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CASE REPORT

ADVANCED

CLINICAL CASE

Distinguishing Lysosomal Acid Lipase Deficiency From Familial Hypercholesterolemia

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ABSTRACT

Lysosomal acid lipase deficiency (LAL-D) is underrecognized because it manifests clinically with lipid and lipoprotein values similar to those observed in heterozygous familial hypercholesterolemia (FH). Although LAL-D is uncommon, understanding the differences between the 2 diseases has significant management implications. We present a case of LAL-D that masqueraded as FH. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;24:102023)

HISTORY OF PRESENTATION

A 26-year-old woman with a past medical history of hypercholesterolemia presented for a consultation. On clinical history, she stated that her cholesterol had been significantly elevated since she was a child. She was told that her hypercholesterolemia was genetic, she was unsure whether she had undergone genetic testing, and she was treated with a statin. Patient was on atorvastatin as a child but stopped this because she noted it caused considerable malaise. She was not taking any medications on presentation and had not been pharmacologically treated for 15 years. She denied any family history of hyperlipidemia or premature atherosclerotic cardiovascular disease (ASCVD) in family members. Review of systems was unremarkable other than eating fatty foods precipitated abdominal discomfort. For this reason, she consumed primarily a low-fat vegetarian diet. Her vital signs were normal. Physical examination was positive for a II/VI systolic ejection murmur along the right upper sternal border. She did not have xanthelasmas, tendinous xanthomas, Achilles tendon thickening, hepatomegaly, or corneal arcus.

LEARNING OBJECTIVES

- To recognize that LAL-D presentation may closely mirror laboratory features of FH.
- To treat LAL-D safely and effectively.

PAST MEDICAL HISTORY

The patient had a past medical history of uncontrolled hyperlipidemia for many years. Laboratory test results since 2004 (age 7 years) showed persistent marked elevations in total cholesterol and low-density lipoprotein cholesterol (LDL-C), mildly elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C), as summarized in **Table 1**.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

ERT = enzyme replacement therapy

FH = familial hypercholesterolemia

HDL-C = high-density lipoprotein cholesterol

LAL = lysosomal acid lipase

LAL-D = lysosomal acid lipase deficiency

LDL-C = low density lipoprotein cholesterol

DIFFERENTIAL DIAGNOSES

The patient's presentation of an untreated LDL-C level greater than the 90th percentile for age and sex is most suggestive of familial hypercholesterolemia (FH). Less common on the differential diagnoses are nonalcoholic fatty liver disease, lysosomal acid lipase deficiency (LAL-D), and Niemann-Pick type B disease. Because her triglycerides were only mildly elevated, FH was considered most likely.

INVESTIGATIONS

The electrocardiogram showed a normal sinus rhythm without ischemic changes. A transthoracic echocardiogram showed preserved left ventricular function (ejection fraction, 60%-65%) with mildly elevated aortic valve gradients (peak and mean gradients of 15 mm Hg and 7 mm Hg, respectively). Laboratory testing obtained at the time of consultation revealed a persistently abnormal lipid panel (total cholesterol of 386 mg/dL, LDL-C of 321 mg/dL, HDL-C of 32 mg/dL, triglycerides of 160 mg/dL, and non-HDL-C of 354 mg/dL, as well as lipoprotein[a] of 39 nmol/L). Mildly elevated liver test results were noted (aspartate transaminase, 25 U/L; alanine transaminase, 30 U/L). The patient was started on rosuvastatin at a low dose because of side effects of fatigue with atorvastatin as a child. Rosuvastatin was also poorly tolerated, and she discontinued it. A combination of simvastatin 20 mg and evolocumab 140 mg every 2 weeks was initiated. These medications were well tolerated, with a mild reduction in LDL-C (252 mg/dL, a 21% decrease). An FH genetic panel was obtained by oral swab (Invitae) and returned as negative for mutations characteristic of this disease. Given the strong suspicion for FH, a repeat swab was done and also returned negative. A full 36-panel genetic analysis was done that identified 2 pathologic variants in the gene *LIPA*, diagnostic of LAL-D ([c796G>T (p.GLY266] heterozygote, c894G>A [silent] heterozygote).

MANAGEMENT

The patient continued receiving simvastatin and evolocumab. Ezetimibe was subsequently added to the medication regimen. LDL-C decreased further to 131 mg/dL. Liver test results remained elevated. A coronary computed tomography angiogram did not reveal any coronary artery disease. The patient was encouraged to remain on a low-fat diet, which improved many of her abdominal symptoms. A hepatology referral was made, and authorization for sebelipase alfa was initiated.

DISCUSSION

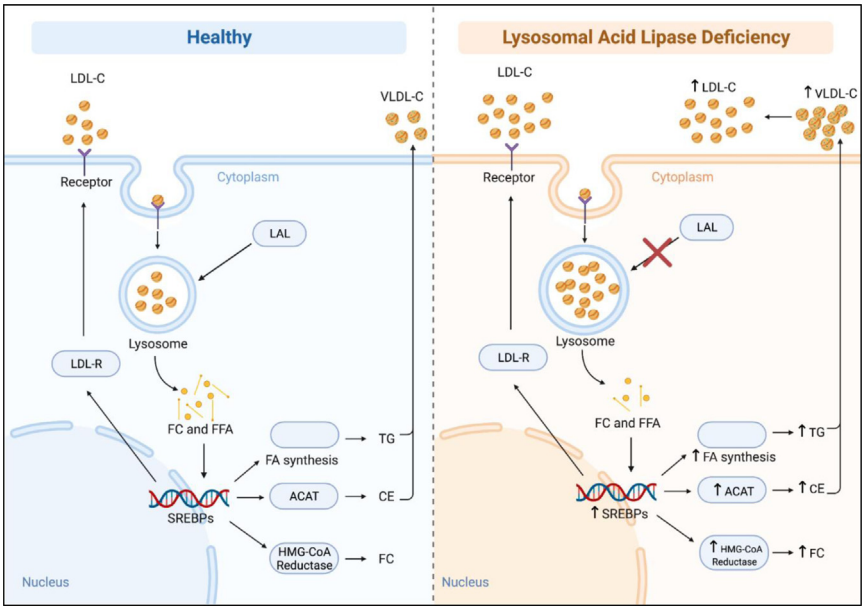
LAL-D is a rare (prevalence of 1 in 40,000 to 1 in 300,000) autosomal recessive disease that arises from mutations in the lipase A gene (*LIPA)*. The E8SJM mutation, the most common causative mutation of LAL-D, has a frequency of 0.0013 in Caucasians, 0.0017 in Hispanics, 0.0005 in Asians, and 0.0000 in African Americans.[1] Lysosomal acid lipase (LAL) plays a critical role in cellular cholesterol homeostasis. LAL hydrolyzes cholesteryl esters and triglycerides in lysosomes. With perturbed LAL function, cholesteryl esters and triglycerides are not degraded and accumulate within lysosomes, thus resulting in decreased levels of intracellular free cholesterol and free fatty acids. Accordingly, LAL-D results in the accumulation of nonhydrolyzed cholesteryl esters and triglycerides within lysosomes of various organs, notably hepatocytes and Kupffer cells, a process progressing to liver dysfunction and structural injury. The intracellular

TABLE 1 Known Laboratory Results Since Age 7 Years, Including Initial Presentation to Clinic

Laboratory Test	2003 (Age 7 y)	2006 (Age 10 y)	May 2021 (Age 26 y)	November 2022 (Age 26 y)	April 2023 (Age 27 y)
Cholesterol, total, mg/dL	396	280	386	321	199
HDL cholesterol, mg/dL	29	23	32	37	42
Triglycerides, mg/dL	284	226	160	153	151
LDL cholesterol, mg/dL	310	212	321	252	131
Lipoprotein (a), nmol/L	–	–	–	39	–
ApoB, mg/dL	–	–	–	194	–
AST, U/L	–	25	–	34	32
ALT, U/L	–	30	–	39	37
Notes	–	–	Initial presentation to clinic	On simvastatin 20 mg daily, evolocumab every 2 wk	On simvastatin 20 mg daily, evolocumab every 2 wk, ezetimibe 10 mg daily

ALT = alanine transaminase; ApoB = apolipoprotein B; AST = aspartate transaminase; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

FIGURE 1 **Intracellular Biochemical Features of LAL Deficiency**



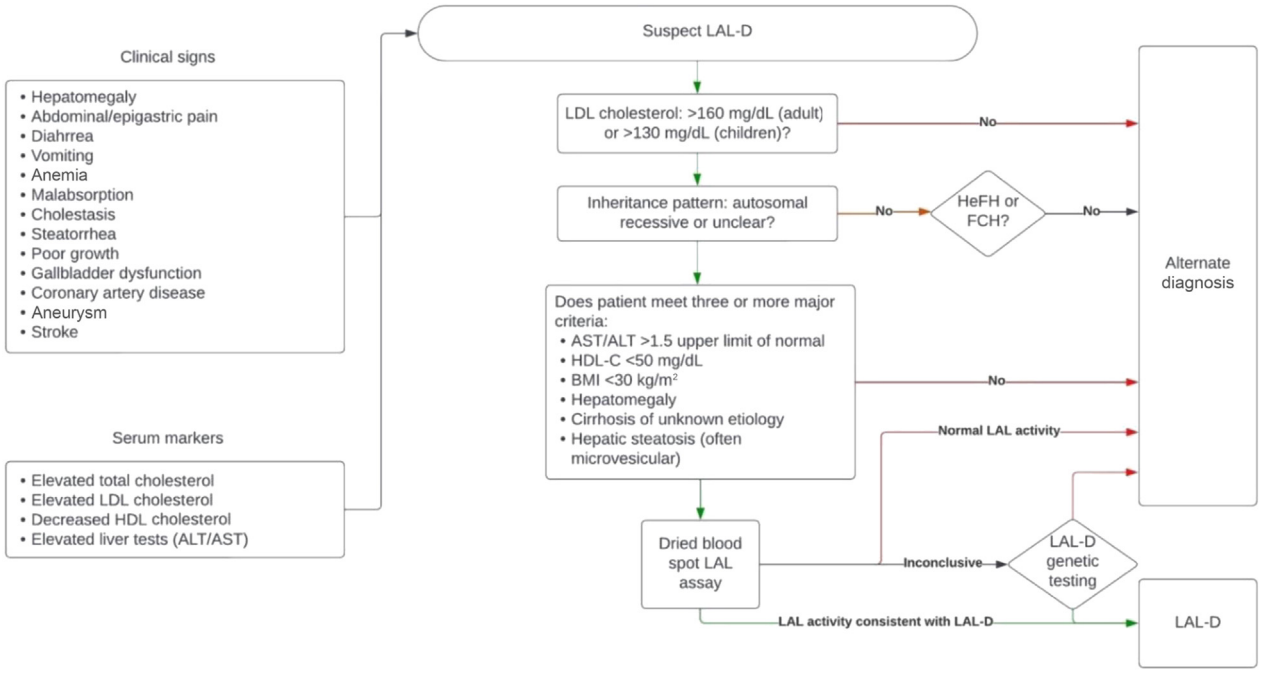
Hepatic low-density lipoprotein cholesterol (LDL-C) metabolism in (left) an individual who is healthy and (right) a patient with a deficiency in lysosomal acid lipase (LAL). In the patient with lysosomal acid lipase deficiency, there is impaired catabolism of low-density lipoprotein particles within the lysosome, thus resulting in reduced hydrolysis of cholesterol esters (CE) and triglycerides (TG). Secondary to low intracellular levels of free cholesterol (FC) and fatty acids (FA), 3 biosynthetic pathways are activated: cholesterol biosynthesis (elevated [↑] 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG-CoA] reductase), cholesterol ester formation (elevated [↑] acyl-coenzyme A: cholesterol acyltransferase [ACAT]), and fatty acid biosynthesis. This increase in lipid and esterified sterol mass is associated with increased very low-density lipoprotein cholesterol (VLDL) production and secretion. FFA = free fatty acid; LDL-R = low density lipoprotein receptor; SREBP = sterol regulatory element binding protein.

biochemical features of LAL-D are outlined in Figure 1.[1,2]

Clinical manifestations of LAL-D vary in severity in from infantile onset Wolman disease with complete deficiency of LAL to later onset cholesteryl ester storage disease with partial residual enzyme function. In adults, patients can present with nonspecific findings such as dyslipidemia with LDL-C and triglyceride elevations and HDL-C reductions.[2] There are often elevated transaminases and hepatomegaly with or without early ASCVD. The lipid profile of LAL-D may be indistinguishable from that observed in common genetic hypercholesterolemias and often masquerades as FH (prevalence of 1 in 200 to 1 in 250), with markedly elevated LDL-C and reduced HDL-C. Given the shared clinical features of LAL-D with other cardiovascular, liver, and metabolic diseases, LAL-D is often underdiagnosed or misdiagnosed in clinical practice, with severe long-term consequences. A diagnostic algorithm for LAL-D is provided in Figure 2.

If LAL-D remains untreated, it can lead to early onset ASCVD and hepatic damage that progresses to fibrosis, cirrhosis, and failure. Cardiovascular complications are not well understood because patients frequently die by age 30 years from liver failure, before atherogenic burden could manifest as acute cardiovascular events. However, there are several reports of subclinical ASCVD in LAL-D patients at autopsy.[3] In the past, liver transplantation had been the only therapeutic option for LAL-D because liver fibrosis progression was refractory to statin therapy. In 2015, enzyme replacement therapy (ERT) with sebelipase alfa (marketed as Kanuma) was approved. In the phase 3 ARISE (Acid Lipase Replacement Investigating Safety and Efficacy) trial, sebelipase alfa was evaluated in a randomized, double-blind, placebo-controlled trial in 66 children and adults with LAL-D.[4] This trial showed that serum transaminase and γ-glutamyl transferase levels and hepatic fat content were reduced significantly more by sebelipase alfa therapy than by placebo over 20 weeks and through a 16-week study extension period.[4] In addition, sebelipase alfa provided significantly better reductions in LDL-C, triglycerides, non-HDL-C, apoprotein B, and elevations in HDL-C and

FIGURE 2 LAL-D Diagnostic Algorithm



Lysosomal acid lipase deficiency (LAL-D) can occur in patients with a body mass index BMI >30 kg/m^2. ALT = alanine transaminase; AST = aspartate transaminase; FCH = familial combined hyperlipidemia; HDL-C = high density lipoprotein cholesterol; HeFH = hereditary familial hypercholesterolemia; LAL = lysosomal acid lipase; LDL = low-density lipoprotein.

apoprotein A1 than placebo. Adverse events were comparable between treatment groups. However, ERT may not resolve all complications of LAL-D because persistent dyslipidemia despite treatment is frequently reported, especially in milder adult onset disease.[5-7] Treatment with statins and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors is often suboptimal; however, the Nieman-Pick C1 like-1 protein (NPC1L1) inhibitor ezetimibe, which blocks intestinal cholesterol absorption, can provide significant incremental benefit in reducing LDL-C in these patients.[8,9] Patients with LAL-D often feel better on a low-fat diet, and symptoms of abdominal distention and discomfort usually resolve. Several unanswered questions remain with ERT, including the ability to delay liver disease progression, long-term efficacy in milder LAL-D phenotypes, and the etiology of poor medication response. Additionally, trials evaluating multimodal (ie, ERT in combination with ezetimibe) and emerging (ie, hematopoietic stem cell transplantation) treatment options are needed.

In our patient, FH was the leading diagnosis, and when genetic testing results came back negative for FH, there was a great deal of surprise. However, several red flags—such as high triglycerides, markedly low HDL-C, liver test elevations, gastrointestinal symptoms related to fat ingestion, poor response to standard lipid-lowering therapy, and no family history of premature heart disease—pointed to another underlying cause. Cases such as these remind us as clinicians that there are other heritable lipid disorders to consider in patients, especially with poor responsiveness to normally effective pharmacologic therapies.

CONCLUSIONS

We present a case of LAL-D which masqueraded as FH on the basis of presentation and lipid profile. LAL-D is an underdiagnosed disease and should be considered in patients with poor responsiveness to statins, abdominal symptoms, transaminase elevations, and elevated triglycerides. Diagnosis should prompt transition to a low-fat diet, initiation of lipid-lowering therapies including ezetimibe, referral to a hepatologist, and provision of ERT.

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