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Consensus statement

Update on lysosomal acid lipase deficiency: Diagnosis, treatment and patient management☆

Carmen Camarena[a], Luis J. Aldamiz-Echevarria[b,c,d], Begoña Polo[e], Miguel A. Barba Romero[f], Inmaculada García[g], Jorge J. Cebolla[h,c], Emilio Ros[i,j,*]

[a] Servicio de Hepatología Infantil, Hospital La Paz, Madrid, Spain
[b] Unidad de Enfermedades Metabólicas Pediátricas, Hospital Universitario Cruces, Bilbao, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[d] CSUR de Enfermedades Metabólicas Congénitas, Ministerio de Sanidad, Madrid, Spain
[e] Servicio de Gastroenterología y Hepatología Pediátrica, Hospital La Fe, Valencia, Spain
[f] Servicio de Medicina Interna, Complejo Hospitalario y Universitario de Albacete, Universidad de Castilla-La Mancha, Albacete, Spain
[g] Unidad de Enfermedades Metabólicas Pediátricas, Hospital Miguel Servet, Zaragoza, Spain
[h] Instituto de Investigación Sanitaria Aragón, Unidad de Investigación Traslacional, Hospital Universitario Miguel Servet, Zaragoza, Spain
[i] Unidad de Lípidos, Servicio de Endocrinología y Nutrición, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain
[j] Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

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ABSTRACT

Lysosomal acid lipase deficiency (LALD) is an ultra-rare disease caused by a congenital disorder of the lipid metabolism, characterized by the deposition of cholesterol esters and triglycerides in the organism. In patients with no enzyme function, the disease develops during the perinatal period and is invariably associated with death during the first year of life. In all other cases, the phenotype is heterogeneous, although most patients develop chronic liver diseases and may also develop an early cardiovascular disease. Treatment for LALD has classically included the use of supportive measures that do not prevent the progression of the disease. In 2015, regulatory agencies approved the use of a human recombinant LAL for the treatment of LALD. This long-term enzyme replacement therapy has been associated with significant improvements in the hepatic and lipid profiles of patients with LALD, increasing survival rates in infants with a rapidly progressive disease. Both the severity of LALD and the availability of a specific treatment highlight the need to identify these patients in clinical settings, although its low prevalence and the existing clinical overlap with other more frequent pathologies limit its diagnosis. In this paper we set out practical recommendations to identify and monitor patients with LALD, including a diagnostic algorithm, along with an updated treatment.

Actualización en deficiencia de lipasa ácida lisosomal: diagnóstico, tratamiento y seguimiento de los pacientes

Palabras clave:
Deficiencia de lipasa ácida lisosomal
Enfermedad de Wolman
Enfermedad por almacenamiento de ésteres de colesterol
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Diagnóstico

RESUMEN

La deficiencia de lipasa ácida lisosomal (DLAL) es una enfermedad ultrarrara causada por un error congénito del metabolismo lipídico, que se caracteriza por el depósito de ésteres de colesterol y triglicéridos en el organismo. En pacientes con nula función enzimática la enfermedad se inicia en el período perinatal y es inevitablemente mortal durante el primer año de vida. En el resto de los casos el fenotipo es heterogéneo, aunque la mayoría de los pacientes desarrollan hepatopatía crónica y pueden presentar enfermedad cardiovascular prematura. Clásicamente, el tratamiento de la DLAL ha consistido en el uso

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* Corresponding author.
E-mail address: eros@clinic.ub.es (E. Ros).

de medidas de soporte, que no evitan su progresión. En 2015, las agencias reguladoras aprobaron el uso de una LAL recombinante humana para el tratamiento de la DLAL. Dicho tratamiento de sustitución enzimática a largo plazo se ha asociado con mejorías significativas de los parámetros lipídicos y hepáticos, incrementándose la supervivencia en lactantes con enfermedad rápidamente progresiva. La gravedad de la enfermedad, junto con la reciente disponibilidad de un tratamiento específico, hace especialmente relevante la necesidad de identificar a estos pacientes en la práctica clínica, aunque la baja prevalencia de la DLAL y el solapamiento clínico con otras enfermedades más frecuentes dificulta su reconocimiento. Con base en la evidencia científica publicada y la experiencia clínica e investigacional de los autores, el presente documento incluye recomendaciones prácticas para la identificación y la monitorización de los pacientes con DLAL, incluyendo un algoritmo diagnóstico, junto con una actualización de su tratamiento.

Introduction

Lysosomal acid lipase deficiency (LALD, MIM #278000) is an ultra-rare disease, due to a congenital error in lipid metabolism at lysosomal level, characterized by the deposition of cholesteryl ester (CE) and triglycerides (TG) in different tissues (liver, spleen, intestine, adrenal glands and mononuclear phagocyte system cells).[1] The disease originates due to a decreased or absent activity of the lysosomal acid lipase enzyme (LAL, EC 3.1.13; catalyst of CE and TG hydrolysis in fatty acids [FA] and free cholesterol) caused by mutations in the *LIPA* gene (MIM *613497). This lack of activity leads to the progressive accumulation of intralysosomal CE and TG, leading to the development of progressive liver disease and dyslipidaemia associated with accelerated atherosclerosis, the main manifestations of the disease.[2] LALD comes with 2 main phenotypes, historically known as Wolman disease in infants and CE storage disease in children and adults.[3] This denomination is currently falling into disuse, with LALD being understood as a single disease entity that may present with various clinical manifestations, which can have an early onset and a rapid progression or have a delayed onset and a variable progression.

In 2015, regulatory agencies in US and Europe approved the marketing of sebelipase alfa (Kanuma®; Alexion Pharmaceuticals, Connecticut, United States),[4,5] the first drug approved for the treatment of LALD. Sebelipase alfa is a recombinant human LAL which replaces the absence of endogenous enzyme activity. The availability of this new therapy represents a paradigm shift in the treatment of LALD.

In order to develop updated guidelines for the diagnosis and monitoring of patients with LALD, a conference was held in Barcelona on 27 and 28 November 2015. Based on published scientific evidence and the attendees' clinical and research experience, various aspects of interest were addressed in connection with LALD. So, prior to the conference, articles published on disease pathophysiology, epidemiology, clinical diagnosis and differential diagnosis, treatment, prognosis and monitoring of patients affected by LALD were identified through a literature search in Medline and Embase. The articles that were finally included in the review were selected from among all the results obtained, according to expert judgment. During the meeting, all the selected evidence was presented and discussed for each of the areas mentioned. Also, recommendations for the diagnosis of LALD, in the form of algorithms, and patient follow-up were agreed upon, with the support of an external moderator. This article summarizes the main conclusions of the meeting, primarily constituting a practical value document with considerations for the identification and monitoring of patients with LALD in daily practice, along with an update on the available evidence regarding treatment. For a detailed understanding of the molecular, pathophysiological and clinical aspects of the disease, consultation of 2 recent comprehensive reviews are recommended.[1,2]

Lysosomal acid lipase deficiency: clinical entity

Pathophysiology

Cellular uptake of *low density lipoproteins cholesterol* (LDL-C) is carried out mainly through its corresponding membrane receptor (LDLR). LDL cholesterol is transported to lysosomes, where the CE and TG are hydrolysed by the LAL, releasing cholesterol and free FA involved in the regulation of several lipoproteins' metabolism (such as *high density lipoproteins* [HDL] and *very low density lipoproteins* [VLDL]).[1] In patients with LALD, decreased or absent LAL activity causes CE and TG accumulation in the lysosomes of various tissues. The reduced availability of free cholesterol in cytosol modulates compensatory molecular mechanisms, the most significant being the upregulation of LDLR and the enzyme hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase expression, which leads to an increased synthesis of endogenous cholesterol (Fig. 1). Additionally, it increases the synthesis of apolipoprotein B (ApoB100) to facilitate the export of intrahepatic cholesterol through VLDL and reduces the synthesis of ABCA1 transporter, responsible for HDL particles exocytosis, leading to its decrease in plasma. The increased secretion of VLDL and its subsequent transformation into plasma LDL explains the hypercholesterolemia, characteristic of the disease. The progressive accumulation of substrates continues to exacerbate the disease due to the absence of inactivation of the mentioned compensatory mechanisms.[1,6]

LALD is an autosomal recessive metabolic disease caused by mutations in the LIPA gene located on the long arm of chromosome 10 (10q23.2-q23.3),[7,8] which result in a very variable clinical expression of the disease depending on the residual enzyme activity. More than 59 mutations have been identified according to the *Human Gene Mutation Database* (Institute of Medical Genetics at the University of Cardiff, www.hgmd.cf.ac.uk), with c.894G>A (p.delS275_Q298) being the most prevalent mutation, located in the canonical sequence for the splicing of pre-mRNA in the region exon 8-intron 8 (E8SJM, of *exon 8 splice junction mutation*) present in ~60% of patients with LALD of European origin. The most common genetic disorders in infants are missense mutations and reading frame alterations, which lead to practically no LAL activity, while those detected in children and adults tend to have a less severe impact on the functionality of the enzyme[9]; however, the genotype–phenotype correlation is not fully elucidated.