline high: 1,300–1,599; high: 1,600–2,000; very high $> 2,000$), small LDL particle concentration of 1,467 nmol/L (optimal < 600 ; near or above optimal: 600–899; borderline high: 900–1,199; high: 1,200–1,500; very high $> 1,500$), total HDL particle concentration of $< 3 \mu\text{mol/L}$ (low < 23 ; intermediate: 23–40) and large HDL particle concentration of $< 1.5 \mu\text{mol/L}$ (low < 4.0 ; intermediate: 4.0–9.0; optimal > 9.0).

She had a tonsillectomy performed previously but did not remember if the tonsils were of any unusual color. There was no history of peripheral neuropathy. Her family history is significant for her father and mother having Alzheimer disease and hypertension, respectively. Her sister was also diagnosed with low HDL levels. On physical examination, our patient did not have any hepatosplenomegaly or corneal opacities and a CT scan of the abdomen failed to reveal organomegaly. She tested negative for *APOA1* mutations, which can cause familial HDL deficiency. She was found to have three mutations in the *ABCA1* gene. These were designated p.A1046D (c.3137C>A) in exon 22; p.Y1532C (c.4595A>G) in exon 34 and p.W1699C (c.5097G>T) in exon 37. All three of these mutations have been reported to be deleterious in functional studies. The p.A1046D mutation has been found to abolish cholesterol efflux (Pisciotta et al. 2009). The p.Y1532C (Cameron et al. 2010) and p.W1699C (Pisciotta

et al. 2009) have been found to prevent the mutant proteins from exiting the endoplasmic reticulum.

Discussion

Although the LDL cholesterol concentration was optimal, our patient was at high risk of coronary heart disease because of increased total LDL particle and small LDL particle concentration, along with low total HDL particle and large HDL particle concentrations. The W1699C and Y1532C mutations have been described in the literature as having some residual function (Pisciotta et al. 2009; Cameron et al. 2010), whereas A1046D mutations causes severe loss of gene product and its function. Because of her phenotype and a heterozygous genotype, the chromosome with only one mutation may have a milder mutation that still provides some function to the transporter, thus giving her a non-classic phenotype. It would be ideal to test her parents to confirm the exact inheritance of these mutations, but this was not pursued further because of the patient's reluctance to get her elderly parents involved. Genetics variants and polymorphisms in *ABCA1* gene have been reported in some Alzheimer disease patients (Koldamova et al. 2010), as well as patients with hypertension (Yamada et al. 2008). Though the data supporting these associations are still preliminary, in our case, it does allow us to infer that both parents most likely carry at least one mutation each. Her sister's history of low HDL indicates that she might be a carrier as well.

We suspect that the prevalence of patients with atypical or non-classical features may be higher than what is known presently. Heterozygous mutations are known to cause familial HDL deficiency. A number of recent publications (Candini et al. 2010; Alrasadi et al. 2006; Berge and Leran 2010) reported patients with low HDL carrying novel heterozygous mutations in their *ABCA1* gene. The patient presented here did not have any corneal lesions, hepatosplenomegaly, or peripheral neuropathy. It is unknown whether she had "yellow orange" tonsils due to their removal at an earlier age and the unavailability of a record of their coloration. Her only features consistent with Tangier disease were low HDL and significant coronary artery disease, which makes it unique compared to other cases discussed in the literature (Bertolini et al. 2001; Ishii et al. 2002; Pichit et al. 2010; Hooper et al. 2009), all of whom presented with at least one typical finding of Tangier disease, except for one patient who never developed any clinical features (Hooper et al. 2009). This leads us to infer that there may be a higher prevalence of patients with compound heterozygous mutations leading to a clinical presentation which may vary between classical Tangier disease and low HDL levels. In addition, the typical

“large yellow orange” tonsils might not be present in Tangier patients due to the increasing number of tonsillectomies being performed at a younger age. These factors likely lead to a lack of ascertainment of some patients with biallelic *ABCA1* mutations. As more patients are reported in the literature, the expanded phenotype of Tangier disease can be further delineated.

Synopsis

Non-classical presentation of Tangier disease.

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OMIM 205400
HGNC:29

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