JACC: CASE REPORTS VOL. 1, NO. 3, 2019

CASE REPORT

BEGINNER

CLINICAL CASE

DYSLIPIDEMIA

Corneal Clouding in a Young Woman With Low HDL Cholesterol

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ABSTRACT

This report describes the early diagnosis of lecithin cholesterol acyl transferase deficiency in a young asymptomatic woman who initially presented to ophthalmology with bilateral corneal clouding. The diagnosis was suggested by characteristic slit-lamp findings, undetectable high-density lipoprotein, and proteinuria, and it was confirmed by cardiology consultation and genetic testing. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2019;1:343–5)

An asymptomatic 34-year-old woman with a history of myopic soft contact lens wear was referred to ophthalmology for evaluation of bilateral corneal clouding refractory to a contact lens holiday and a short course of topical corticosteroids. Her best-corrected visual acuity was 20/25 in the right eye and 20/20 in the left eye. Slit-lamp examination revealed fine, grayish-white deposits throughout all layers of the corneal stroma. Diffuse corneal clouding was appreciated not only on slit-lamp examination (**Figure 1**), but also with the naked eye. Dilated fundus examination was normal. Her height was 1.6 m, weight was 102.8 kg, and blood pressure was 124/78 mm Hg.

MEDICAL HISTORY

Her past medical history was remarkable for obesity, mild anemia, and "low cholesterol." A lipid test several years previously was notable for undetectable high-density lipoprotein (HDL). The patient was adopted with unknown family history. Her medication history was noncontributory.

LEARNING OBJECTIVES

- To recognize the differential diagnosis of very low HDL with corneal opacification.
- To appreciate the role of extracardiac (specifically ophthalmic) findings in the early detection and diagnosis of LCAT deficiency.

DIFFERENTIAL DIAGNOSIS

Low HDL is most commonly seen as part of the metabolic syndrome, in association with insulin resistance, elevated blood pressure, and abdominal obesity (1). Pharmacologic causes of low HDL exist as well, including beta blockers, benzodiazepines, and anabolic steroids (2,3). However, other primary (monogenic) causes of extremely low HDL levels that may also present with diffuse corneal opacification include fish-eye disease, Tangier disease, and apolipoprotein A1 (apoA1) deficiency, all disorders of the lecithin cholesterol acyl transferase (LCAT) system.

INVESTIGATIONS

Because the clinical history and slit-lamp findings suggested a probable hypolipoproteinemia, the patient was referred to cardiology. Testing revealed hemoglobin of 10.8 (normal 11.5 to 15.5) g/dl with stomatocytes, normal serum creatinine, and urine

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Manuscript received May 18, 2019; revised manuscript received July 10, 2019, accepted July 17, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.07.020

ABBREVIATIONS AND ACRONYMS

HDL = high-density lipoprotein

apoA1 = apolipoprotein A1

LCAT = lecithin cholesterol acyl transferase

NIH = National Institutes of Health

protein of 30 mg/dl with no bacteria. A repeat fasting lipid panel, in addition to apoA1 and apolipoprotein B testing, was performed (Table 1). Genetic testing via Gene DX Xome Slice, sequencing ABCA1, APOA1, and LCAT, was positive for LCAT c.490 C>T (p.R164C) as the likely pathogenic variant, confirming the diagnosis of LCAT deficiency.

MANAGEMENT

The patient was placed on an angiotensin-converting-enzyme inhibitor, a heart-healthy, calorie-restricted diet for weight loss, and is being monitored by cardiology and nephrology. She has been referred to the National Institutes of Health (NIH) for possible inclusion in a recombinant human LCAT study.

DISCUSSION

LCAT deficiency is a rare (incidence < 1:1,000,000) autosomal recessive disorder resulting from a mutation of the LCAT gene. It leads to low HDL and elevated triglyceride levels. It is characterized by proteinuria, anemia, turbid plasma, and bilateral corneal opacification. The corneal opacification may begin in adolescence, and vision may remain normal until late stages of the disease (4).

LCAT is synthesized in the liver and small intestine and secreted in the plasma, where it is found in association with HDL. The enzyme promotes esterification of free cholesterol, which allows the maturation of HDL and may help in reverse cholesterol transport (5). Low levels of HDL seen in LCAT-deficient patients may increase the risk of coronary artery disease, although the association of LCAT deficiency with any increased risk is controversial (6,7). The anemia is usually mild to moderate and may be caused by clearance of red blood cells secondary to hypersplenism (7). The most severe complication of LCAT deficiency is renal insufficiency, which usually presents as proteinuria and hematuria early in life and progresses to chronic renal failure in later years. Renal biopsies demonstrate foam cells in the glomerular tufts, subendothelial lipid deposits in the renal arteries and arterioles, and free cholesterol and phospholipid in the renal glomeruli (7). Patients may require hemodialysis or renal transplantation, although the disease may recur in the donor kidney.

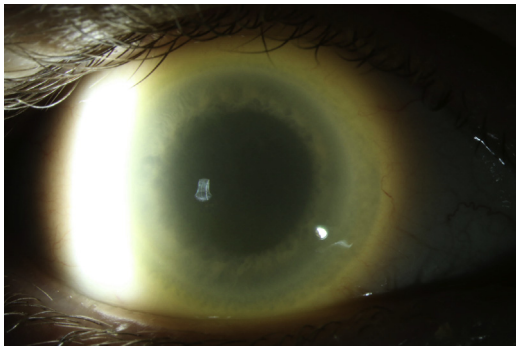
TABLE 1 Fasting Lipid Panel, in Addition to Apolipoprotein A1 and Apolipoprotein B Testing

	Result (Reference Range)
Total cholesterol	98 mg/dl
Triglycerides	164 mg/dl
HDL	<10 mg/dl
LDL	68 mg/dl
Non-HDL	100 mg/dl
Apolipoprotein A1	48 (116–209) mg/dl
Apolipoprotein B	25 (54–133) mg/dl

The LCAT gene lies on chromosome 16 (16q22) (8). Patients with complete loss of LCAT function are designated as having LCAT deficiency. In this patient, the 490th base of LCAT (c.490) was subject to a C>T mutation. Thus, the 164th amino acid in the protein's primary structure was a cysteine rather than an arginine (p.R.164 C). Patients with fish-eye disease have LCAT gene mutations causing a partial reduction in LCAT activity, leading to low HDL and low cholesterol ester but no nephropathy (9). Tangier disease is caused by a mutation in the ABCA1 gene, leading to low serum HDL levels. It may be distinguished from familial LCAT deficiency clinically by the presence of hepatosplenomegaly, yellow-orange tonsils, xanthoma, and premature coronary artery disease (9,10). Finally, a mutation in the apoA1 gene results in low HDL, coronary artery disease, and xanthomata (10).

There is no cure for LCAT deficiency. Treatment is aimed at reducing blood triglyceride levels and controlling blood pressure via a low-fat diet, weight loss, and exercise (7–9). Dialysis, further blood-pressure management, and renal transplantation may be necessary to manage end-stage renal disease. The first in-human trials of recombinant human

FIGURE 1 Slit-Lamp Photograph of the Right Eye Demonstrating Corneal Clouding



This diffuse clouding was also appreciable with the naked eye.

LCAT replacement therapy have been performed with transient improvement in anemia, stabilization of renal function, and normalization of HDL levels (6).

FOLLOW-UP

The patient is followed annually at the NIH in the Rare Lipids Disorder clinic. She was informed that ocular involvement is slowly progressive and may eventually affect vision. This team of experts agreed that lisinopril for renal protection was appropriate, and a nutritionist reiterated our recommendations for weight loss, including a low-sodium diet to prevent hypertension and further insult to the kidneys. LCAT enzyme replacement therapy in humans is in process and expected to enter phase 3 clinical trials soon. At present, her disease is not severe enough to warrant this therapy, although she is being monitored closely for progression of disease.

CONCLUSIONS

The combination of corneal clouding and low HDL cholesterol should raise clinical suspicion for a rare, inherited low HDL disorder. These monogenic disorders present with a unique constellation of physical and biochemical findings. Although some of these disorders may be associated with premature atherosclerotic disease, additional laboratory work-up and genetic testing can confirm the correct diagnosis and guide further management and treatment. Premature coronary artery disease is usually not part of the LCAT deficiency phenotype, although renal involvement is a concern. LCAT-replacement therapies show promise in the treatment of this rare disorder and associated renal disease.

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KEY WORDS genetic disorders, lipid metabolism disorders, metabolic syndrome X