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CASE REPORT

BEGINNER

CLINICAL CASE

ABCA1 Deficiency

A Rare Cause of Premature Coronary Artery Disease

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ABSTRACT

ATP-binding cassette transporter A1 (ABCA1) deficiency results in very low high-density lipoprotein cholesterol levels. Complete ABCA1 deficiency, or Tangier disease, is characterized by premature atherosclerotic cardiovascular disease, yellow-orange tonsils, hepatosplenomegaly, peripheral neuropathy, and corneal opacification. Early recognition of this condition can lead to regular monitoring for atherosclerotic cardiovascular symptoms and treatment of major modifiable risk factors. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2023;18:101904)

HISTORY OF PRESENTATION

A 49-year-old man with a history of central serous retinopathy, gout, and nephrolithiasis was referred to the Metabolism and Lipids Unit at Mount Sinai Hospital for evaluation of very low high-density lipoprotein-cholesterol (HDL-C). His physical examination results were notable for bilateral corneal arcus, and he did not have yellow or orange discoloration of his tonsils (**Figure 1**). The liver and spleen size were normal. His family history was notable for his father requiring coronary artery bypass grafting at age 58 years and percutaneous coronary intervention at age 72 years. His brother underwent percutaneous coronary intervention at age 54 years. His lipid values between age 37 years and the present are shown in **Table 1**. The fasting lipid values in mg/dL on treatment with niacin 1,000 mg daily included a total cholesterol (TC) 137, low-density lipoprotein-cholesterol (LDL-C) 109, HDL-C 4, and triglycerides (TG) 124.

LEARNING OBJECTIVES

- To recognize the causes of markedly low HDL-C and understand the pathophysiology behind early atherosclerosis.
- To understand the role of HDL in atherosclerosis
- To summarize treatment recommendations for prevention of coronary artery disease events in patients with an inability to generate HDL.

PAST MEDICAL HISTORY

The patient's pertinent medical history began at age 37 years when he was referred for evaluation of very low HDL-C. He had been taking extended-release niacin 1 gram daily in an effort to increase his HDL-C. His medical history was otherwise unremarkable. Coronary calcium scoring revealed an Agatston score of 7 (81st percentile adjusted for age, sex, and race). He started simvastatin 20 mg daily to

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ABBREVIATIONS AND ACRONYMS

ABCA1 = ATP binding cassette A1

apoA-I = apolipoprotein A-I

HDL = high-density lipoprotein

LCAT = lecithin-cholesterol acyl transferase

LDL = low-density lipoprotein

TG = triglycerides

lower his LDL-C and to prevent progression of coronary atherosclerosis. Subsequently, the niacin was discontinued, owing to its lack of efficacy in increasing HDL-C and to its side effects. He received a maintenance dosage of simvastatin 20 mg daily for several years.

At age 45 years, a repeated coronary calcium score showed progression of his calcified plaque, with an Agatston score of 336 HU, placing him at the 99th percentile for his age and sex.

DIFFERENTIAL DIAGNOSIS

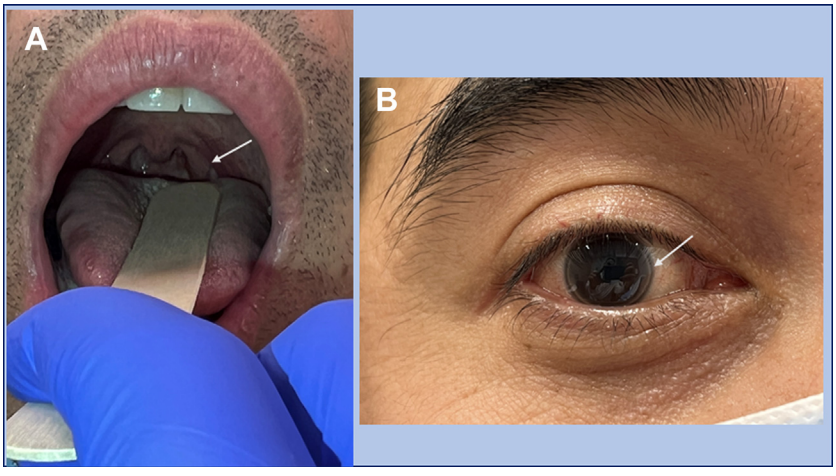
The differential diagnosis included secondary causes and primary monogenic causes. Secondary causes include severe hypertriglyceridemia, liver failure, paraproteinemia due to multiple myeloma, and use of androgenic steroids. Primary causes include apolipoprotein (apo) A-I deficiency, partial or complete (Tangier disease) ABCA1 deficiency, and lecithin-cholesterol acyltransferase (LCAT) deficiency.

INVESTIGATION

A fasting blood sample was sent for further HDL analysis. Analysis of serum apoA-I, HDL particles (electrophoresis and apoA-I immunoblotting),[1] small dense LDL-C, lipoprotein(a), high-sensitivity C-reactive protein, and liver transaminases were measured as previously described.[1,2] The results of HDL particle analysis (**Table 2**) indicated that plasma levels of HDL-C, total apoA-I, and apoA-I in very large α-1 HDL, large α-2 HDL, medium α-3 HDL, small α-4 HDL, and very small pre-β HDL were 3.9%, 6.5%, 6.8%, 6.5%, 3.9%, 7.8%, and 19.0% of control values, respectively. The total apoA-I concentration was 9.7 mg/dL (6.5% of control). The patient's other values included a small dense LDL-C 32 mg/dL (elevated >50 mg/dL), direct LDL-C 33 mg/dL (elevated >160 mg/dL), Lp(a) 49 mg/dL (elevated >50 mg/dL), h-sensitivity C-reactive protein 0.5 mg/L (elevated >2.0 mg/L), and liver transaminases that were just above the upper limits of normal.

Because of these HDL abnormalities, a sample of the patient's cells was shipped to a specialized laboratory for next generation DNA sequencing of 24 genes involved in lipid metabolism, including *ABCA1* and *LCAT*.[3] DNA sequencing revealed 3 heterozygous variants in the *ABCA1* gene, namely, p.G592G frameshift X37, p.A2028V, and p.R2081Q. The frameshift variant is a likely pathogenic nonsense mutation, whereas the other 2 missense variants were of uncertain significance. The chromosomal phase of the 3 variants could not be determined from DNA sequencing, but it is highly unlikely that all 3 are on the same chromosome. These findings were consistent with severe ABCA1 deficiency, but not Tangier disease, in as much as 2 variants were of undetermined significance.

FIGURE 1 Physical Exam Findings



(A) Patient's tonsils did not show any yellow-orange deposits, which can be seen in ABCA1 (ATP Binding Cassette A1) transporter deficiency. **(B)** Dense white rims around the iris consistent with corneal arcus due to cholesterol deposits can be seen.

TABLE 1 Lipid Panels 2010-2022

Test	2010	2011	2013	2016	Feb 2018	Sept 2018	Oct 2018	Mar 2019	Sept 2019	Jan 2020	Aug 2020	Feb 2021	May 2022
Meds	Nspn 1,000 mg	Simv 20 mg	Simv 20 mg	Rsv 10 mg	Rsv 40 mg Ezet 10 mg	Rsv 40 mg Ezet 10 mg	Rsv 40 mg Ezet 10 mg Nspn 1,000 mg	Rsv 40 mg Ezet 10 mg Nspn 1,500 mg	Rsv 40 mg Ezet 10 mg Nspn 1,500 mg	Rsv 40 mg Ezet 10 mg Nspn 1,500 mg	Rsv 40 mg Ezet 10 mg Nspn 1,500 mg	Rsv 40 mg Ezet 10 mg Nspn 1,000 mg	Rsv 40 mg Ezet 10 mg
Total cholesterol, mg/dL	137	103	85	69	80	55	45	39	44	50	50	57	50
LDL-C, mg/dL	109	79	58	38	54	35	26	20	29	33	33	34	32
HDL-C, mg/dL	4	3	5	<5	<3	<5	<5	<5	<5	<5	<5	<3	<5
TGs, mg/dL	124	104	139	128	113	75	68	68	50	59	59	102	67
apoA-I, mg/dL							<3				<10		
apoB, mg/dL	98		71										
Lp(a)							125 nmol/L						

apoA-I = apolipoprotein A-I; apoB = apolipoprotein B; Ezet = ezetimibe; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); Nspn = extended release niaspan; Rsv = rosuvastatin; Simv = simvastatin; TG = triglycerides.

MANAGEMENT

The treatment of patients with ABCA1 deficiency requires optimization of non-HDL risk factors, given that therapies targeted toward increasing HDL-C are futile because the defect is in the ABCA1 transporter. The patient most recently had an LDL-C of 32 mg/dL during treatment with rosuvastatin 40 mg daily and ezetimibe 10 mg daily.

DISCUSSION

Conditions such as familial apoA-I deficiency, LCAT deficiency, and ABCA1 deficiency or Tangier disease can lead to low levels of HDL particles.[1,4] Tangier disease was first described by Donald Fredrickson and colleagues[5] in 2 children from Tangier Island in the Chesapeake Bay, who presented with enlarged orange tonsils containing cholesteryl esters, hepatosplenomegaly, mild corneal opacification, and marked HDL deficiency. Their lipid profiles were characterized by mild hypertriglyceridemia, decreased LDL-C levels (<70 mg/dL), and very low levels of HDL-C and apoA-I, resulting from hypercatabolism. However, Tangier patients with LDL-C levels >70 mg/dL often experience premature cardiovascular disease.[4] It was later established that the defect in Tangier disease was due to homozygous or compound heterozygous pathogenic mutations in the *ABCA1* transporter gene, whose gene product is important for facilitating cellular cholesterol efflux (**Figure 2**).[4]

TABLE 2 Characterization of HDL Particles

Lipid Test	Value	Reference Range[a]	% of Control
HDL-C	2.0 mg/dL	51.0 (16.0) mg/dL	3.9%
apoA-I	9.7 mg/dL	149.0 (30.0) mg/dL	6.5%
α-1	1.8 mg/dL	26.3 (13.6) mg/dL	6.8%
α-2	3.9 mg/dL	59.8 (13.7) mg/dL	6.5%
α-3	0.9 mg/dL	22.9 (6.0) mg/dL	3.9%
α-4	1.5 mg/dL	19.2 (5.7) mg/dL	7.8%
Preβ-1	1.6 mg/dL	8.4 (5.4) mg/dL	19.0%

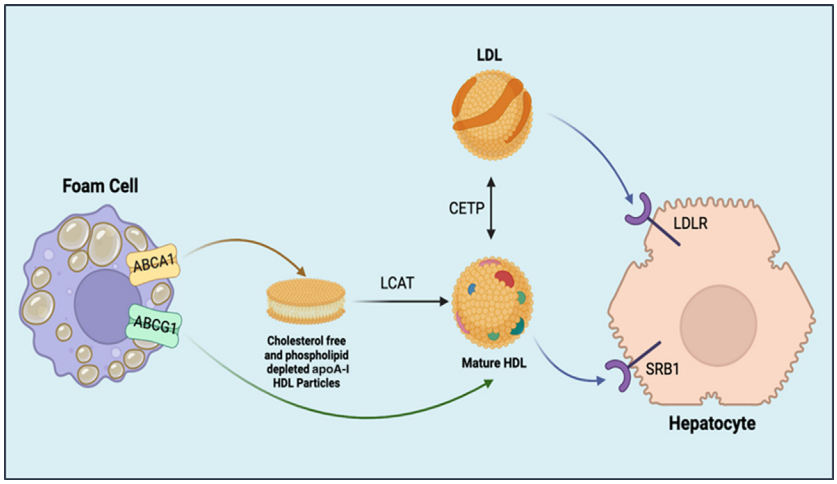
[a]Reference ranges are median values (interquartile range) based on 88,812 men of median age 56 (21) years with normal HDL-C values (≥40 mg/dL).[1]

Abbreviations as in Table 1.

Reverse cholesterol transport is an HDL-mediated process in which cholesterol is transported from peripheral tissues to the liver for excretion ultimately via bile and feces. ABCA1 is the quintessential mediator of cholesterol efflux and HDL generation,[4] and it mediates cholesterol exocytosis. Foam cells use ABCA1 to lipidate cholesterol-absent and phospholipid-depleted apoA-I complexes as the first step in loading cholesterol onto developing HDL particles. Deficient ABCA1 transporter impairs cholesterol efflux capacity, and the development of mature HDL is severely compromised. Without cholesterol efflux, foam cells accumulate cholesterol, leading to sustained plaque growth.

This patient illustrates the diagnostic importance of combining HDL mapping with next-generation DNA sequencing, which was highly suggestive of Tangier disease but not definitive because 2 *ABCA1* variants were of uncertain significance.[6] Pre-β-1 HDL particles refer to very small discoidal precursor HDL particles that contain apoA-I and phospholipids. Small α-4 particles contain apoA-I, phospholipids, and free cholesterol. Medium α-3 and large α-2 particles are spherical particles and contain apoA-I, apoA-II, phospholipids, free cholesterol, cholesteryl ester, and TGs. Very large α-1 HDL particles contain the same lipoproteins as α-2 particles except they

FIGURE 2 Reverse Cholesterol Transport



HDL particles promote cholesterol efflux from cholesterol-laden macrophages (foam cells). Through ABCA1, free cholesterol is effluxed to cholesterol-absent and phospholipid-deficient apoA-I complexes. Through ABCG1, cholesterol is effluxed to mature HDL particles. Lipidated apoA-I complexes carry LCAT, which esterifies cholesterol to cholesteryl esters, allowing HDL to mature into larger HDL particles. Mature HDL transports cholesterol directly to the liver, where it is cleared via the SRB1 receptor. Alternatively, mature HDL can exchange cholesteryl esters with LDL particles for triglycerides via CETP. The LDL transports cholesterol to the liver to be cleared via LDLR. Abbreviations: ABCA1 = ATP binding cassette transporter A1; ABCG1 = ATP binding cassette transporter G1; apoA-I = apolipoprotein A-I; CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase enzyme; LDL = low-density lipoprotein; LDLR = LDL receptor; SRB1 = scavenger receptor class B type 1.

have very little apoA-II particles. Cholesterol-absent and phospholipid-depleted apoA-I complexes detected as pre-β-1 particles are the most efficient in interacting with ABCA1 for the purpose of cholesterol efflux, whereas α-1 particles are the most efficiently cleared via the hepatic SR-B1 receptor.[4,6]

The patient described here had no mutations in the *LCAT* or gene but did have 1 *ABCA1* pathogenic mutation, namely, p.G592G frameshift X37, as well as 2 mutations causing amino acid substitutions, namely, p.A2028V and p.R2081Q. Unlike severe homozygous Tangier disease, in which the patients have only apoA-I detectable in very small pre-β HDL, this patient was able to generate some larger HDL articles, indicating some potential ABCA1 function. However, the concentration of such particles were all <10% of normal. Conversely, in LCAT deficiency, pre-β HDL and α-4 HDL particles can be significantly elevated, but α-1 and α-2 particles are virtually absent—a profile that is distinct from that observed in our patient.[4]

FOLLOW-UP

At this writing, the patient continues to take rosuvastatin 40 mg daily and ezetimibe 10 mg daily. He has no symptoms of obstructive atherosclerotic disease at this time.

CONCLUSIONS

ABCA1 deficiency should be considered in the setting of marked HDL deficiency. Other potential diagnoses include familial apoA-I deficiency and LCAT deficiency. These patients should be referred to a lipid clinic that can perform HDL mapping and targeted next-generation DNA sequencing. Treatment should be focused on optimizing non-HDL risk factors.

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Dr Malick has received a training grant from the New York Academy of Medicine. Dr Schaefer has received a salary from Boston Heart Diagnostics and consulting fees from Denka Corporation. Dr Hegele has received consulting fees from Acasti, Aegerion, Ionis Pharmaceuticals, Amgen, Arrowhead, Boston Heart Diagnostics, HLS Therapeutics, Pfizer, Novartis, Regeneron, Sanofi, and Ultragenyx. Dr Rosenson has received research funding to his institution from Amgen, Arrowhead, Eli Lilly, Novartis and Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, and Verve Therapeutics; honoraria from nonpromotional educational activities from

Amgen and Kowa; royalties from Wolters Kluwer; stock holdings in MediMergent, LLC, and pending patents on analytical methods and systems for biocellular marker and detection using microfluidic profiling (PCT/US2019/026364) and compositions and methods relating to the identification and treatment of immunothrombotic conditions (PCT/US2020/63104926), and quantification of Lp(a) vs non-Lp(a) apoB concentration novel validated equation (PCT/US2021/63248837).

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KEY WORDS genetic disorders, lipid metabolism disorders, primary prevention