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Liver disease and dyslipidemia as a manifestation of lysosomal acid lipase deficiency (LAL-D). Clinical and diagnostic aspects, and a new treatment. An update

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ABSTRACT

Lysosomal acid lipase deficiency (LAL-D) is still a little recognized genetic disease with significant morbidity and mortality in children and adults. This document provides guidance on when to suspect LAL-D and how to diagnose it. It is recommended to add lysosomal acid lipase deficiency to the list of differential diagnoses of sepsis, oncological diseases, storage diseases, persistent diarrhea, chronic malnutrition, and hemophagocytic lymphohistiocytosis. It should also be considered in young patients with dyslipidemia and atherosclerosis as well as diseases associated with fatty liver and/or hepatomegaly. LAL-D should be suspected in patients with hepatomegaly, hyperlipidemia and/or elevated transaminases found during routine checks or testing for other conditions, and in patients with cryptogenic cirrhosis. At present, there is the option of a specific enzyme replacement treatment.

Key words: *cirrhosis, dyslipidemias, Wolman disease, non-alcoholic fatty liver disease, lysosomal acid lipase deficiency.*

INTRODUCTION

Liver disease and dyslipidemia are frequent findings in everyday practice, and common signs of lysosomal acid lipase deficiency (LAL-D), a low-prevalence storage disease. It follows an autosomal recessive inheritance pattern and is caused by mutations in the LIPA gene, located in chromosome 10q23.2-23.3.[1] This enzyme is involved in the metabolism and breakdown of cholesteryl esters and triglycerides that accumulate in different tissue cells when the enzyme is reduced or absent. The most commonly affected organs and systems include the liver, spleen, adrenal glands, hematopoietic system, vascular endothelium, intestines, and lymph nodes. The clinical manifestations of LAL-D vary depending on age.[2] Liver involvement and dyslipidemia are the prevalent clinical presentations, and for this reason some patients may be misdiagnosed.

OBJECTIVE

To review LAL-D, its clinical manifestations, differential diagnoses, diagnostic confirmation, and new therapeutic options.

Clinical manifestations

The age at the time of onset, clinical spectrum, and disease course vary widely. There is a severe infant form or Wolman disease,[4,5] first described in 1956, and a late onset pediatric, adolescent, or adult form known as cholesteryl ester storage disease (CESD), first described in 1963.[2] The phenotype depends on the type of LIPA gene mutation and the severity of enzyme deficiency.

The severe form occurs in the first months of life, with an almost null enzyme activity (LAL) or < 1% of normal activity.[5] Children appear healthy at birth but, between 1 and 2 months old, they have malaise, failure to thrive, progressive malnutrition, marked abdominal distension caused by malabsorption and

hepatosplenomegaly, recurrent vomiting, chronic diarrhea (steatorrhea), and liver involvement with rapid development of fibrosis and/or cholestasis and/or liver failure. Elevated transaminases (50-95% of cases) and hypersplenism (anemia/thrombocytopenia) are also observed.[2] Approximately 50% of patients have bilateral calcifications of the adrenal glands.[6,7]

Cholesterol levels are elevated or normal with reduced high-density lipoproteins (HDL) and increased very low-density lipoproteins (VLDL); triglycerides may be normal or elevated.[8] Developmental delay and/or irritability are secondary to malnutrition, overall compromise, and hospitalization resulting from the central nervous system involvement caused by this disease.[9] The natural course of this clinical form results in death in the first year of life.[10-12]

The subtype of LAL-D that starts during childhood, adolescence, or adulthood implies 1-12% of normal enzyme activity; lipid accumulation leads to progressive liver damage, elevated transaminases, steatosis, fibrosis and/or cirrhosis. These patients develop chronic dyslipidemia, which leads to early atherosclerosis (infarction, aneurism, stroke).[13-14]

In a series of 48 patients with this subtype of LAL-D, the median age at the time of disease reporting was 5.8 years old (maximum: 46 years old); 56% were younger than 20 years old and 17%, younger than 10 years old. Symptoms started before 10 years old in 75% of patients. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were elevated in 92%, 59%, and 20% of patients, respectively. Hepatomegaly, which is less common in the early onset subtype, was reported in 54% of patients whereas splenomegaly was reported in only 23%.[16]

Dyslipidemia in LAL-D is indistinguishable from that occurring in other more common etiologies. Total cholesterol, LDL-C, VLDL-C, and triglycerides are elevated, and HDL-C is reduced.[1,4,5] Pediatric patients have shown LDL-C ≥ 130 mg/dL and HDL-C ≤ 45 mg/dL.[11] Cerebral infarction and hyperlipidemia have been reported at 13 years old, with symptomatic gallbladder dysfunction[16] (*Table 1*).

Prevalence

Although more than 40 mutations have been described,[17] the mutation in exon 8, E8SJM (c.894G > A) has been identified in 50-60% of patients with the late onset subtype and of European descent.[18] It was detected in approximately 1:200 heterozygous healthy German individuals. Thus, prevalence may be expected to be 1:40 000 German newborn infants, and 1:300 000 Hispanics and Caucasians.[19,20] The number of reported cases has been much lower than these estimates, which suggests a non-specific clinical course and the absence of a characteristic phenotype. No studies have been conducted regarding the prevalence of LAL-D in Argentina.

Diagnosis of lysosomal acid lipase deficiency at the lab

The definitive diagnosis of LAL-D is made by demonstrating the deficiency or absence of LAL enzyme activity (EC 3.1.1.13) in isolated peripheral blood leukocytes or fibroblast cell cultures.[21] Enzyme determination may also be done from blood spots dried on filter paper,[22] which allows for the proper submission of lab specimens from remote locations, retrospective diagnosis, and population level screening. However, if filter paper samples are abnormal, results should be confirmed using leukocytes or fibroblasts. This test is useful to confirm the diagnosis of homozygous individuals, but not for heterozygous ones, who may have a normal enzyme activity.

The molecular genetic test consists in identifying the pathogenic mutations in both alleles of the LIPA gene, and is considered a supplementary diagnostic test.[23] Mutation identification is useful to carry out family studies and, therefore, provide a diagnosis and genetic counseling to heterozygous family members.

Pathophysiology

Acid lipase acts on hepatocyte lipid metabolism, and acid lipase deficiency, as described from a pathophysiological perspective in *Figure 1. A*, explains dyslipidemia and neutral lipid accumulation in the lysosome, resulting in liver damage.[24]

Differential diagnosis

Although there are biochemical and genetic tests for the diagnosis of LAL-D, detecting this disease depends on clinical suspicion, which is low.[11,12] Clinical and biochemical manifestations are consistent with other cardiovascular, liver or metabolic diseases.[1,12] LAL-D should be included in the list of differential diagnoses of liver conditions and dyslipidemias. Given its severe morbidity and early mortality, patients should

TABLE 1. *Lysosomal acid lipase deficiency phenotype: from the severe form in infants (Wolman disease) to the late-onset form in children, adolescents, and adults (cholesteryl ester storage disease) (modified from Grawoski, 2014)*

Clinical signs	Newborns and infants	Children, adolescents and adults
Age at onset	0-3 months old	From childhood to adulthood
Age at death	±6 months old	Varied
Hepatomegaly	++++	+/++
Liver fibrosis/cirrhosis	++	+/+++
Splenomegaly	+++	+/-
Malabsorption	+++	+/-
Emaciation	+++	±
Adrenal calcifications	++	±
Dyslipidemia	±	++/+++
Cholesteryl ester storage	5-160 times higher than normal	150-350 times higher than normal
Triglyceride storage	In the liver: 2-10 times higher than normal	
	In the spleen: 8-100 times higher than normal	
	In the adrenal glands: 1.5-8 times higher than normal	1.5-3 times higher than normal

FIGURE 1. **A.** *Effect of LAL-D on the liver and lipid metabolism. A hepatocyte receptor is responsible for LDL and VLDL cholesterol uptake, which are then carried to the lysosome. LAL-D results in cholesterol ester (CE) and triglyceride accumulation, and reduces free cholesterol (FC) and fatty acid (FA) production. The reduction in cholesterol increases sterol regulatory-element binding protein (SREBP) activity and cholesterol and FA synthesis, thus increasing LDL and VLDL cholesterol levels. The reduction in FC decreases liver X receptor (LXR) activation and the expression of ABCA1 transporter, thus reducing cholesterol flow to apolipoprotein A1 (ApoA-1) and plasma HDL cholesterol levels. **B**. Effect of treatment with sebelipase alfa (rhLAL); the mannose-6-phosphate (M6P) receptor is responsible for sebelipase alpha uptake, which is carried to the lysosome, where it reverses lipid metabolism defects. It prevents hepatocyte lipid accumulation. Modified from Rader D.*[24]
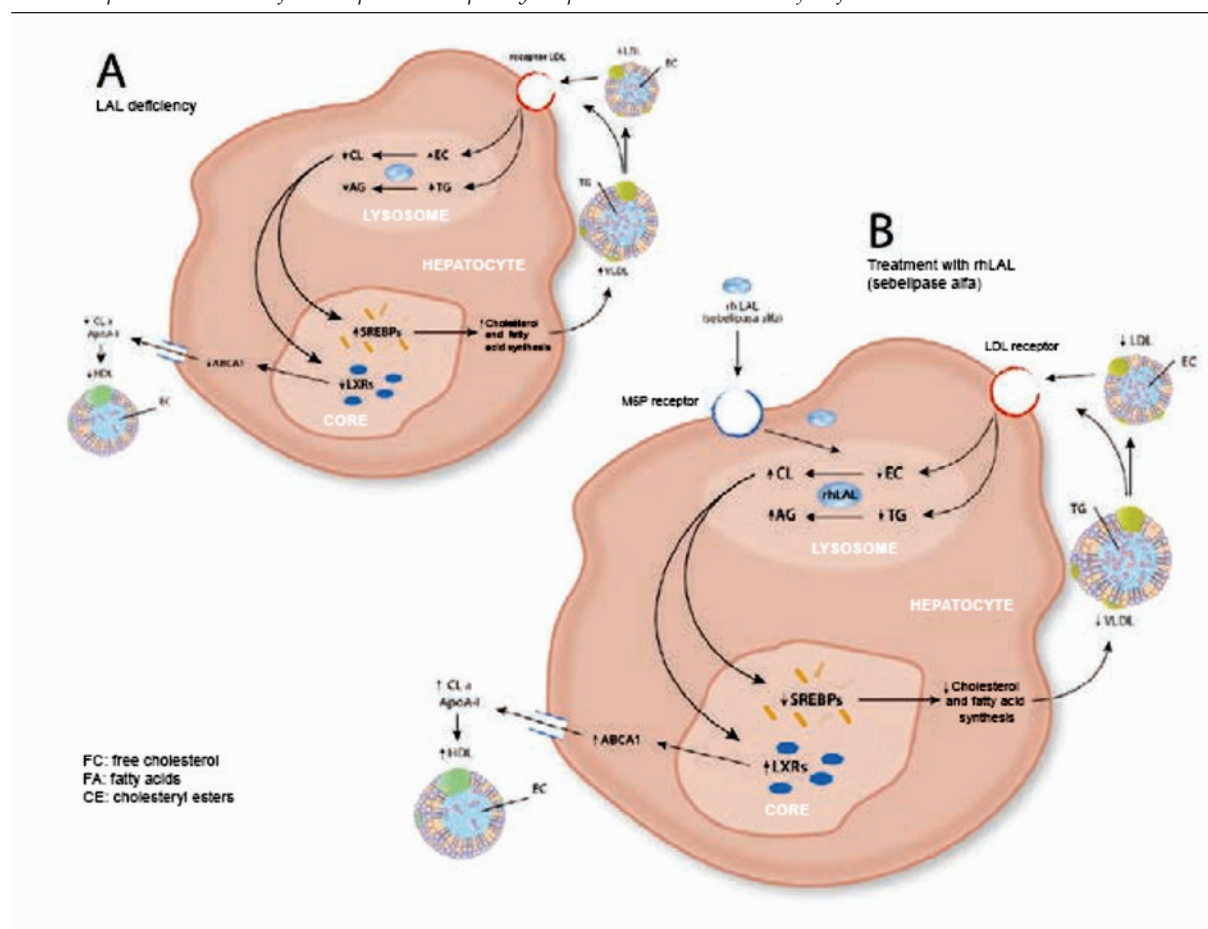
LAL: lysosomal acid lipase; HDL: high-density lipoproteins; LDL: low-density lipoproteins;
VLDL: very low density lipoproteins; TG: triglycerides.

be diagnosed quickly, before any permanent damage occurs (in the liver, spleen, digestive tract, vascular system).[11,12] Below we will review differential diagnoses.

Visceromegaly in the severe infant presentation or Wolman disease is also common in other storage diseases (Niemann-Pick disease, Gaucher disease, glycogen storage disease type IV). In the case of hemophagocytic lymphohistiocytosis, similarities have been described between this disease and LAL-D[25] and other oncological diseases. Although these other conditions have their own typical phenotypes and biochemical features, the severe clinical form in the first year of life may be confused with acid lipase deficiency.[26-31]

Adrenal calcifications should be differentiated from neuroblastoma and adrenal hemorrhage, although in these cases, the lesion is usually unilateral.

Sepsis, congenital infections with visceromegaly, subacute or chronic gastroenteritis, malabsorption disorders, Hirschsprung disease, and cow's milk allergy may be confused with LAL-D,[21] so it should be included in the differential diagnosis when any of these more common etiologies is not confirmed or if the patient's course does not improve as expected.

LAL-D should be included in the differential diagnosis of older patients (children, adolescents and adults) with normal weight or overweight, elevated levels of total cholesterol and LDL-C, low levels of HDL-C, elevated transaminases and/or hepatomegaly and/or hepatic steatosis.[12]

Overweight or obese patients with metabolic syndrome,[32] elevated transaminases, signs of hepatic steatosis in imaging tests, and alcohol intake < 140 g/week, it is necessary to rule out other muscle or liver diseases besides non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH).[32,33]

Obesity itself does not warrant looking for NAFLD based on elevated transaminases,[34] although LAL-D should be ruled out in those patients who lose weight on treatment but whose biochemical markers are not modified as expected.[25,35]

As there is no specific biochemical marker for NAFLD and NASH, doing a liver biopsy has been the recommendation,[36,37] although it does not provide a definitive diagnosis either. Patients with microvesicular steatosis may be wrongly diagnosed as having NAFLD[35] or NASH. At present, NAFLD is the most common cause of elevated transaminases during childhood and adolescence, resulting from the increase in obesity incidence.[38,39] Adolescents and adults with NAFLD usually have insulin resistance and hyperglycemia, but this is not the case in patients with LAL-D.[40] NAFLD is rare among children younger than 3 years old, and uncommon among those younger than 10 years old. *Table 2* describes the characteristics of NAFLD/NASH and LAL-D.

In Latin America, cirrhosis[41] is associated with chronic alcohol abuse, hepatitis virus (hepatitis C virus [HCV]: 29%; hepatitis B virus [HBV]: 27%), alterations in liver drainage (19%), NASH (8%), and cryptogenic cirrhosis (6%).[42]

In pediatrics, 5-15% of cirrhosis cases are cryptogenic, and LAL-D should be included

TABLE 2. *Differential diagnosis of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis and lysosomal acid lipase deficiency (late onset)*

	NAFLD/NASH	LAL-D (late onset)
Prevalence	20/100	1:40 000
Hepatomegaly	+/-	+++
Splenomegaly	+/-	++
BMI	Overweight/obesity	Normal/overweight
AST/ALT ↑	20% in the general population	+++
Carbohydrate metabolism	Abnormal	Normal
Triglycerides	↑ ↑	Normal or ↑
HDL-C	↓	↓
LDL-C	Normal or ↑	↑ ↑
Liver biopsy	Macrovesicular steatosis	Microvesicular steatosis

NAFLD/NASH: non-alcoholic fatty liver disease/non-alcoholic steatohepatitis; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

in screening tests for both children and adults. Microvesicular or mixed steatosis of the liver in children and adolescents leads to the suspicion of Wilson's disease, rather than LAL-D, because steatosis in Wilson's disease is secondary to copper accumulation, although LAL-D should also be included in the differential diagnosis.[43,35]

In the case of early liver failure, LAL-D should be included in screening tests in addition to tyrosinemia, galactosemia, beta-oxidation disorders, neonatal hemochromatosis, and mitochondrial diseases.[44,45]

In the case of LAL-D, the histology of the liver shows cholesteryl ester accumulation in hepatocytes and Kupffer cells. Almost 50% of cases present with septal fibrosis that progresses to cirrhosis. A liver transplant may be required in the three years following symptom onset.[6,11,12] The histopathological examination is facilitated by immunostaining of cathepsin D, a lysosomal protein.[11]

In relation to dyslipidemia, there are national recommendations in place for its screening in children and adolescents aged 6 to 17.[46,47] This allows for the detection of hypercholesterolemia and its early management. If there is no clear family history, and dyslipidemia does not improve with regular treatment (diet and physical activity to achieve a normal body mass index [BMI]), LAL-D should be investigated, as well as other causes of secondary hypercholesterolemia.

Pediatric patients with LDL > 130 mg/dL and/ or HDL < 40 mg/dL without a clear family history, obesity, or central fat distribution, or with normal fasting glucose may have LAL-D[48] (*Table 3*).[8]

TREATMENT

No effective treatment for LAL-D has been established; lipid lowering drugs have been poorly effective and failed to improve liver involvement.[1,11] There is scarce information about the history and follow-up of liver transplantation, although in the past it has been the only plausible option in the case of progression to end-stage liver failure.[1]

In 2015, the use of an enzyme replacement therapy with a recombinant human form of the lysosomal enzyme (sebelipase) was approved for intravenous use every 15 days. A double-blind, randomized, multicenter clinical trial,[49] demonstrated a significant decrease in transaminases, liver fat as observed in a magnetic resonance imaging (MRI) study, and hepatomegaly. LDL-C and triglycerides were significantly reduced, and HDL-C increased. Only a few, mild adverse reactions were reported in this study (*Figure 1. B*).

In a phase 2/3 clinical trial with sebelipase alfa in children with the early onset subtype, 5 out of 9 patients survived beyond 2 years old, and 1, beyond 5 years old. Liver disease markers, gastrointestinal symptoms, and nutritional status improved.[50]

Although no long-term follow-up has been completed for this treatment, given the mechanism of action of sebelipase, it may have a potential effect on the reduction of liver fibrosis and its progression to cirrhosis, as well as on the improvement of dyslipidemia and the prevention of cardiovascular complications.[51] ■

TABLE 3. *High-risk populations that should be considered in the screening for lysosomal acid lipase deficiency*

Modified from Burton B, *JPGN* 2015;61:619-625.[8]

Non obese patients with the following:
- Persistent hepatomegaly
- Elevated transaminases without a definite cause
- High levels of LDL (> 130 mg/dL, 4.1 mmol/L)
- Low levels of HDL (males: < 40 mg/dL; females: < 50 mg/dL)

Obese patients diagnosed with metabolic syndrome and the following:
- Persistent hepatomegaly
- No hyperglycemia
- Elevated transaminases without a definite cause that do not improve with a reduction in BMI

Obese patients who manage to reduce their BMI but whose lipid profile does not improve
Patients with microvesicular steatosis

HDL: high-density lipoproteins; LDL: low-density lipoproteins; BMI: body mass index.

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