

The Physician's Guide to **Lipoprotein Lipase Deficiency (LPLD)**

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Introduction

Welcome to the **NORD Physician Guide to Lipoprotein Lipase Deficiency (LPLD)**. The NORD Online Physician Guides are written for physicians by physicians with expertise on specific rare disorders. This guide was reviewed by John JP Kastelein, MD, PhD, Department of Vascular Medicine, Academic Medical Center, University of Amsterdam.

NORD is a nonprofit organization representing all patients and families affected by rare diseases. The information NORD provides to medical professionals is intended to facilitate timely diagnosis and treatment for patients.

LPLD is an inherited disorder of triglyceride metabolism characterized by pronounced accumulation of chylomicrons and triglycerides in the plasma, severe abdominal pain, hepatosplenomegaly, and eruptive xanthomas.

What Is Lipoprotein Lipase Deficiency (LPLD)?

Lipoprotein lipase deficiency (LPLD) is a rare monogenic disorder of triglyceride metabolism. Deficiency of the enzyme lipoprotein lipase results in pronounced accumulation of triglycerides in the plasma. Specifically, the clearance of chylomicrons is impaired. Chylomicrons, fatty droplets that transport fat in the form of triglyceride, appear in the bloodstream shortly after the ingestion of dietary fat. Chylomicrons are normally cleared from the body after a period of fasting. Lipoprotein lipase recognizes a protein in chylomicrons called apolipoprotein C2, and is then activated to metabolize and clear out triglycerides. However, deficiency or lack of lipoprotein lipase results in the accumulation of chylomicrons and triglycerides in the body. High triglyceride levels are present from infancy and childhood, and various associated symptoms may occur. Some patients remain undiagnosed until

adulthood. LPLD is caused by mutations in the LPL gene and is inherited in an autosomal recessive manner.

LPLD is estimated to occur in 1-2 people per 1,000,000 in the general population. The disorder has been described in individuals of all races and affects both males and females. The prevalence is much higher in certain populations including Quebec, Canada due to a founder effect. In the past, LPLD has also been called hyperlipoproteinemia type I.

Several rare genetic disorders can be associated with chylomicronemia including familial apolipoprotein C-II, familial apoAV deficiency, and familial lipase maturation factor 1 (LMF1) deficiency. Apolipoprotein C-II is a cofactor required for lipoprotein lipase to function. Consequently, apolipoprotein C-II deficiency is extremely similar to LPLD, although the age of onset is later (13-60 years). Additionally, patients tend to develop chronic pancreatic insufficiency, steatorrhea, and insulin-dependent diabetes. Apolipoprotein C-II is caused by mutations in a different gene, the APOC2 gene.

Symptoms and Signs

LPLD can present during infancy or childhood with episodes of severe abdominal pain. Most cases are diagnosed by the age of 10, but some cases may not present or may remain unrecognized until adulthood.

Abdominal pain is episodic in nature and can range in degree from mild to severe to incapacitating. Pain is usually felt in the mid-epigastric region and may radiate to the back. Pain may become diffuse and can be mistaken for peritonitis, potentially resulting in unnecessary exploratory surgery.

Abdominal pain can also result from recurrent episodes of pancreatitis. Pain associated with pancreatitis is most often felt in the upper left side or middle of the abdomen and can be intense. Pancreatitis can also cause nausea, sweating, weakness, chills, clammy skin, and mild jaundice. Chronic pancreatitis can be associated with additional complications including diabetes, steatorrhea, and pancreatic calcification. Such complications are rare in LPLD patients and are not usually seen before middle age. Although uncommon, some patients can develop total pancreatic necrosis, a potentially fatal complication.

On physical examination, additional symptoms can be detected including hepatosplenomegaly, eruptive xanthomas, and an eye condition called lipemia retinalis. The degree of liver and spleen enlargement can vary depending upon several factors such as the amount of dietary fat.

Xanthomas usually appear as small, yellow papules most often located on the trunk, buttocks, knees and extensor surfaces of the arms. These papules are lipid deposits and can appear rapidly once plasma triglyceride levels exceed 2000 mg/dL. Individual lesions may measure approximately 1 millimeter, but xanthomas often cluster and coalesce to form larger lesions. Xanthomas are usually not painful or tender, unless they develop on an area of the body prone to repeated trauma or abrasion.

Lipemia retinalis can develop when triglyceride levels exceed 4000 mg/dL. Large chylomicrons accumulate in the retinal arterioles, venules, and sometimes the fundus, causing incoming light to scatter and giving the eye a pale, pink color. This condition is reversible with treatment and vision is not affected.

Patients have been reported who exhibit various reversible neuropsychiatric findings including depression, memory loss, and dementia.

LPLD is generally not associated with an increased risk of atherosclerotic vascular disease.

Causes

LPLD is caused by loss-of-function mutations in the LPL gene located on human chromosome 8. The disorder is inherited in an autosomal recessive manner. The LPL gene encodes for the enzyme, lipoprotein lipase, which is important for the proper metabolism of triglycerides. Both parents must carry a mutation in the LPL gene in order to produce a child who is affected by the disorder. Such parents are called carriers or heterozygotes. When two heterozygotes mate, there is a 25% (1 in 4) chance with each pregnancy that the child will inherit the disorder. There is a 50-50 chance that the child will be a heterozygote carrying a mutation from one of the parents. There is a 25% chance with each pregnancy that a child will be affected (i.e. inherited two mutations).

Lipoprotein lipase is primarily expressed in cardiac, adipose, and muscle tissue. As stated, this enzyme is required for the proper metabolism of triglycerides. Large lipoproteins known as chylomicrons transport the fat in

the form of triglyceride, which is used by the body for fuel. Chylomicrons are released into the bloodstream shortly following the ingestion of dietary fat. When chylomicrons are released, a protein within chylomicrons called apolipoprotein C2 is activated. This protein is recognized by the enzyme lipoprotein lipase, ultimately resulting in the breakdown of triglyceride. When lipoprotein lipase is inadequate or impaired, chylomicrons accumulate in the plasma, which, in turn, causes abnormal amounts of triglyceride to accumulate in the plasma as well. The accumulation of excess triglyceride and chylomicrons in the blood causes the symptoms of LPLD.

Heterozygous carriers of an LPL mutation do not develop LPLD. These individuals may have a slightly increased risk of developing mixed dyslipidemia with low HDL cholesterol levels. They may also have a mild susceptibility to developing atherosclerosis compared to non-carriers, particularly if they gain weight or remain on a high fat diet.

Diagnosis

A diagnosis is suspected in infants or children who display:

- Early-onset, severe hypertriglyceridemia, defined as >2000 mg/dL, occurring with episodic abdominal pain in an untreated state.
- Persistent severe hypertriglyceridemia, defined as >1000 - 2000 mg/dL, that is responsive to regulating dietary fat intake.
- Chylomicronemia – the presence of chylomicrons in the plasma, causing the accumulation of triglycerides and giving the plasma a milky ('lipemic') appearance.
- The presence of characteristic findings including hepatosplenomegaly; recurrent, acute pancreatitis; and eruptive, cutaneous xanthomas.

A diagnosis can be ascertained through an enzyme-linked immunosorbent assay that can reveal reduced activity of lipoprotein lipase in the plasma. An assay is performed following the administration of heparin, a normally-occurring compound found in the liver that stimulates the release of lipoprotein lipase in the body. The absence of lipoprotein lipase enzyme activity following the administration of heparin is diagnostic of LPLD.

A diagnosis can be confirmed through molecular genetic testing that can detect mutations in the LPL gene known to cause the disorder, but it is only available as a diagnostic service at specialized laboratories. The test is often not necessary to confirm a diagnosis of LPLD.

Treatment

Patients should receive a measurement of baseline plasma triglyceride levels in order to establish the extent of the disease and to determine the patient's specific needs moving forward.

The mainstay of treatment for patients with LPLD is restriction of the intake of dietary fats to reduce chylomicronemia and hypertriglyceridemia enough to prevent symptoms. Both unsaturated and saturated fat must be restricted. Therapy should maintain plasma triglyceride levels at less than 2000 mg/dL with a good clinical goal of less than 1000 mg/dL. Many individuals learn on their own to avoid foods containing fat. However, many physicians recommend reducing fat intake significantly to no more than 20 g/day or 15% of total energy intake in order to prevent symptoms. A proportion of LPL-deficient patients can be successfully treated by dietary restriction of fats, but many still experience recurrent abdominal pain and episodes of acute pancreatitis.

Pancreatitis associated with LPLD is treated by routine, standard guidelines, but adherence to appropriate dietary restriction of fat intake is critical to prevent recurrence. Severe cases can result in hospitalization.

Hepatosplenomegaly usually resolves within one week of lowering triglyceride levels. Xanthomas may take longer to resolve, requiring weeks to months to ameliorate. Recurrence or persistence of eruptive xanthomas is indicative of inadequate therapy.

Medium-chain triglycerides are recommended for cooking because they are not integrated into chylomicrons and instead are absorbed directly into the portal vein of the liver.

Fish oil supplements, effective in disorders of excessive hepatic lipase production, are ineffective and contraindicated in LPLD due to the potential to contribute to chylomicron levels. Medications that lower lipid levels such as fibrates, which are used beneficially to treat other disorders of lipid metabolism, are generally ineffective in LPLD.

PREVENTION AND FOLLOW UP

Patients should avoid agents that cause increased endogenous triglyceride levels including alcohol and specific medications including diuretics, oral estrogens, isotretinoin, glucocorticoids, Zoloft®, and beta-blockers.

A patient's initial and continued response to the restriction of dietary fat requires regular surveillance, which is accomplished through periodic assessment of plasma triglyceride levels.

Parents of children with LPLD should receive counseling on the importance of restricting fat intake, the benefits of medium chain triglycerides, and the avoidance of agents that raise triglyceride levels. Genetic counseling is recommended for patients and family members as well. Patients or parents of affected children should contact their physician if abdominal pain develops.

PREGNANCY

Women with LPLD may require strategies to lower fat intake during pregnancy. These women may experience significant changes in lipid levels during the second or third trimester, with triglyceride levels potentially rising two to four-fold. Modest increases in cholesterol and phospholipids may also occur. In one case report, a healthy infant with normal concentrations of essential fatty acids was born to a woman who was managed with extreme dietary restriction of less than 2 grams of fat per day.

Individual case reports also describe the use of fibrates, nicotinic acid and omega-3 fatty acids during pregnancy. However, because of significant safety concerns many physicians discourage their use and any consideration of these therapies requires a comprehensive analysis of the risks versus the benefits.

Gene Therapy

In 2012, the European Commission approved the marketing authorization of alipogene tipavovec gene therapy (Glybera®) for the treatment of a subset of patients with LPLD, specifically patients who have not responded to other treatments and who are experiencing severe symptoms such as acute, recurrent pancreatitis or very severe episodes of pancreatitis. Glybera is the first approved gene therapy in the Western world. Glybera uses the adeno-associated, non-replicating virus (AAV), serotype 1, to deliver healthy copies of the LPL gene to cells in affected individuals. The product has a particular affinity for muscle cells. These healthy copies of the LPL gene will produce LPL enzyme in order to facilitate the proper metabolism of fat-carrying chylomicrons. Glybera is administered via one-time small injections into the legs. Follow-up studies of patients have shown significant reduction in the incidence of pancreatitis and overall symptom frequency.

Glybera has not been approved by the U.S. Food and Drug Administration (FDA). UniQure, the company that developed Glybera, reportedly plans to seek approval by 2018. Until attaining FDA approval, Glybera will be unavailable in the United States.

Investigative Therapies

The lipid-lowering drug orlistat (Xenical®) in conjunction with a low fat diet has been used to treat some patients with compound heterozygous LPLD. Initial results from anecdotal case reports suggest that orlistat boosts the impact of a low fat diet and reduces the risk of pancreatitis. More research is necessary to determine the long term safety and effectiveness of orlistat for the treatment of LPLD.

Enzyme replacement therapy (ERT), which has been successfully developed for similar metabolic diseases, is not a therapeutic option for LPLD due to the short half-life of the LPL protein, which is approximately 15-30 minutes.

Isis Pharmaceuticals is currently conducting a randomized, double-blind, placebo-controlled, phase 3 study of ISIS 304801 administered subcutaneously to patients with familial chylomicronemia syndrome:

<https://clinicaltrials.gov/ct2/show/NCT02211209?term=Lipoprotein+Lipase+Deficiency&rank=5>

Information on current clinical trials is posted at www.clinicaltrials.gov

NORD does not endorse or recommend any particular studies.

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Resources

CLIMB (Children Living with Inherited Metabolic Diseases)

Climb Building

176 Nantwich Road

Crewe, CW2 6BG United Kingdom

Phone #: 440-845-2412173

800 #: N/A

Email: enquiries@climb.org.uk

Home page: www.CLIMB.org.uk

GeneReviews®

www.ncbi.nlm.nih.gov/books/NBK1308/

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- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

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Patient Support and Resources

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