Lysosomal acid lipase deficiency, a rare pathology

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Abstract

Lysosomal acid lipase deficiency is a genetic disease with a low prevalence and high morbidity and mortality in children and adults. It is characterized by an alteration of lipid metabolism, which generates cholesterol and triglyceride esters deposits in the body. Its clinical presentation depends on enzymatic activity. This condition should be suspected in patients with lipid or liver alterations after ruling out other diagnoses. Currently, there is the option of using a recombinant enzyme, which can improve lipid and liver parameters, as well as disease progression. Establishing a timely diagnosis in order to initiate specific treatment early is imperative for the prevention of morbidity and mortality. The purpose of this work is to perform a review of the literature about lysosomal acid lipase deficiency and to guide about its pathophysiology, clinical manifestations, diagnosis and treatment.

KEY WORDS: Dyslipidemia. Cirrhosis. Cholesterol esters deposition disease. Lysosomal acid lipase deficiency. Steatohepatitis. Cryptogenic liver disease.

Introduction

Lysosomal acid lipase (LAL; EC 3.1.13) is a glycoprotein that is mainly expressed in macrophages, hepatocytes, intestinal cells and Kupffer cells. It is encoded in the *LIPA* gene (MIM: 613497) located at chromosome 10 long arm (q), region 23.2-23.3.¹⁻⁶ This glycoprotein acts as an enzyme that plays a key role in cholesterol metabolism.⁶

Cholesterol and triglyceride esters are transported in cholesterol lipoprotein particles, especially low density lipoproteins (LDL) and very low density lipoproteins (VLDL) to hepatocytes; they enter the cell through receptor-mediated (LDL-R) endocytosis until reaching the lysosome, where they are hydrolyzed by LAL to free cholesterol and free fatty acids.¹⁻⁶ Free cholesterol inhibits 3-hydroxy-3-methyl-glutaryl-CoA reductase

(HMG-CoA) action, thus preventing cholesterol de novo formation, activation of proteins that bind to sterols regulatory elements and transcription factors responsible for the activation of cholesterol synthesis genes.⁶ Cholesterol plays an important role as a precursor in the synthesis of steroids and bile acids and as a component of cell membranes.⁶

Deficit of this enzyme (LAL-D; MIM: 278000) results in decreased hydrolysis and accumulation of cholesterol and triglyceride esters in liver lysosomes, blood vessels, the spleen, adrenal glands, hematopoietic system, lymph nodes and gastrointestinal tract. In addition, it is associated with reduced generation of free cholesterol and free fatty acids.^{1,3-10} The decrease in free cholesterol translates into sterol regulatory elements and HMG-CoA increased activity, with a corresponding increase in free cholesterol and free fatty acids synthesis.^{4,11} On the other hand, there is an

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Figure 1. Diagram of cell cholesterol homeostasis **A)** in healthy individuals and **B)** in patients with lysosomal acid lipase deficiency. ACAT = acetyl-coenzyme A acetyltransferase, FA = fatty acids, FFA = free fatty acids, EC = esterified cholesterol, FC = free cholesterol, LDL-C = low-density lipoprotein cholesterol, VLDL-C = very low density lipoprotein cholesterol, HMG-CoA = hydroxy-methyl-glutaryl-coenzyme A, LAL = lysosomal acid lipase, LDLR = low-density lipoprotein receptor, SREBP = sterol regulatory element-binding proteins, TG = triglycerides.

increase on VLDL cholesterol secretion and LDL levels.^{11,12} The decrease in free cholesterol reduces hepatic X receptor activation, ABCA1 transporter expression and apolipoprotein A1 (ApoB100) and plasma HDL cholesterol flow^{12,13} (Figure 1).

LAL-D is an orphan disease, with an autosomal recessive transmission pattern.^{4,11,14,15} More than 50 mutations have been identified according to the Human Gene Mutation Data Base; exon 8- splicing site mutation, E8SJM (c.894G> A; p.del S275 Q298), is the most common, and it produces exon 8 deletion in mRNA.^{4-6,11,14-17} Previously, LAL-D was divided in two phenotypes, where enzymatic activity determines the clinical presentation: the childhood form, or Wolman disease, and one less severe form known as cholesterol ester storage disease;^{1,3,4,6-10,18} in the first one, enzymatic activity is almost nil, while in the second there is residual enzymatic activity (1 to 12 % of normal).¹² Currently, this denomination is not used, since LAL-D is understood as the only nosological entity that has different presentation phenotypes, starting early and with rapid progression or with a late onset and variable progression¹¹ (Table 1).

The purpose of this work is to carry out a review of the literature on LAL-D and provide guidance about its pathophysiology, clinical manifestations, diagnosis and treatment.

Epidemiology

The true prevalence of LAL-D is not known; however, it is assumed to range from 1 in 40,000 to 1 in 350,000 individuals according to the population.^{5,11,16,19-21} In Germany, prevalence was estimated at 1 among 50,000 cases of cholesterol ester storage disease and 1 in 350,000 cases of Wolman disease.^{16,20} This disease occurs more frequently in individuals of Iranian-Jewish ancestry. According to Valles-Ayoub, the rate in this population is about 1 in 4200 people, which appears to correspond to a mutational variant associated with the entity (c.260G> T).²² The mutation of c.894G> A (E8SJM) is present in approximately 50 to 70 % of patients with late LAL-D, which have residual activity of the enzyme.^{14,23} On the other hand, the mutations of c.892C> T (E8SJM-3) and c.894p1G> A

Table 1. Lysosomal acid lipase deficiency phenotype

Clinical manifestations	Early form (formerly WD)	Late form (CESD)
Disease onset	First months of life	From childhood to adulthood
Hepatomegaly	Marked	Variable
Liver fibrosis	Present	Variable
Splenomegaly	Present	Variable
Malabsorption	Marked	Variable
Adrenal calcifications	Variable	Variable
Dyslipidemia	Variable	Present
Cholesterol ester storage disease	Variable (5-160 times of normal)	Present (150-350 times of normal)

WD = Wolman disease; CESD = cholesterol ester storage disease.

(E8SJMp1) have been detected in early-onset LAL-D.^{14,24}

This disease affects both genders equally and has been reported more frequently in children, with a peak incidence at between three and 15 years of age.^{12,25} There are phenotypes with mild manifestations that are not diagnosed due to the lack of suspicion and limited access to confirmatory diagnostic tests, which suggests that the real prevalence of the entity is higher. No studies have been reported on the prevalence of this disease either in Colombia or Latin America.

Clinical manifestations

Clinical manifestations are variable, with the most common including dyslipidemia, hepatomegaly and liver alterations.⁴ Early-onset LAL-D or Wolman disease is characterized by a severe and fulminant clinical presentation expressed in the first weeks of life.^{4-6,10,26-28} Clinically, these patients have chronic diarrhea (steatorrhea), vomiting, chronic malnutrition, malabsorption (due to steatorrhea and emetic episodes), failure to thrive, hepatosplenomegaly, liver compromise with development of fibrosis, cholestasis and liver failure.^{3-5,12,22,29} In addition, most of patients have adrenal gland bilateral calcification (50 %), which leads to adrenal primary insufficiency, multiple organ failure and death within the first year of life.^{3-5,22,29}

Late-onset LAL-D or cholesterol ester storage disease is characterized by a more benign clinical presentation and a broad spectrum of manifestations.⁶ It can be asymptomatic until adulthood, during which hepatomegaly (99 %) with microvesicular or mixed hepatic

steatosis, splenomegaly (74 %), gastrointestinal alterations and dyslipidemia occur, which generates early atherosclerosis with increased cardiovascular risk.^{3-6,10,19,28-31} If the natural course of disease persists, chronic liver disease can cause liver failure, with the consequent need for liver transplantation.^{3-5-5,19,28-30}

Due to the progressive accumulation of cholesterol and triglyceride esters, liver profile abnormalities are generated in both spectra, which are characterized by increased levels of serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), hyperbilirubinemia and dyslipidemia (increase in LDL, low levels of high-density lipoproteins [HDL] and increased triglycerides).^{3-6,12,22,29}

Diagnosis

LAL-D recognition is difficult due to its low prevalence and to an overlapping with other diseases. In addition, the absence of clinical suspicion can lead to diagnostic errors, with a consequent disease progression and delay in treatment initiation.

In general, LAL-D should be suspected in patients with hepatosplenomegaly or hepatic or lipid profile alterations without a family history thereof. The diagnosis of this pathology should be established accordingly with the medical history, suggestive findings on physical examination and lipid profile results. Reiner et al. suggest that patients with lipid profile alterations who do not have a family history thereof should be assessed according to diagnostic criteria; should there be three or more clinical or paraclinical signs present, enzyme activity should be determined in blood⁴ (Figure 2).

Some diagnostic resources to support the diagnosis are liver biopsy and magnetic resonance imaging, which quantifies content of liver fat.¹² On the other hand, liver biopsy shows liver morphology findings that can be suggestive but not confirmatory, such as microvesicular steatosis with Kupffer cell involvement, fibrosis, micronodular cirrhosis, sea-blue histiocytosis and cholesterol ester crystals.^{4,6,12,30,32,33} Other findings include lipid accumulation in reticuloendothelial cells of the spleen and vacuolated macrophages with lipids that infiltrate the lamina propria with gastrointestinal tissue architecture destruction and the consequent dysfunction of enterocytes absorbent and enzymatic activity.⁶ In immunohistochemical testing, cathepsin D lysosomal markers, and lysosomal membrane-associated proteins 1 and 2 (LAMP1 and LAMP2) can be used.³²

Confirmatory diagnosis is established by measuring enzymatic activity in peripheral blood, skin fibroblasts

Figure 2. Guideline for lysosomal acid lipase clinical suspicion. ALT = alanine aminotransferase, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LAL-D = lysosomal acid lipase deficiency, NAFLD = non-alcoholic fatty liver disease, ARH = autosomal recessive hypercholesterolemia, HFH = heterozygous familial hypercholesterolemia, FCH = familial combined hyperlipidemia, BMI = body mass index, LAL = lysosomal acid lipase, CNS = central nervous system, HBV = hepatitis B virus, HCV = hepatitis C virus, NV = normal value. *According to availability.

or dried blood spot leukocytes.^{5,12,34} Molecular analysis with *LIPA* gene regions genetic sequencing is used to identify point and deep intronic mutations or rearrangements.¹² On the other hand, the dried blood spot technique determines LAL's in vitro activity in the presence of substrates (oleate, palmitate, etc.) modified with fluorochrome (4-methylumbelliferone), which allows quantification of the amount of released product through emission spectroscopy or fluorimetry.^{6,12,35}

Given that the presence of other lipases in blood can interfere with the measurement, a LAL inhibitor called Lalstat 2® is used (Chemical Tools, South Bend, IN, USA).³⁵ LAL activity is determined by comparing total lipase activity with lipase activity in the presence of the inhibitor; the difference between both is attributable to the LAL enzyme. Reduced values of enzymatic activity according to the ranges established by the laboratory are considered diagnostic of LAL-D. Complete sequencing of the *LIPA* gene coding region allows the identification of mutations that cause the disease. Most patients are homozygotes or compound heterozygotes;^{4,12,35} however, some can have intronic mutations or other variants that may not be detected by sequencing. Therefore, the method of choice for

diagnosis is enzymatic activity measurement, and molecular tests are considered complementary.⁴

Treatment

In the past, the treatment consisted only in prevention of disease complications. Lifestyle changes were recommended and treatment with lipid-lowering agents (statins) for the management of hypercholesterolemia. Statins decrease LDL levels; however, they do not generate changes in the development of liver fibrosis.^{4,6,12,36,37}

Bone marrow transplantation has been used in cases of LAL-D with early diagnosis to prevent cardiovascular complications or in infants with rapidly progressive LAL-D; however, further studies are still needed to rigorously assess this strategy.^{3,4,6,12} In turn, liver transplantation is the treatment indicated for liver failure, and should be performed in conjunction with bone marrow transplant bone due to the risk of disease recurrence. So far, follow-up of these patients does not allow drawing conclusions on the efficacy of this intervention in LAL-D.^{2,6,36,38,39}

Enzyme replacement therapy is currently used, which seeks to restore physiological levels of the enzyme and

thus prevent the accumulation of cholesterol and triglyceride esters by delaying disease progression.^{4,12} Replacement can be carried out with recombinant human lysosomal acid lipase (rhLAL) enzyme or recombinant sebelipase-alfa (Kanuma®, Alexion Pharmaceuticals), a glycoprotein that contains 378 53-55-kDa amino acids, six N-linked glycosylation sites and is extracted from chicken eggs.^{5,40-42}

This drug penetrates different cells (Kupffer cells and hepatocytes, among others) through the mannose-6-phosphate receptors; once inside, the recombinant enzyme replaces LAL, hydrolyzing cholesterol and triglyceride esters within the lysosome to reverse its effects.^{3,12,43} It has been used in biomodels with rodents, where it has been observed to correct abnormalities associated with this condition: it decreases the lipid content at the hepatic level, splenomegaly, transaminase levels and atherosclerosis.^{2,43-46} Six studies have been carried out to assess the efficacy and safety of this drug in infants with LAL-D (LAL-CL03 and LALCL08) and in pediatric and adult patients with LAL-D (LAL-CL01, LAL-CL04 and LAL-CL02).^{3,6,29,41,47} In clinical trials in humans, it has been shown to decrease blood liver enzymes, liver volume and fat at the liver level; in addition, it has achieved improvements in plasma lipid levels (LDL and HDL), with increases in HDL-cholesterol and decreases in LDL-cholesterol.^{2,3,6,12,29,40,47} Furthermore, phase I and II clinical trials were performed in adults with LAL-D to whom 0.35, 1 or 3 mg/kg intravenous sebelipase-alfa was applied for seven days; a decrease in transaminase levels was observed.^{41,43}

The same patients from the above study were subsequently included in a 52-week follow-up investigation; all were started with the same pharmacological management with sebelipase-alfa and, at 15 days, an adjustment to 1 or 3 mg/kg was applied. Decreases were observed in total cholesterol, LDL-cholesterol and triglycerides, associated with other findings such as reduction of the fat fraction and liver volume.^{41,48} Finally, in the ARISE phase III study, pediatric (≥ 4 years) and adult patients with LAL-D were included and randomly received sebelipase-alfa (1 mg/kg every two weeks, $n = 36$) or placebo ($n = 30$) for 20 weeks; among the results, decreases in transaminases and LDL-cholesterol were observed in the group managed with sebelipase-alfa in comparison with the group that only received placebo.²⁹

Enzyme replacement therapy (sebelipase-alfa) in patients younger than six months starts with 1 mg/kg once weekly and should be escalated to 3 mg/kg

depending on the patient. In those with late-onset LAL-D, the dose is 1 mg/kg every 15 days and should not be adjusted if they are older than 65 years or if they have kidney or liver failure.^{3,43} Adverse effects reported that are not attributable to the medication include nausea, headache, diarrhea and abdominal pain.^{4,6,29,40,41}

Follow-up

Camarena et al. state that patients should have strict clinical and paraclinical follow-up (every three months during the first year). In the first visit, patient baseline status should be assessed with liver biopsy, diagnostic imaging and paraclinic tests (blood count, coagulation tests, lipid and liver profile).¹¹ Subsequently, treatment response should be evaluated with clinical and paraclinical serial assessment. As for specific follow-up in children, growth and nutritional status should be monitored, while in adults, follow-up should be carried out according to disease severity.⁴⁹

Differential diagnosis

LAL-D has clinical characteristics that can be mistaken for other diseases, such as non-alcoholic hepatic steatosis, non-alcoholic fatty liver disease, metabolic syndrome, autosomal recessive hypercholesterolemia (MIM: 603813), sitosterolemia (MIM: 210250) or familial hypercholesterolemia (MIM: 143890).^{4,5,11,50}

Regarding the differences between familial hypercholesterolemia and LAL-D, the former is an autosomal dominant genetic disease, i.e. patients must have a family history of the condition. On the other hand, the lipid profile shows higher levels of LDL and HDL in familial hypercholesterolemia.^{4,5} In general, unlike patients with LAL-D, patients with metabolic syndrome have obesity.⁴ As for the differences between non-alcoholic fatty liver disease and LAL-D, patients usually have obesity or overweight and findings in the liver biopsy are different: in most cases, macrovesicular steatosis is observed.⁵⁰

Conclusions

LAL-D is a poorly prevalent and underdiagnosed disease, generated by mutations in the *LIPA* gene. In this pathology, lipid metabolism is affected at the lysosomal level and is characterized by systemic and progressive accumulation of esterified cholesterol and triglycerides. The presentation phenotype depends on

the degree of enzymatic activity; when it is nil, LAL-D occurs early and severely, with high mortality at one year of life. The late presentation has a heterogeneous phenotype: most patients develop chronic liver disease and, some, early cardiovascular disease.

Diagnosis represents a challenge, since clinical manifestations overlap with those of other diseases. LAL-D should be suspected in the presence of persistent liver or lipid alterations without a clear cause. Early diagnosis is essential for management with enzyme replacement therapy, which has been shown to improve lipid and liver parameters, as well as survival of infants with rapidly progressing disease.⁵¹ However, the actual prevalence of this disorder is thought to be underestimated given the absence of knowledge and limitation of diagnostic tests for this disease, and the conduction of prevalence studies in Latin America is therefore necessary.

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