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Original Contribution

Childhood/adult-onset lysosomal acid lipase deficiency: A serious metabolic and vascular phenotype beyond liver disease—four new pediatric cases

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BACKGROUND: The childhood/adult-onset lysosomal acid lipase deficiency (LALD; late-onset LALD) is a rare genetic disease. Children present severe fatty liver disease with early cirrhosis. Before enzyme replacement therapy, statins were the standard treatment to improve the severe dyslipidemia. However, late-onset LALD should be considered as a systemic metabolic disease: chronic hyper-low-density lipoprotein and hypo-high-density lipoprotein cholesterolemia induces early atherosclerosis in addition to the liver morbidity.

OBJECTIVE: To assess 4 new pediatric cases of late-onset LALD with an evaluation of hepatic, metabolic, and vascular evolution under statin.

METHODS: Four patients were retrospectively described. Anthropometric data (weight, height, and body mass index) and laboratory data (*LIPA* mutations, acid lipase residual activity, liver and lipid profile, and homeostatic model assessment index) were collected. Liver histology was assessed by the noninvasive tests FibroScan and FibroTest and confirmed by liver biopsy. Vascular impact was followed up by carotid intima-media thickness (cIMT) assessment.

RESULTS: The 4 cases of late-onset LALD came from 2 families, each with a boy (aged 8.6 and 11 years at diagnosis) and a girl (aged 10.6 and 13 years at diagnosis). Treatment with statins was

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performed for 8 and 5 years, respectively, from diagnosis. Statins decreased the low-density lipoprotein cholesterol mean value of 40%. All children showed significant liver fibrosis (F3 [n = 3]; F2 [n = 1]). cIMT showed the following for all children: abnormal measures without improvement and atherosclerotic plaques. One child developed a deleterious metabolic phenotype with obesity and insulin resistance (homeostatic model assessment = 3.08) associated with higher mean hepatic transaminases (149 vs 98, 88, and 61 IU/L) and increased mean cIMT values (raising from 0.47 to 0.5 mm vs 0.43 and 0.43 mm).

CONCLUSION: Late-onset LALD is a rare metabolic disease with a larger impact than liver disease. Our work shows the importance of having a global metabolic view and to evaluate the cardiovascular impact of the new enzymatic treatment.

Introduction

Lysosomal acid lipase deficiency (LALD) is a rare autosomal recessive disease due to *LIPA* mutations.[1,2] LIPA is an essential protein needed to hydrolyze cholesteryl ester (CE) and triglycerides (TGs) in the lysosome. These breakdown products, including free fatty acids and cholesterol, can then be released into the cytoplasm. LIPA deficiency results in CE and TG accumulation. This has been shown to occur in the lysosomes of hepatocytes (where it causes microvesicular steatosis), adrenal glands, intestinal mucosa, and macrophages. Moreover, the cytosolic deprivation in nonesterified cholesterol and free fatty acid leads to an upregulation of peroxisome proliferator–activated receptor γ and sterol regulatory element binding protein pathways. It results in a severe dyslipidemia with increased very low–density lipoprotein synthesis, increased plasmatic LDL cholesterol (LDLc), and decreased plasmatic HDL cholesterol (HDLc) leading to an early cardiovascular (CV) risk.[3]

The clinical presentation of LALD may involve 2 major phenotypes. First, infantile-onset lysosomal acid lipase deficiency (LALD), with 1% or less than 1% of residual LAL activity: the disease occurs neonatally with hepatosplenomegaly, adrenal calcification, severe malabsorption, vomiting, and malnutrition. It generally leads to death by liver failure before 1 year of age.[4] Second, childhood/adult-onset LALD (formerly cholesterol ester storage disease), with 1% to approximatively 12% of residual LAL activity: patients exhibit elevated serum LDLc, low HDLc levels, and progressive liver steatosis. Its evolution is marked by fibrotic microvesicular nonalcoholic fatty liver disease (NAFLD), with an early risk of cirrhosis.[5,6]

The historical treatment of late-onset LALD used 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) inhibitors. Statins were effective in treating dyslipidemia but failed to stop the development of hepatic fibrosis/cirrhosis.[5,7,8] More recently, replacement enzyme therapy with sebelipase alpha has been shown to improve hepatic cytolysis, liver fat content, and plasmatic dyslipidemia.[9,10]

Fibrotic steatosis progression is the major prognostic factor; consequently, literature on vascular and metabolic complications in these children is weak. The metabolic profile of these children needs a more global follow-up, including metabolic assessments and vascular imaging. The "multiple hit" theory of nonalcoholic steatohepatitis (NASH) clearly involves insulin resistance in liver injuries.[11] Because NASH shares several pathogenesis features with late-onset LALD liver injuries, it seems reasonable to hypothesize that insulin resistance may worsened the hepatic and vascular lesions. Although several studies found a correlation between CV risks and LAL activity polymorphism.[3,12] However, the atheromatous process potentially induced by the chronic dyslipidemia of late-onset LALD has never been investigated in children. Determination of arterial intima-media thickness, an early surrogate of atheromatous process, may identify pediatric patient with early CV risk.[13]

The aim of this work was to describe extensively the progression of hepatic, metabolic, and vascular factors in 4 new pediatric cases of late-onset LALD in addition to the 135 cases already published.[5]

Materials and methods

We report 4 new cases of children with late-onset LALD: 2 girls and 2 boys (1∼1M; 1∼2F; 2∼1M; 2∼2F), born from 2 different nonconsanguineous families. One family was monitored for 8 years and the other for 5 years. The parents' consent and the agreement of the local ethic committee were obtained for collection of data.

Diagnosis of late-onset LALD

For all the children, the residual LAL enzyme activity was measured via dried blood spot testing using 4-methylumbelliferyl palmitate as a substrate of LAL. The LAL enzyme activity was measured in the presence and absence of a specific inhibitor, as previously described.[14] For diagnostic confirmation, *LIPA* exons and their flanking regions were amplified by PCR and then bidirectionally sequenced using the Sanger method.[15] Amino acid sequence changes are described according to the National Center for Biotechnology Information reference sequence using NM_000235.3.