The Emerging Battle: Lysosomal Acid Lipase Deficiency vs Familial Hypercholesterolemia in Children

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ABSTRACT

Lysosomal acid lipase is an under-recognized enzyme involved in the modulation and expression of genes that part-take in the synthesis and uptake of cholesterol. We describe the unusual course of a 2-year-old patient who presented with hypercholesterolemia and elevated liver enzymes, initially misdiagnosed with familial hypercholesterolemia. The absence of a suggestive family history triggered further testing that revealed complete lysosomal acid lipase deficiency that typically presents in infancy as Wolman disease with failure to thrive, malabsorption, and liver failure. Interestingly, the patient’s clinical picture suggested cholesteryl ester storage disease instead, a milder phenotype in older patients.

INTRODUCTION

Lysosomal acid lipase deficiency (LAL-D) results from homozygous, compound heterozygous, or even occult mutations in the Lipase A (LIPA) gene.1 LAL-D is an undervalued entity with only a handful of cases reported in the literature.2 The enzyme deficiency causes 2 broad disease phenomena. When present in infancy, the enzyme is usually completely deficient and causes Wolman disease leading to malabsorption, failure to thrive, liver failure, and death if untreated. Older children and adults may present with cholesteryl ester storage disease (CESD) because of low but detectable levels of the enzyme. The latter causes elevated liver enzymes and hyperlipidemia, notably high total cholesterol (TC), low high-density lipoprotein (HDL-C), normal/elevated triglyceride (TG), early cardiovascular morbidity and can lead to missed cases of LAL-D in patients labeled with familial hypercholesterolemia (FH) or nonalcoholic fatty liver disease (NAFLD). Other findings include hepatomegaly on examination and liver biopsy consistent with microvesicular steatosis.1,3 This case report aims to increase awareness on LAL-D and focuses on a rare case of complete enzyme deficiency, presenting clinically as CESD.

CASE REPORT

The patient was a 2-year-old boy with hepatomegaly on physical examination and abnormal lipid panel. He had notably elevated TC 280 mg/dL, low-density lipoprotein cholesterol (LDL-C) 200 mg/dL, TG levels 255 mg/dL, and normal HDL-C 40 mg/dL. His liver enzymes were abnormally elevated: alanine aminotransferase (ALT) 73 U/L and aspartate aminotransferase 68 U/L. Moreover, he had microcytic anemia with hemoglobin 10.4 g/dL and mean corpuscular volume 68 fL. He had normal weight and height percentiles, 65th and 76th, respectively.

Bloodwork from first-degree relatives was reviewed and did not show signs of hyperlipidemia. Nevertheless, the patient received a diagnosis of FH and was advised to abstain from fatty food and continue with conservative management. On follow-up a year later, he had worsening hyperlipidemia with TC 295 mg/dL, LDL-C 241 mg/dL, HDL 41 mg/dL, and normalization of TG 96 mg/dL.

Because of his atypical presentation and course, he was referred to the gastroenterology department for further workup that was initially nonrevealing. A screening test for lysosomal acid lipase enzyme activity on a dried blood sample was abnormal 0 nmol/punch/hour. LIPA gene sequencing revealed compound heterozygosity at c.894G>A, the most commonly associated mutation with LAL-D, as well as heterozygosity for the c.599T>C mutation, previously reported in LAL-D, confirming the diagnosis of CESD.
Sebelipase alfa, an Food and Drug Administration approved enzyme replacement therapy, was started with interval improvement in the patient’s aminotransferases ALT 38 U/L, aspartate aminotransferase 46 U/L, and lipid profile TC 264 U/L, LDL-C 195 U/L, and no reported side effects.

**DISCUSSION**

This case describes a patient with hyperlipidemia and elevated liver enzymes diagnosed with LAL-D after initially being managed for familial hypercholesterolemia. The lack of a family history of hyperlipidemia, along with worsening hyperlipidemia and liver enzymes on follow-up, led our team to challenge the initial diagnosis. Although LAL-D has been receiving more recognition, it is still a rare entity in pediatrics. The enzyme deficiency is known to present on a broad phenotypic spectrum, and multiple questions about the disease may remain unanswered because we gather more information and learn more about it. To our knowledge, this is the first case report focusing on a patient with hyperlipidemia diagnosed with LAL-D after initial management for familial hypercholesterolemia. Moreover, this is the first patient where complete LAL enzyme deficiency presents outside of infancy with a less severe phenotype. It remains unclear why this patient presented with CESD phenotype instead of Wolman’s disease despite the complete enzyme deficiency.

The enzyme plays a crucial role in cholesterol synthesis and uptake. Specifically, it hydrolyzes LDL-derived cholesteryl esters and triglycerides in lysosomes to free cholesterol and free fatty acids, which leads to negative feedback on 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, thereby slowing triglyceride production.5 When LAL has reduced activity, precursor triglycerides and cholesteryl esters accumulate and upregulate the synthesis of very-low density lipoprotein and LDL-C, inhibit LDL receptor activity, and reduce LDL clearance from the circulation.5,6

The myriad clinical presentations of LAL-D make it a vastly underdiagnosed condition, manifesting with varying severity based on remaining enzymatic activity. The complete absence of LAL usually presents in the first year of life and is known as Wolman disease. It causes lipid deposition in intestinal villi by 1–2 months of age, leading to symptoms of malabsorption, failure to thrive from nutritional deficiencies, progressive liver failure, and death in infancy if missed or untreated.7,8

Low but detectable LAL levels present with CESD at a median age of 5.8 years. Physicians have also tested and diagnosed some adults with CESD due to early atherosclerosis, cardiovascular morbidity, and liver failure.8 Similar to our patient, 67% of LAL-D patients are anemic, arguably because of malabsorption and splenic sequestration from hepatomegaly.8 Autosomal dominant heterozygous familial hypercholesterolemia can be a masquerader of CESD. Absent family history and, if tested, absent gene mutations in low-density lipoprotein receptor (LDLR), apolipoprotein B (ApoB), or proprotein convertase subtilisin/kexin (PCSK9) go against a diagnosis of FH. Maintaining a high index of suspicion for LAL-D is crucial when patients do not fit the proper phenotype because their prognoses and treatment options differ.10–12

Screening with an enzyme assay on dried blood is a good option for patients in remote locations or retrospective testing. If abnormal, the provider should check enzyme assay on either fibroblast cell cultures or leukocytes or obtain genetic testing. Genetic testing is a powerful supplemental tool to detect mutations located in the alleles of the LIPA gene and is also helpful in counseling heterozygous family members.13,14 Although NAFLD and LAL-D share similar presenting features, steatosis patterns on liver biopsy differ. Patients with NAFLD typically have macrovesicular steatosis, whereas patients with LAL-D have microvesicular steatosis in initial stages that can progress to fibrosis and micronodular cirrhosis.15,16

Enzyme replacement therapy with sebelipase alfa is now available for the treatment of LAL-D. Studies have shown that it lowers LDL and TG, increases HDL, and leads to a decline in ALT at 20 weeks with a statistically significant normalization of levels in 31% of the patients. Treated patients also had decreased fat content in the liver on multiecho gradient magnetic resonance imaging.17 Sebelipase alfa is also proven to halt the progression to cirrhosis, improve dyslipidemia, and decrease cardiac complications, thereby improving prognosis and outcome.18

**DISCLOSURES**

Author contributions: M. Saad wrote the manuscript, approved the final manuscript, and is the article guarantor. S. Syed edited the manuscript and approved the final manuscript.

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Informed consent was obtained for this case report.

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**REFERENCES**


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