Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Case Study

Lysosomal acid lipase deficiency in all siblings of the same parents

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KEYWORDS:
Lysosomal acid lipase deficiency;
Hyperlipidemia;
Hepatic enzyme elevation;
Sebelipase alfa;
LIPA gene

Abstract: We present 4 normal-weight sibling children with lysosomal acid lipase deficiency (LAL-D). LAL-D was considered in the differential diagnosis based on the absence of secondary causes and primary inherited traits for their marked hyperlipidemia, together with unexplained hepatic transaminase elevation. Residual lysosomal acid lipase activity confirmed the diagnosis. DNA sequencing of *LIPA* indicated that the siblings were compound heterozygotes (c.894G>A and c.428+1G>A). This case describes the unusual occurrence of all offspring from the same nonconsanguineous mother and father inheriting compound heterozygosity of a recessive trait and the identification of an apparently unique *LIPA* mutation (c.428+1G>A). It highlights the collaborative effort between a lipidologist and gastroenterologist in developing a differential diagnosis leading to the confirmatory diagnosis of this rare, life-threatening disease. With the availability of an effective enzyme replacement therapy (sebelipase alfa), LAL-D should be entertained in the differential diagnosis of children, adolescents, and young adults with idiopathic hyperlipidemia and unexplained hepatic transaminase elevation.

Introduction

Lysosomal acid lipase deficiency (LAL-D; Online Mendelian Inheritance in Man, Trademark John Hopkins University [OMIM]: 278000) is a rare autosomal recessive lipid disorder characterized by progressive accumulation of cholesteryl ester (CE) and to a lesser extent triglyceride (TG), in liver, spleen, intestine, adrenal glands, and macrophages throughout the body including those in the subendothelial spaces of arteries.[1,2] The involvement of these organs and cells appears to correlate with their participation in the receptor-mediated endocytosis and lysosomal degradation of lipoproteins.[2,3] Classically, LAL-D is divided into 2 phenotypes: the fulminant, infantile-onset, Wolman disease, and the less severe, later-onset, CE storage disease.[1,2] The variable rates of onset and severity are presumed to be the result of the different disease-causing mutations in the lysosomal acid lipase (LAL) gene (*LIPA*; OMIM: 613497) resulting in different degrees of impaired enzyme activity.[4,5] *LIPA* contains 10 exons and is localized to chromosome 10q23.2-23.3.[6] More than 40 *LIPA* mutations have been identified.[1,2,7]

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Submitted September 12, 2016. Accepted for publication February 13, 2017.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2017.02.006

The infantile-onset phenotype of LAL-D is thought to occur as a result of the absence of LAL activity and affected infants generally present within 1 month of age with significant hepatomegaly, vomiting, diarrhea, inanition, failure to thrive, and calcification of the adrenal glands.[8,9] The total cholesterol and TG plasma levels are usually normal.[1] Death occurs within the first 6 to 12 months of life as a result of malabsorption, cachexia, growth retardation, and severe liver disease.[1,8,10]

Later-onset LAL-D usually presents in early childhood to adolescence with LAL activity ranging from <0.1% to 12% of normal.[1,11,12] The progressive hepatic accumulation of CE leads to the characteristic liver (ie, mixed steatosis and fibrosis) and spleen pathology, and serum transaminase elevation. Significant lysosomal TG accumulation is not characteristic of later-onset LAL-D because the catalytic activity of LAL has a significant preference for TGs, diglycerides, and monoglycerides compared with CE.[13] This substrate preference and the presence of residual amounts of normal LAL in the cells of most patients with later-onset LAL-D is a biologically plausible explanation for why TG and CE accumulate in the lysosomes of patients with infantile-onset LAL-D and only CE in those with the later-onset phenotype.[1]

Residual LAL activity in the later-onset phenotype mitigates the release of free cholesterol (FC) from lysosomes causing a drop in its cytoplasmic concentration. This stimulates the transcriptional activity of nuclear sterol regulatory element-binding proteins leading to increased synthesis of cholesterol and fatty acids[14,15] and enhanced secretion of apolipoprotein B-100–containing lipoproteins from the liver.[16] The low FC cytoplasmic concentration also reduces the transcriptional activity of nuclear liver X receptors, thereby decreasing the expression of hepatic cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) and the efflux of nascent high-density lipoproteins (HDL) into the blood.[17] These derangements in cellular cholesterol homeostasis caused by LAL-D lead to the characteristic dyslipidemia of elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) and low levels of HDL cholesterol (HDL-C).[18,19] The morbidity and premature death associated with later-onset LAL-D are caused by either accelerated atherosclerotic cardiovascular disease (ASCVD) secondary to the dyslipidemia or liver failure.[2,20,21]

Case presentation

Four biological brothers (aged 9, 11, 14, and 17 years), the only offspring born to nonconsanguineous parents, were referred by their pediatric gastroenterologist to the Pediatric Lipid Clinic at St. John Providence Children's Hospital for evaluation of hyperlipidemia and unexplained hepatic transaminase elevation. A prior gastroenterology consult eliminated obesity, hepatitis B and C, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1–antitrypsin deficiency, and Celiac disease as possible causes of the hepatic transaminase elevations. A prior cardiology consult diagnosed familial combined hyperlipidemia (FCHL; OMIM: 144250)[22,23] as the cause of the hyperlipidemia and recommended statin therapy, which was not initiated per the parents request.

The 11-year-old (index patient) also had a significant past medical history relative to his brothers. He was initially evaluated by the pediatric gastroenterologist at age 4 years (2008) for unexplained hepatic transaminase elevation identified from a routine laboratory assessment before having strabismus surgery. This initial gastroenterology evaluation identified hepatomegaly by palpation and eliminated celiac disease, autoimmune hepatitis, and metabolic and infectious causes for the elevated hepatic transaminases (alanine aminotransferase: 120U/L; aspartate aminotransferase: 84U/L). A fasting lipid profile indicated a type IIb hyperlipoproteinemia (total cholesterol: 281 mg/dL, TG: 280 mg/dL, LDL-C: 210 mg/dL, HDL-C: 15 mg/dL). A percutaneous liver biopsy revealed mixed steatosis with microvesicular preponderance (Fig. 1A) and moderate (stage 2) periportal and septal fibrosis (Fig. 1B). It was also noted that he was short of stature, measuring 36 inches (<1st percentile for age and gender). He was referred for an endocrinology evaluation and a diagnosis of growth delay because of a deficiency of insulin-like growth factor-1 (IGF-1) was rendered. Exogenous growth hormone was initiated with no significant improvement in his growth pattern after 2 years of treatment. Growth hormone therapy was terminated, and IGF-1 was initiated for 1 year with no improvement in growth. IGF-1 was subsequently discontinued.

The past medical histories of the other 3 siblings were relatively unremarkable except for hyperlipidemia and unexplained elevated hepatic transaminase levels 3 to 4 times the upper limits of normal. These laboratory abnormalities were identified through testing that had been ordered by their primary care physician and prompted by the index patient's medical history. An elevated total bilirubin level (2.9 mg/dL) due to elevated unconjugated bilirubin was identified in the 17-year-old brother and determined to be the result of Gilbert's syndrome (OMIM: 143500).

All brothers live with their parents, do not smoke, or are not exposed to second-hand smoke, routinely participate in organized sporting activities, and are academically above average. None of the brothers were receiving drug therapy. All had been consuming a healthy low-fat diet (<7% of total calories from saturated fat) for several years because of their history of hyperlipidemia. The physical and clinical chemistry assessments are summarized in Table 1. All the brothers had normal body mass indices and blood pressures. Bilateral, periorbital dark circles with a waxy appearance to the facial skin were conspicuously apparent in all 4 brothers. The 9- and 14-year-old brothers had several 3 to 5 mm tuberous xanthomas, bilaterally on their knees. The index sibling was short of stature (49 inches; 1st percentile