

LYSOSOMAL ACID LIPASE DEFICIENCY (LAL-D)

LAL-D OVERVIEW

Lysosomal acid lipase deficiency (LAL-D) is a genetic, chronic, and progressive ultra-rare metabolic disease in which infants, children, and adults experience continuous, uncontrolled accumulation of cholesteryl esters (CEs) and triglycerides (TGs) that may lead to multiorgan damage and premature death.¹ Infants diagnosed with LAL-D experience early and severe symptom onset at a median age of 1.1 months (range: 0.0 to 3.0 months).² In pediatric and adult patients, the median age of onset is 5.8 years (range: 0-42 years of age)³, with 89% of LAL-D patients presenting at 12 years of age or younger.¹

CAUSES

LAL-D, historically known as Wolman disease and cholesteryl ester storage disease (CESD), is caused by genetic mutations that result in a marked decrease or loss in lysosomal acid lipase (LAL) enzyme activity.¹ The LAL enzyme is responsible for the breakdown of lipid particles (CEs and TGs). In patients with LAL-D, however, deficient LAL enzyme activity can lead to the continuous build-up of fatty material in the liver, blood vessel walls and other tissue, potentially resulting in progressive, multi-organ damage, including fibrosis, cirrhosis, liver failure, accelerated atherosclerosis, cardiovascular disease, and other devastating consequences.^{1,4}

MORTALITY AND MORBIDITY

LAL-D is a serious, life-threatening disease often associated with premature mortality and significant morbidity.¹ In infants, LAL-D is a rapidly progressive and imminently fatal disease characterized by profound malabsorption, growth failure, liver fibrosis, cirrhosis, and liver failure.^{2,3} The median age of death in infants with LAL-D is 3.7 months, and nearly 90% of infants with LAL-D will die within 1 year of birth.² In an observational study, nearly 50% of pediatric and adult patients with LAL-D with a clinical biopsy assessment progressed to fibrosis, cirrhosis, or liver transplant within 3 years after first clinical manifestation.⁵ In addition, published literature on 135 LAL-D cases showed that 51% progressed to fibrosis, cirrhosis, or death.^{1,5}

SYSTEMIC MANIFESTATIONS

LAL-D threatens multiple vital organ systems, including the liver, heart, spleen and gastrointestinal tract.¹ In fact, 87% of patients with LAL-D experience disease manifestations in more than one organ system.¹⁺

Liver

Liver manifestations are among the most common and prevalent clinical symptoms of LAL-D, affecting approximately 86% of patients.¹⁺ An observational study of pediatric and adult patients with LAL-D found that death due to liver failure occurred in patients as young as 7 years of age, with 50% of the reported liver-related deaths occurring in patients younger than 21 years of age.¹

Liver manifestations of LAL-D may include:

- Elevated ALT⁴
- Enlarged liver^{1,4}
- Fibrosis and/or cirrhosis⁴
- Liver dysfunction or failure⁴
- Abnormal, enlarged veins in the lower part of the esophagus^{1,3}

Cardiovascular

Overall, 87% of patients with LAL-D experience cardiovascular manifestations.¹⁺ Elevations in total cholesterol, triglycerides and low-density lipoprotein cholesterol (LDL-c), as well as decreased levels of high density lipoprotein cholesterol (HDL-c), are common in patients with LAL-D.^{4,6} Lipid abnormalities and the associated risk of accelerated atherosclerosis—the premature buildup of fats, cholesterol, and other substances in and on the artery walls—may contribute to premature mortality and morbidity in the broader LAL-D population.⁴

Other cardiovascular manifestations of LAL-D may include coronary artery disease, heart attack, and stroke.¹

Spleen

Spleen manifestations occur in 36% of patients with LAL-D, including splenomegaly (enlarged spleen), hypersplenism (overactive spleen), anemia, and thrombocytopenia.^{1,7,8+} Severe spleen damage may require removal of the spleen.⁹

Gastrointestinal

Gastrointestinal manifestations of LAL-D, caused by the accumulation of lipid substrates in the intestines, occur in 22% of patients.¹⁺ In infants, vomiting, diarrhea, malabsorption, and growth failure are the first signs of LAL-D.¹ Other gastrointestinal manifestations of LAL-D may include abdominal and epigastric pain, gallbladder dysfunction, and fluid in the abdominal cavity.^{1,4}

DIAGNOSIS AND MANAGEMENT

Misdiagnosis is common among patients with LAL-D, leaving them at an increased risk for severe, unpredictable complications.^{1,4} LAL-D can be diagnosed with an enzymatic blood test.^{4,10}

Historical supportive care, including the use of statin therapy, liver transplants, and hematopoietic stem cell transplantation (HSCT), is reported to be generally ineffective in halting disease progression in patients with LAL-D.^{1,4} No well-controlled studies have proven these approaches to be safe or effective in treating patients with LAL-D.^{1,4}

For more information on LAL-D, visit LALDSource.com.

References

1. Bernstein DL, et al. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol.* 2013;58:1230-43. doi:10.1016/j.jhep.2013.02.014.
2. Jones SA, Valayannopoulos V, Schneider E, et al. Rapid progression and mortality of lysosomal acid lipase deficiency presenting in infants. *Genet Med.* 2016;18:452-458. doi: 10.1038/gim.2015.108.
3. Burton et al. Clinical Features of Lysosomal Acid Lipase Deficiency - a Longitudinal Assessment of 48 Children and Adults. *Journal of Pediatric Gastroenterology & Nutrition* (2015). doi: 10.1097/MPG.0000000000000935
4. Reiner Z, et al. Lysosomal acid lipase deficiency - an under-recognized cause of dyslipidemia and liver dysfunction. *Atherosclerosis.* 2014;235:21-30. doi:10.1016/j.atherosclerosis.2014.04.003.
5. Data on file, Alexion Pharmaceuticals.
6. Grabowski G. Lysosomal acid lipase deficiencies: the Wolman disease/cholesteryl ester storage disease spectrum [online]. In: Valle D, Beaudet AL, Vogelstein B, et al. *The Online Metabolic and Molecular Bases of Inherited Disease.* New York, NY: McGraw Hill; 2012.
7. Ferry GD, et al. Liver transplantation for cholesteryl ester storage disease. *J Pediatr Gastroenterol Nutr.* 1991;12:376-8.
8. Rockey DC, et al. Liver biopsy. *Hepatology.* 2009;49:1017-44. doi:10.1002/hep.22742.
9. Guzzetta PC et al. Elective subtotal splenectomy. Indications and results in 33 patients. *Ann of Surgery.* 1990;211(1):34-42.
10. Hamilton J, et al. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. *Clin Chim Acta.* 2012;413:1207-10. doi:10.1016/j.cca.2012.03.019.

* Based on modeling, using a subset of 31 patients (≥5 years of age) in an observational study who received a liver biopsy, and 1 additional patient with no biopsy who received a liver transplant. Patients selected by their clinician for liver biopsy are expected to have more evidence of disease progression than patients with LAL-D overall.

+ Based upon an analysis of 55 genotyped patients with LAL-D in a cohort of 135 cases.