Lysosomal Acid Lipase Deficiency, a Rare Pathology: The First Pediatric Patient Reported in Colombia

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Patient: Male, 14
Final Diagnosis: Lysosomal acid lipase deficiency (LAL-D)
Symptoms: Dyslipidemia • isolated hepatomegaly
Medication: —
Clinical Procedure: Genetic sequencing
Specialty: Gastroenterology and Hepatology
Objective: Rare disease
Background: Lysosomal acid lipase deficiency is a rare genetic metabolic lipid storage disease, with a high morbidity, and mortality, in children and adults. It is characterized by a mutation in the LIPA gene that causes an alteration of lipid metabolism, resulting in deposits of cholesterol esters and triglycerides in organs such as the liver, blood vessels, and gastrointestinal tract. Lysosomal acid lipase deficiency is predominantly caused by the mutation c.894G>A, seen in approximately 50–70% of patients. Our objective is to report the first pediatric case of lysosomal acid lipase deficiency in a pediatric patient in Colombia.

Case Report: The patient is a 14-year-old boy with isolated hepatomegaly since 6 years of age without a family history of dyslipidemia. In the pediatric control, laboratory exams revealed dyslipidemia, and a hepatic biopsy was performed, revealing severe fibrosis with septation and grade 3 microvesicular steatosis (>75%). He was referred to our center and was suspected to have lysosomal acid lipase deficiency. Enzymatic activity was measured, showing absent activity. Confirmatory diagnosis with genetic sequencing showed a pathological homozygous mutation of c.894G>A.

Conclusions: Lysosomal acid lipase deficiency can manifest as early- or late-onset, with variable and severe signs and symptoms. The late-onset form has a broad spectrum of manifestations with mild symptoms, leading to under-diagnosis, which increases the actual disease burden. Early diagnosis is essential to initiate enzyme replacement therapy, since the natural disease course can be changed. More studies should be conducted in Latin America to evaluate the prevalence of the disease.

MeSH Keywords: Dyslipidemias • Rare Diseases • Sterol Esterase • Wolman Disease

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**Background**

Lysosomal acid lipase deficiency (LAL-D; OMIM: 278000) is an autosomal recessive metabolic lipid storage disease, first described in 1965 by Moshe Wolman [1]. This glycoprotein is a hydrolase encoded by the LIPA gene in the long arm of chromosome 10q region 23.2–23.3 locus and plays a crucial role in lipid metabolism by hydrolyzing cholesterol and triglyceride esters at the lysosomal level [2]. Homozygous and compound heterozygous LIPA mutations result in little or absent LAL activity, generating an accumulation of cholesterol esters and triglycerides in the lysosomes of the liver, blood vessels, spleen, adrenal glands, hematopoietic system, lymph nodes, and gastrointestinal tract; resulting in a progressive, multiorgan damage, including cirrhosis, liver failure, accelerated atherosclerosis, and other devastating consequences [3,4]. The exact prevalence of LAL-D in children and adults is not yet established, and it is presumed to affect 40 000 to 300 000 newborns [5].

Previously, LAL-D was divided into 2 phenotypes: the early-onset form or Wolman's disease, and the late-onset form known as cholestereryl ester storage disease [6]. Currently, these names are not used, as it is understood that this pathology is a unique nosological entity and can present different phenotypes of presentation, ranging from the early-onset with rapid progression to the late-onset with chronic progression [7]. The early-onset form debuts in the first weeks of life, since there is absent LAL activity, generating severe infantile-onset disorder characterized by steatorrhea, emesis, chronic malnutrition, adrenal calcification, hepatosplenomegaly, failure to thrive, and multiorgan failure resulting in death typically before 1 year of age [8,9]. However, the late-onset debuts at 3–15 years of age; there is residual enzyme activity, generating a benign and broad spectrum of clinical manifestations such as hepatosplenomegaly, hepatic steatosis, dyslipidemia, and accelerated atherosclerosis, with increased cardiovascular risk [10–12]. We report a case of LAL-D from Colombia, which was confirmed by clinical and molecular characterization.

**Case Report**

The patient is a 14-year-old white male, an only child with a prenatal history of a patent ductus arteriosus, who underwent surgical correction at age 5 years. He had no other co-existing diseases and was not receiving medication. He had non-consanguineous parents with normal lipid profile and no family history of hypercholesterolemia, dyslipidemia, or other disorders.

During a pediatric checkup at 6 years of age, isolated hepatomegaly was detected. He underwent a hepatic ultrasound, which showed hepatic steatosis, without focal lesions or Doppler abnormalities. Due to these findings, he was eventually referred to the pediatric gastrohepatology division in our center 2 years later.

His serum lipid profile results showed: total cholesterol (TC) 390 mg/dL, high-density lipoprotein (HDL-c) 45 mg/dL, and triglyceride (TG) 204 mg/dL, which were compatible with the diagnosis of dyslipidemia (Table 1). A hepatic function test showed elevated transaminase levels, with aspartate amino-transferase (AST) 89 U/L and alanine aminotransferase (ALT) 137 U/L (Table 1). Coagulation time was normal and tests for infectious disease were negative.

Considering the presence of isolated hepatomegaly with dyslipidemia, a hepatic biopsy was performed. The results showed hepatic tissue with adequate representation of portal tracts (>12) and the hepatocytes with microvesicular steatotic changes in 80%, without inflammatory infiltrate in the portal tracts or hepatocytes. Reticular staining (400×) showed fibrous tracts within the portal tracts. There were also multiple clear vacuoles in the cytoplasm of the hepatocytes, which did not displace the nucleus (HE400×). Staining of lysosomal markers, electronic microscopy, and immunochemistry were not performed (Figure 1). Pharmacological treatment with atorvastatin 10 mg daily was started from the age of 10 years and improvements in the lipid profile were observed (Table 1).

**Table 1. Variations of lipid profile and liver enzymes.**

| Test          | 8 years | 10 years | 12 years | 14 years | 15 years | Reference range |
|--------------|---------|----------|----------|----------|----------|-----------------|
| AST, U/L     | 89      | 58       | 45       | 60       | 122      | 10–59          |
| ALT, U/L     | 137     | 51       | 47       | 133      | 52       | 6–34           |
| C total, mg/dL | 290    | 263      | 250      | 228      | 214      | <200; limit 200–239 |
| HDL-c, mg/dL | 45      | 80       | 62       | 33       | 42       | 40–60          |
| LDL-c, mg/dL | ND      | 169      | ND       | 166      | 168      | 0–100          |
| TG, mg/dL    | 204     | 72       | 69       | 143      | 131      | 30–100         |

AST – aspartate aminotransferase; ALT – alanine aminotransferase; C total – total cholesterol; HDL-c – high-density lipoprotein; LDL – low-density lipoprotein; TG – triglycerides.
At age 14 years, LAL activity was measured by dried blood spot, and results showed no activity. Confirmatory diagnosis of LAL-D was performed with genetic sequencing, which showed a pathological homozygous mutation in c.894G>A, as reported previously. Enzyme replacement therapy (ERT) with recombinant sebelipase alpha was prescribed intravenously at a dose of 1 mg/kg/weekly. However, the drug was unavailable due to administrative problems. In addition, cardiovascular assessment with pediatric echocardiogram was normal. To date, the patients continues to be clinically stable with pharmacological treatment with atorvastatin.

**Discussion**

LAL-D is a rare lipid storage disease, and the natural course of the patients with the late-onset form results in inflammatory processes due to the chronic hepatic accumulation of cholesterol, which culminates in fibrosis, cirrhosis, and hepatic failure [13]. Over 50 causative mutations have been identified according to the Human Gene Mutation Database, and the most common LIPA mutation is c.894G>A, which is an exon 8 splice junction mutation [14].

LAL-D is a rare lipid storage disease. Its prevalence is approximately 1/40 000–1/350 000 in newborns; it is more frequent in individuals with Iranian–Jewish ancestry, with an incidence of 1: 4200 in this population [7,8]. Our case is the first reported from Colombia with enzymatic and molecular confirmation. We performed clinical, enzymatic, and molecular analysis for our patient, who was in the age range reported in the literature [15]. Hepatomegaly is the most common finding in pediatric patients with LAL-D, associated with lipid profile abnormalities [10]. This disease is difficult to recognize because of its low prevalence, and it overlaps with other diseases that have similar symptoms and signs. Reiner et al. suggested that patients with lipid profile (increased levels of TC, TG, and LDL levels, and decreased HDL levels) or liver enzymes abnormalities (increased ALT and AST levels) without family history should be evaluated according to the diagnostic criteria, and levels of LAL enzymatic activity levels should be measured [4]. However, diagnostic tests for LAL-D in Colombia are limited, and the absence of clinical suspicion can lead to errors in the diagnosis, with a consequent disease progression and delay in treatment initiation. After ruling out other diagnoses, the patient’s findings generated a clinical suspicion of LAL-D.

Diagnostic images such as liver ultrasound and biopsy are relevant because they demonstrate changes in hepatic morphology, which may be suggestive of LAL-D such as microvesicular steatosis with Kupffer cell involvement, fibrosis, and cholesterol-ester-crystal deposition [4,16,17]. As seen in the findings of the present case, the disease manifests as an idiopathic microvesicular hepatosteatosis disease. Hence, our patient was referred to our institution and was evaluated by the pediatric gastroenterology and hepatology division, after which a presumptive diagnosis of LAL-D was made.

The confirmatory diagnosis is the measurement of enzyme activity in peripheral blood leukocytes, cutaneous fibroblasts, or in blood drops collected on filter paper [8,18]; in the present case, LAL activity was absent. Homozygous mutation of c.894G>A is present in approximately 60% of patients with late-onset LAL-D, as well as in our patient. This mutation results in a transcript with an in-frame deletion of exon 8 that encodes a mutant enzyme with no residual LAL activity [10]. Carrier frequency analysis of c.894G>A in Colombia would provide valuable information on the prevalence of this disease.
recurrent mutation and would facilitate selecting patients for genetic counseling.

Lipid-lowering therapy with statins is considered ineffective in patients with LAL-D and does not result in improvement of the hepatic involvement [4,7,11]. However, in low-income countries such as Colombia, where administrative problems are an obstacle for using ERT, statins are the best option to reduce LDL levels, decrease the cholesterol synthesis, and decrease cardiovascular risk, despite hepatic damage progression, until initiation of ERT [4]. ERT with sebelipase alfa was approved by the FDA in 2015, and its administration achieves physiological levels of the enzyme and prevents the accumulation of cholesterol esters and triglycerides; this is achieved because it enters various cells (e.g., Kupffer cells and hepatocytes) through the mannose-6-phosphate receptors and hydrolyzes cholesterol esters and triglycerides [11,19]. However, in terminal chronic liver disease, liver transplantation is a therapeutic option [6,19,20].

Conclusions

LAL-D is a rare disease with an unknown actual prevalence because of its overlapping clinical manifestations, thus increasing the actual disease burden if it is diagnosed late. To the best of our knowledge, this is the first report of a pediatric patient from Colombia with LAL-D in which clinical, enzymatic, and molecular characterization was performed.

Conflict of interest

None.

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