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Case Report

A novel homozygous *ABCA1* variant in an asymptomatic man with profound hypoalphalipoproteinemia

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Abstract: Low high-density lipoprotein cholesterol (HDL-C) can be caused by several acquired secondary causes as well as primary genetic disorders. However, only a few conditions are associated with profoundly reduced levels below 10 mg/dL. We present an unusual case of a healthy man with severely decreased HDL-C because of a novel homozygous variant causing a Proline > Arginine amino acid change at position 1312 in the ATP-binding cassette transporter A1 gene. Homozygous variations in ATP-binding cassette transporter A1 typically cause Tangier disease, a rare autosomal recessive condition linked with several other abnormalities (eg, enlarged discolored tonsils). Despite having an HDL-C below 10 mg/dL, our patient presented without any other clinical symptoms or physical signs suggestive of Tangier disease. This case of presumptive Tangier disease adds support to the growing body of evidence that this genetic disorder may have greater phenotypic heterogeneity along with a more varied presentation than traditionally considered.

Decades of epidemiological research have demonstrated an inverse association between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular disease.[1] Conversely, recent Mendelian randomization studies and negative clinical trials have cast skepticism on its direct causal role in the etiology of cardiovascular disease.[1] These findings corroborate earlier reports of patients with genetic low HDL-C conditions, who paradoxically did not suffer from premature heart disease.[2–5] In this context, the overall evidence now supports the paradigm that a host of anti-atherosclerotic actions mediated by HDL particles, rather than the cholesterol content per se, is the primary determinant of its cardio-protective nature.

Marked reductions in HDL-C, defined as serum levels <20 mg/dL, can occur due to primary (monogenetic) or acquired (secondary) etiologies.[3,4] While many secondary causes are often associated with premature atherosclerosis (particularly with concomitant hypertriglyceridemia), the clinical consequences due to inherited genetic etiologies are heterogeneous.[2–5] Here, we present a case of an asymptomatic man referred to the University of Michigan preventive cardiology services and lipid management clinic for severely low HDL-C identified during routine health maintenance. He was found to be homozygous for a novel Proline > Arginine missense variant at position 1312 in the ATP-binding cassette transporter A1 gene (*ABCA1*$_{P1312R}$), the likely cause of his profound hypoalphalipoproteinemia.[2,5–10]

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Case report

The patient was a 38-year-old man of Indian decent with a past medical history significant only for (resolved) atypical chest pain thought to be due to gastroesophageal reflux disease. He was referred for evaluation of low HDL-C. A routine lipoprotein profile obtained during the new patient visit and at 2-year follow-up is provided in Table 1. The results showed low levels of all lipoproteins, including disproportionately reduced HDL-C. The findings corroborated those obtained several weeks earlier by his primary care physician (HDL-C of 6 mg/dL). On further questioning, he remembered having lipid measurements performed in 2007 and 2010 also showing low HDL-C levels <10 mg/dL.

He was without active complaints and specifically denied any symptoms suggestive of cardiovascular disease (eg, chest pain), recent illness or infection (eg, fever, weight loss), or extreme dietary fat restriction. He reported no visual changes, symptoms concerning for peripheral sensory neuropathy, proteinuria, tonsillar abnormalities (eg, odynophagia), or hepatosplenomegaly (eg, right upper quadrant pain). His past medical history was positive for low HDL-C but unrevealing for common secondary causes including diabetes mellitus, hypertriglyceridemia, liver disease, thyroid abnormalities, cancer, recent or ongoing major illness, chronic infection (eg, human immunodeficiency virus), or gastrointestinal disorders (eg, inflammatory bowel disease, malabsorption). He had no other traditional cardiovascular risk factors. Other than omeprazole for occasional dyspepsia, he was not taking prescription or over-the-counter therapies and specifically denied use of drugs linked to low HDL-C (eg, androgenic steroids, peroxisome proliferator-activated receptor agonists). He had a 5 pack-year history of smoking but quit 4 years ago. Alcohol intake was reported as 1–2 drinks per month. He had met with dieticians and was following a reduced carbohydrate diet. He reported aerobic exercising on a treadmill for 1 hour 3 times per week without problems. He emigrated from India 4 years ago and had not travelled abroad since and did not have evidence (eg, weight loss, diarrhea, fevers) of any chronic infections (eg, parasitic) diseases. There was no family history of known or premature atherosclerotic cardiovascular disease in the first degree relatives or grandparents. He reported that both his parents and 2 sisters have "normal" lipoprotein profiles and HDL-C levels; however, the results were not available during the new patient visit. He was married with 2 young children: healthy 6-year-old and 1-month-old sons.

On exam, his blood pressure and vital signs were normal. He was overweight with a body mass index of 29 kg/m^2. His skin exam revealed no xanthelasma palpebrarum, planar, palmar, or tendon xanthomas. He had no arcus cornea or corneal opacities (Fig. 1). His oral pharynx was clear without discolored or enlarged tonsils (no history of tonsillectomy) (Fig. 1). Heart sounds were normal without murmur. Vascular exam revealed no carotid or abdominal bruit and normal peripheral pulses. The remainder of his physical exam was unremarkable, specifically without hepatosplenomegaly, abdominal tenderness, reduced peripheral pulses, or evidence of peripheral sensory neuropathy.

Table 1 Lipoprotein results from clinical chemistry laboratory testing on initial presentation (2015) and 2-year follow-up (2017)

Lipoprotein	2015 Results (mg/dL)	2015 Mayo ultracentrifugation (mg/dL)	2017 Results (mg/dL)
Total cholesterol	80	89	105
Triglycerides	58	106	70
HDL-C	**8**	**7**	**12**
LDL-C (calculated)*	72	67	80
Apolipoprotein B	61	71	81
Apolipoprotein A-1	30	27	35

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Friedewald formula.

Further laboratory and test results

An evaluation for secondary causes of low HDL-C was unrevealing. Routine laboratory results were normal including a comprehensive panel, liver and muscle enzymes, a complete blood count (eg, no anemia or thrombocythemia), HbA1c (4.9%), a thyroid panel, and repeat values for fasting glucose (<100 mg/dL), creatinine (<0.8 mg/dL), and estimated glomerular filtration rate calculations (>60 ml/min). Urine testing including a urinalysis and microalbumin level was also normal. Low HDL-C can result from laboratory errors or interference[3,4] (eg, paraproteinemia), and thus, a Mayo Clinic lipoprotein metabolism profile (ultracentrifugation) and apolipoprotein measurements were ordered (see Table 1). The results were confirmatory: total cholesterol 89 mg/dL; triglycerides: 106 mg/dL; low-density lipoprotein-C: 67 mg/dL; HDL-C 7 mg/dL; apolipoprotein B: 71 mg/dL and apolipoprotein A-I: 27 mg/dL. No lipoprotein-X or beta-VLDL-C was detected.

The patient's only traditional cardiovascular risk factor was low HDL; however, given its severity, he was extremely concerned about early atherosclerotic disease. To evaluate for preclinical disease, we ordered a 128-slice helical computed tomography for coronary artery calcium (CAC) and a treadmill stress echocardiogram. The latter was performed due to his anxiety that prior atypical chest pain symptoms were misattributed to gastroesophageal reflux disease. He had no measurable CAC (zero Agatston units) and no symptoms, ECG, or echocardiogram abnormalities during exercise testing, reaching a peak of 10.8 metabolic equivalents (98% maximal predicted heart rate).