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Journal

Journal of pediatric gastroenterology and nutrition, 71(6)

ISSN

0277-2116

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Publication Date

2020-12-01

DOI

10.1097/mpg.0000000000002870

Peer reviewed

Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2020 December ; 71(6): 726–730. doi:10.1097/MPG.0000000000002870.

A Case of Lysosomal Acid Lipase Deficiency Confirmed by Response to Sebelipase Alfa Therapy

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Abstract

Lysosomal acid lipase (LAL) deficiency, or cholesterol ester storage disease, is a disorder affecting the breakdown of cholesterol esters and triglycerides within lysosomes. Clinical findings include hepatomegaly, hepatic dysfunction, and dyslipidemia, with a wide range of phenotypic variability and age of onset (1-3). The available clinical and molecular information of the patient presented herein was consistent with a diagnosis of LAL deficiency, but her LAL activity assay repeatedly showed normal or borderline low results. Her response to enzyme replacement therapy (4,5) and demonstrable deficiency on a newer specific enzymatic assay (6) ultimately confirmed her diagnosis of LAL deficiency.

Keywords

cholesterol ester storage disease; lysosomal acid lipase deficiency; LIPA gene; pathogenic variant; sebelipase alfa; variant of uncertain significance

CASE PRESENTATION

Patient was first seen in the genetics clinic at 14 months of age for hepatomegaly. Her growth parameters were age-appropriate and she was otherwise healthy. A comprehensive work-up was notable for elevated liver transaminases (AST 179 U/L, normal 3-69 U/L; ALT 145 U/L, normal 5-30 U/L) and fasting lipid panel showed elevations of total cholesterol (240 mg/dL, normal 125-170 mg/dL), triglycerides (297 mg/dL, normal 33-115 mg/dL), and LDL cholesterol (171 mg/dL, normal <110 mg/dL), with HDL cholesterol 10 mg/dL. Her

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The authors report no conflicts of interest.

adrenal function on ACTH stimulation testing was normal (data not shown). Liver biopsy performed at 29 months of age showed cirrhosis with severe small droplet and microvesicular steatosis, and numerous giant cell aggregates with cholesterol clefts (Fig. 1A). At 40 months of age her AST was 100 U/L, ALT 47 U/L, total cholesterol 261 mg/dL, triglycerides 282 mg/dL, LDL cholesterol 196 mg/dL, and HDL cholesterol 9 mg/dL.

Sequencing of *LIPA* revealed compound heterozygous variants in *trans*, with one variant (c.260G>T; p.Gly87Val) previously reported as being pathogenic, while the other variant (c.853C>T; p.Pro285Ser) was classified as a variant of uncertain significance. Clinical whole exome sequencing did not uncover any additional phenotypically relevant variants.

LAL deficiency was strongly considered because of the combined clinical, pathological, and molecular information. However, on repeated analyses the diagnostic Lalistat2 *in vitro* assay was normal or borderline low (Table 1).

Sebelipase alfa infusions were started at 41 months of age (compassionate use protocol, Alexion Pharmaceuticals, New Haven, CT). There has been improvement of her abnormal liver and lipid serum values (Fig. 2A and B). Liver volumes were calculated from hand traced areas of coronal MRI images spanning the liver, and demonstrated reduction of her hepatomegaly (Fig. 2C). Another liver biopsy was performed at 67 months of age after 26 months of therapy. Pathological studies dedicated to disorders of lipid metabolism (1,8) were consistent with the diagnosis of LAL deficiency (Fig. 1B-F), and there was subjective improvement in the degree of steatosis. LAL activity in dried blood spots assayed through a non-inhibitor-based *in vitro* assay utilizing a specific substrate (P-PHMC) (6) measured at 22.6 μM/hr (normal 85.3–624.7 μM/hr, affected 0.8-22.2 μM/hr).

DISCUSSION

Lysosomal acid lipase breaks down cholesterol esters and triglycerides into cholesterol and free fatty acids as part of the lipoprotein and cholesterol utilization pathways. Deficiency of LAL leads to dyslipidemia and elevated transaminases with a wide spectrum of clinical severity and age of onset, ranging from a mostly asymptomatic adult form with early atherosclerosis and liver disease, to an early onset form (classically referred to as Wolman disease) exhibiting additional manifestations of failure to thrive, adrenal insufficiency, and steatorrhea, with death in infancy (1-3). The recent availability of sebelipase alfa enzyme replacement therapy improves the hepatic dysfunction and dyslipidemia of affected individuals, and prolongs survival in severe cases (4,5).

The patient in this case report presented with hepatomegaly in infancy, but otherwise was asymptomatic. Liver biopsy showed severe small droplet and microvesicular steatosis, molecular genetic testing revealed *LIPA* variants *in trans* (although only one was known to be pathogenic), and the persistently elevated transaminases and dyslipidemia all pointed to LAL deficiency as her diagnosis.

The “gold standard” of confirming LAL deficiency involves the quantification of lipase activity in the presence and absence of a LAL-specific inhibitor, Lalistat2. All known cases of LAL deficiency demonstrate reduced activity by this assay (personal communication,

Alexion Pharmaceuticals). However, on repeated measurements, this patient's leukocytes indicated normal or borderline low activity levels; this was not tissue-specific as analyses of fibroblasts and hepatocytes showed similar results (data not shown).

The diagnosis of LAL deficiency ultimately was confirmed in this patient through several means. More than 2 years of sebelipase alfa enzyme replacement therapy led to normalization of her liver transaminases, improvement of her dyslipidemia (decrease of ~16% in total cholesterol, ~56% in triglycerides, and ~9% in LDL cholesterol), and reduction of her hepatomegaly as measured through serial volumetric MRIs (decrease of ~16%). Lipid pathological studies performed on a repeat liver biopsy was consistent with LAL deficiency, and showed improvement in steatosis when compared to the liver biopsy obtained prior to the initiation of therapy. Clear enzymatic deficiency (7% of controls).was demonstrated with a newer LAL activity assay using a specific substrate (P-PHMC) (6).

This case report illustrates the importance of clinical suspicion in the diagnostic odyssey. In contrast to the typical situation in which arriving at a diagnosis leads to the initiation of treatment, the sequence for this patient was reversed – she was started on enzyme replacement therapy and it was her positive response that confirmed her diagnosis of LAL deficiency. Additionally, disease confirmation provided evidence that her *LIPA* variant classified as of uncertain significance is indeed pathogenic.

Many diagnoses can be confirmed through enzymatic assays, but this methodology is not infallible because they are performed under *in vitro* conditions and utilize artificial substrates. With wider implementation of next generation sequencing, diagnoses also can be made quickly through molecular techniques, but only if variants known to be pathogenic are identified. As more therapies are being developed for various diseases, it is particularly important to confirm a diagnosis when treatment options can be initiated. The lessons learned from this case report increases our ability to diagnose those affected by LAL deficiency, allowing us to capture additional cases of this rare and underdiagnosed condition, and offer more patients therapy to improve their medical care.

Acknowledgments:

We thank the family for their participation. Informed consent was obtained for publication.

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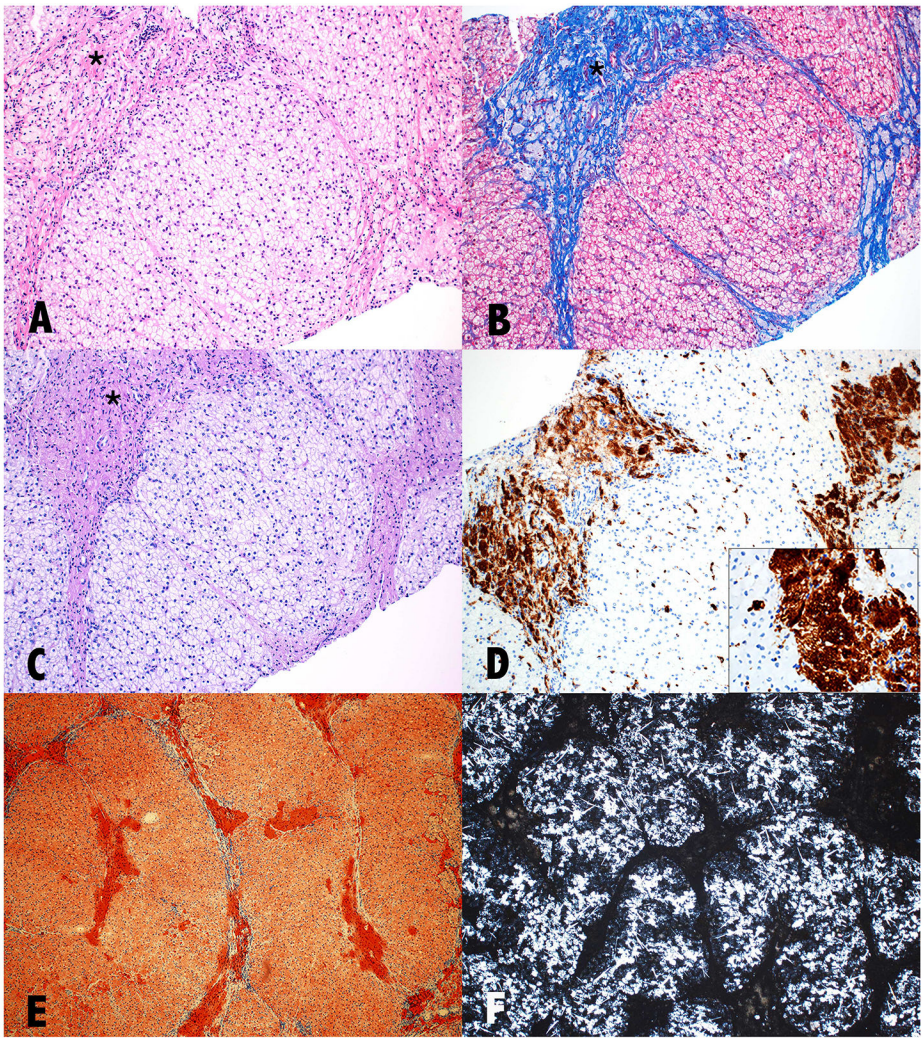
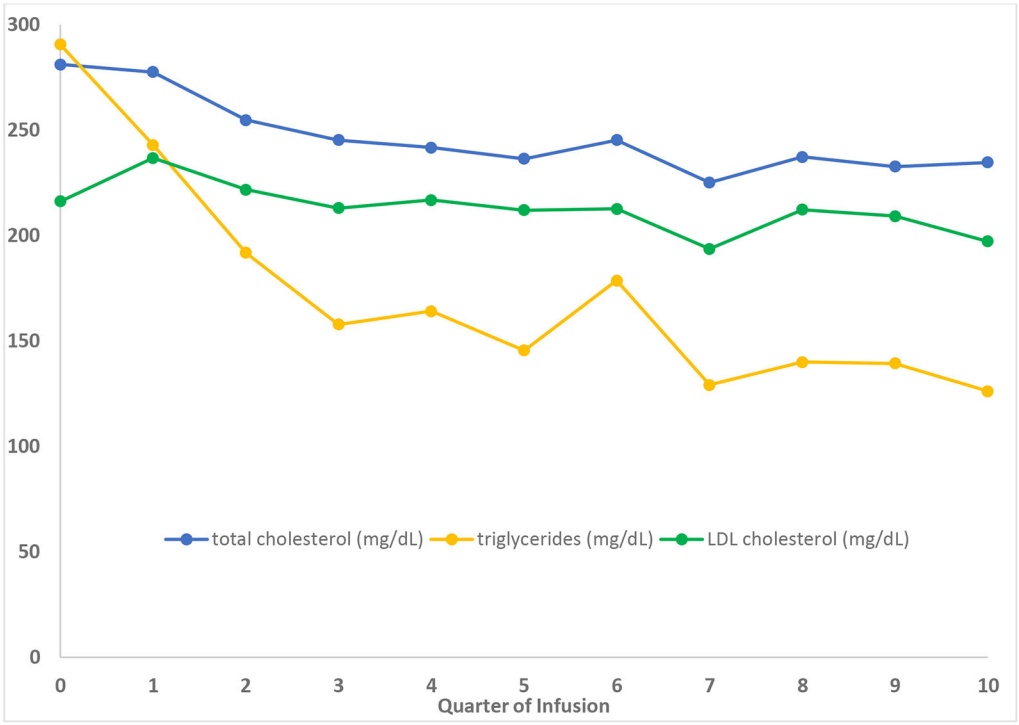
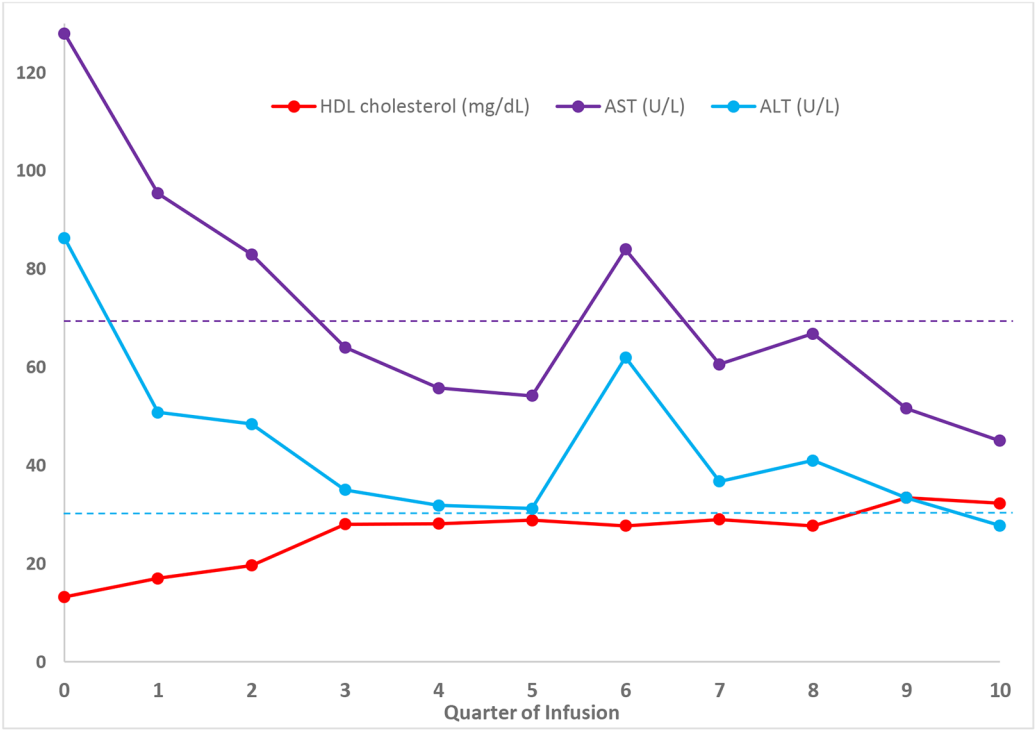


FIGURE 1.

Liver needle core biopsy with cirrhosis and severe microvesicular steatosis from 2014 (A) and 2017 (B-F). Most notable within the portal tracts, but also within the lobules are prominent xanthomatous macrophages (*). (A) H& 200x. (B) H& 100x. (C) Trichrome stain highlights fibrosis/cirrhosis; 100x. (D) CD68, immunohistochemical stain for macrophages, highlights macrophages within the portal tracts; inset shows empty spaces/clefts within the cytoplasm of macrophages consistent with crystal remnants (crystals dissolve in processing); 100x. (E) Oil red O stain on alcohol fixed slide shows strong staining in the portal macrophages and sinusoidal macrophages/Kupffer cells, consistent with ceroid/fat accumulation within macrophages; the hepatocytes also show fat accumulation with Oil red O stain, consistent with diffuse steatosis; 40x. (F) On frozen section slide under polarized light, abundant polarized crystals are seen, including within the hepatocytes and in the Kupffer cells and portal macrophages; the majority of the crystals have silver birefringence, a smaller subset have yellow-blue birefringence; the majority of the crystals are morphologically consistent with cholesterol crystals; 40x.





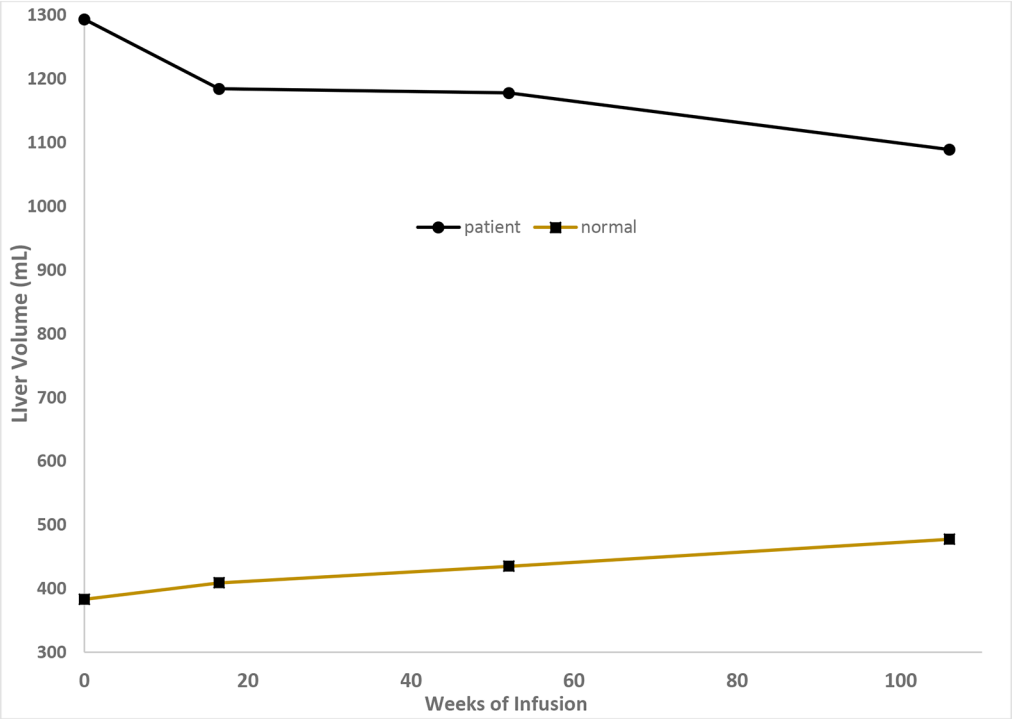


FIGURE 2.

Graph of serum values averaged per quarter for the first two and a half years of sebelipase alfa infusions for total cholesterol, triglycerides and LDL cholesterol (A), and HDL cholesterol, AST and ALT (B). The dotted lines represent the upper limits of normal for AST and ALT. (C) Graph of patient liver volumes measured by serial volumetric MRIs at 0, 16, 52, and 106 weeks of therapy. Normal volumes were calculated using the formula from Johnson et al (7).

TABLE 1.

Lysosomal acid lipase activity on dried blood spots and leukocytes (Lalistat2 inhibitor assay)

Assayed Value	Normal Range	Affected Range	Performing Laboratory
27 pmol/hr/spot	40 – 600	not provided	*a*
0.23 nmol/punch/hour	0.37 – 2.30	<0.15	*b*
120 pmol/hr/spot	40 – 600	not provided	*a*
105.6 nmol/hr/mg protein	116.4 – 695.6	17.3 ± 7.8	*c*
48 pmol/min/mg protein	25 – 70	6 (affected control)	*d*

a – Seattle Children's

b – South Glascow

c – Mt. Sinai

d – Baylor Miraca