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Lysinuric Protein Intolerance

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Summary

Clinical characteristics

Lysinuric protein intolerance (LPI) typically presents after an infant is weaned from breast milk or formula; variable findings include recurrent vomiting and episodes of diarrhea, episodes of stupor and coma after a protein-rich meal, poor feeding, aversion to protein-rich food, failure to thrive, hepatosplenomegaly, and muscular hypotonia. Over time, findings include: poor growth, osteoporosis, involvement of the lungs (progressive interstitial changes, pulmonary alveolar proteinosis) and of the kidneys (progressive glomerular and proximal tubular disease), hematologic abnormalities (normochromic or hypochromic anemia, leukopenia, thrombocytopenia, erythroblastophagocytosis in the bone marrow aspirate), and a clinical presentation resembling the hemophagocytic lymphohistiocytosis/macrophagic activation syndrome. Hypercholesterolemia, hypertriglyceridemia, and acute pancreatitis can also be seen.

Diagnosis/testing

The diagnosis is established in an individual with clinical and laboratory features suggestive of LPI including elevated 24-hour urinary excretion of cationic amino acids, especially lysine. Identification of biallelic *SLC7A7* pathogenic variants confirms the diagnosis.

Management

Treatment of manifestations: In acute hyperammonemic crises: intravenous administration of arginine chloride and nitrogen-scavenger drugs (sodium benzoate, sodium phenylacetate) to block ammonia production; reduction of excess nitrogen in the diet; provision of energy as carbohydrates to reduce catabolism. Long-term: dietary protein restriction; oral supplementation with citrulline and nitrogen-scavenger drugs, L-lysine-HCl,

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and carnitine; whole-lung lavage to improve respiratory function in persons with pulmonary alveolar proteinosis.

Prevention of primary manifestations: Long-term protein restriction and administration of citrulline and nitrogen-scavenging drugs.

Prevention of secondary complications: Minimize the risk of respiratory infections; vaccination against influenza is recommended. Varicella immunization in those without previous history of chickenpox or varicella zoster; treatment of those exposed as immune-compromised persons; revaccination may be required if poor response to polysaccharide-containing vaccines.

Surveillance: Plasma concentration of amino acids to identify deficiencies of essential amino acids secondary to protein-restricted diet; fasting and postprandial blood ammonia concentrations and attention to signs of hyperammonemia, urinary orotic acid excretion; periodic evaluation of renal function; evaluation of lung involvement; periodic serum LDH and ferritin.

Agents/circumstances to avoid: Large boluses of protein or amino acids.

Evaluation of relatives at risk: It is appropriate to evaluate at-risk sibs of a proband by molecular genetic testing or biochemical testing in order to reduce morbidity and mortality through early diagnosis and treatment.

Genetic counseling

LPI is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal diagnosis for a pregnancy at increased risk are possible using molecular genetic techniques if both pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Lysinuric protein intolerance (LPI) **should be suspected** in an infant who presents after weaning from breast milk or formula with the following features.

Early clinical features

- Recurrent vomiting with episodes of diarrhea
- Episodes of stupor and coma after a protein-rich meal
- Poor feeding
- Aversion to protein-rich food
- Failure to thrive
- Enlargement of the liver and spleen
- Muscular hypotonia

Later clinical features. In some individuals, the diagnosis is established in adulthood. Over time, additional clinical features appear:

- Poor growth
- Early (often severe) osteoporosis
- Subclinical or overt pulmonary involvement
- Renal involvement
- Hemophagocytic lymphohistiocytosis/macrophagic activation syndrome

Biochemical laboratory features

- Elevated plasma ammonia after a protein-rich meal. Fasting values are usually normal.
- Increased urinary orotic acid*
- Plasma amino acid concentrations:
  - Cationic amino acid (lysine, arginine, and ornithine) concentrations are usually below normal for age, but may be within the normal range.
  - Serine, glycine, citrulline, proline, alanine, and glutamine concentrations are increased.
- Urinary amino acid excretion. 24-hour urinary excretion of cationic amino acids, especially lysine, is increased.**

*Note: (1) In some affected individuals, elevated urinary orotic acid excretion occurs in the absence of hyperammonemia. (2) Urinary orotic acid excretion may be within the normal range if an untreated person has had a prolonged fast or has excluded protein-rich food from the diet.

**Note: (1) In some affected individuals, calculation of the renal clearances of cationic amino acids (lysine, arginine, and ornithine) may be necessary to clarify the urinary loss of these amino acids. (2) Renal clearance of an amino acid is calculated using the same formula as for creatinine clearance, but substituting creatinine values with values of 24-hour urinary amino acid excretion and of the fasting plasma amino acid concentrations. (3) Mean values and ranges of the renal clearances of cationic amino acids in individuals with LPI were reported in Simell [2001]. (4) Serine, glycine, citrulline, proline, alanine, and glutamine are found in excess in urine but have normal renal clearances.

Other laboratory features

- Plasma concentrations of LDH, ferritin, and zinc are usually elevated.
- Normochromic or hypochromic anemia, leukopenia, and thrombocytopenia are nonspecific hematologic findings.
- Hypertriglyceridemia and hypercholesterolemia are frequently observed.

Establishing the Diagnosis

The diagnosis of LPI **is established** in a proband with the above clinical and laboratory features. Identification of biallelic pathogenic variants in *SLC7A7* by molecular genetic testing confirms the diagnosis (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of LPI has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of LPI, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SLC7A7* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Testing may begin with targeted analysis for the Finnish founder variant c.895-2A>T in individuals of Finnish ancestry or for the founder variant c.1228C>T in individuals of Japanese ancestry. For individuals of other ancestry, targeted analysis for a known recurrent pathogenic variant in those populations may be performed (see Molecular Genetics, **Pathogenic variants**).

- **A multigene panel** that includes *SLC7A7* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of LPI is not considered because an individual has atypical phenotypic features, comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) is the best option. Exome sequencing is most commonly used; genome sequencing is also possible. Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Lysinuric Protein Intolerance (LPI)

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SLC7A7	Sequence analysis [3]	92%-95% [4]
	Gene-targeted deletion/duplication analysis [5]	15%-20% in non-Finnish populations

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Presently, of around 400 alleles of persons in whom LPI is suspected, only around 5%-8% have not been characterized, giving a detection rate of approximately 92%-95%.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Sperandeo et al [2005], Cimbalistiene et al [2007], Sperandeo et al [2008], Font-Llitjós et al [2009], Esseghir et al [2011]

Clinical Characteristics

Clinical Description

Usually infants with lysinuric protein intolerance (LPI) present with gastrointestinal symptoms (feeding difficulties, vomiting, and diarrhea) soon after weaning from breast milk or formula.

Most affected infants show failure to thrive early in life. Neurologic presentation with episodes of coma is less common. Moderate hepatosplenomegaly is present. Muscular hypotonia and hypotrophy are observed from early infancy. Poor growth and delayed skeletal maturation are common after the first year of life. Osteoporosis may result in pathologic fractures.

Intellectual development is usually normal unless episodes of prolonged coma cause neurologic damage.

Classic symptoms of protein intolerance may remain unnoticed during the first and second decades of life because of subconscious avoidance of dietary protein.

Treatment with a low-protein diet and supplementation with citrulline and nitrogen-scavenging drugs (see Management, Treatment of Manifestations) significantly improve symptoms related to the metabolic abnormality. However, some complications, representing the major causes of morbidity and mortality, are not amenable to treatment.

Complications

Lung disease. Progressive interstitial changes in the lung are frequently detected from early years without overt clinical symptoms. Progression to severe pulmonary alveolar proteinosis (PAP) is a well-known life-threatening complication, occurring as early as childhood in many individuals with LPI [Valimahamed-Mitha et al 2015, Mauhin et al 2017]. Pulmonary fibrosis may develop independently from PAP.

PAP usually presents with progressive exertional dyspnea, tachypnea, and cough that are exacerbated by respiratory infections and complicated by viral or bacterial pneumonia. Diminished breath sounds, inspiratory crackles, subcostal and suprasternal retractions, cyanosis, and, more rarely, digital clubbing can be found on physical examination.

Diffuse reticulonodular densities are common on radiologic evaluation. Chest high-resolution computed tomography reveals ground-glass opacities with superimposed smooth septal thickening.

The pathogenesis of the PAP in LPI is poorly understood, but may be associated with intracellular nitric oxide accumulation [Mauhin et al 2017].

Renal involvement. Glomerular and tubular involvement is common. Isolated mild proteinuria is the initial sign of renal disease leading to proximal tubular dysfunction and nephrocalcinosis [Estève et al 2017, Mauhin et al 2017]. Serum creatinine concentration and cystatin C concentration are frequently increased. In a study on 39 Finnish individuals with LPI, proteinuria and hematuria were observed in 74% and 38%, respectively. Elevated blood pressure, mild to moderate renal insufficiency, and, in some cases, end-stage renal disease were also reported in this cohort [Tanner et al 2007]. Urine beta2-microglobulin may serve as an early marker of renal involvement in LPI [Kärki et al 2016].

Renal tubular acidosis or findings consistent with reduced phosphate reabsorption and generalized aminoaciduria indicate underlying complex proximal tubular disease (Fanconi syndrome).

Kidney histology reveals immune-mediated glomerulonephritis as well as chronic tubulointerstitial nephritis with glomerulosclerosis in the absence of immune deposits [Estève et al 2017].

The pathogenesis of the renal involvement is unknown but may be associated with nitric oxide overproduction [Nicolas et al 2016].

Hematologic complications and bone marrow anomalies. A clinical presentation resembling hemophagocytic lymphohistiocytosis/macrophagic activation syndrome has been repeatedly observed.

Erythroblastophagocytosis and decreased megakaryocytes may be found in bone marrow aspirate. Hematologic findings also include slight normochromic or hypochromic anemia, leukopenia, thrombocytopenia, and subclinical intravascular coagulation.

Hypercholesterolemia and hypertriglyceridemia. Increased plasma concentrations of cholesterol and triglycerides are relatively common in individuals with LPI [Tanner et al 2010]. No clear explanation has been proposed for this dyslipidemic state; a higher-carbohydrate diet may contribute to the increased plasma concentration of triglycerides, but it is not sufficient to explain either the hypercholesterolemia or the severe hypertriglyceridemia (triglycerides >1,000 mg/dL or >11 mmol/L).

Autoimmunity and immunologic abnormalities. Various immunologic abnormalities including impaired function of lymphocytes, the presence of lupus erythematosus cells, antinuclear and anti-DNA antibodies, hypergammaglobulinemia or low serum immune globulin concentrations, hypocomplementemia, and life-threatening varicella and bacterial infections can be observed.

Growth, growth hormone deficiency. Growth retardation is commonly observed in children with LPI and is usually related to protein malnutrition. In some cases, growth hormone deficiency or arginine depletion causing impaired secretion of growth hormone is observed. Growth hormone has been used in several individuals with good response [Niinikoski et al 2011].

Pancreatitis. Acute pancreatitis is a life-threatening complication in some persons with LPI. A clear relationship with severe hypertriglyceridemia has not been defined.

Pregnancy and childbirth. A Finnish study demonstrated that maternal LPI is associated with increased risk of anemia and toxemia during pregnancy and increased risk of bleeding complications during delivery. Intrauterine growth retardation was noted in a significant number of unaffected neonates born to mothers with LPI [Tanner et al 2006].

Pathophysiology. LPI is an inborn error of metabolism caused by pathogenic variants in *SLC7A7*, the gene encoding the light chain of system y^+L. This system mediates the transport of cationic amino acids at the basolateral membrane of enterocytes and renal tubular cells. Most of the clinical findings of LPI may be related to the metabolic abnormality originating from altered absorption and reabsorption of cationic amino acids. In this respect, hyperammonemia is caused by functional impairment of the urea cycle probably resulting from an intracellular deficiency of ornithine in the liver. However, nutritional imbalance of cationic amino acids does not explain the complex multiorgan involvement of LPI, especially the complications affecting lung, kidney, and immune and hematologic systems.

System y^+L activity has been shown to be markedly reduced in monocytes and alveolar macrophages from an individual with LPI [Barilli et al 2010]. This could explain the pathogenesis of the severe complications of LPI including those affecting lung and kidney. A paradox may occur in LPI: on one hand, pathogenic variants in *SLC7A7* cause a general depletion of cationic amino acid secondary to defective intestinal uptake and renal reuptake; additionally, in immunocompetent cells the impairment of system y^+L activity may cause intracellular arginine accumulation, with a potential risk of surcharging the nitric oxide pathway [Sebastio et al 2011]. A lower dosage of citrulline supplementation is now recommended, given that citrulline is converted into arginine, notably in kidney.

Genotype-Phenotype Correlations

Genotype-phenotype correlations have not been found.

Variable expressivity is observed in individuals of Finnish origin who are homozygous for the same founder variant.

In a large Italian pedigree, homozygosity for c.1381_1384dupATCA gave rise to different clinical presentations: severe short stature with pancreatic and renal involvement in a girl; early pulmonary alveolar proteinosis causing death in a boy; a very mild clinical presentation in another boy whose brother had a similar clinical picture but died suddenly after a flu-like episode [Sperandeo et al 2000]. The pathogenic variant c.726G>A was found in 13 individuals belonging to nine independent families from Italy, Morocco, and North Africa. Five of the 13 had a severe phenotype with pulmonary alveolar proteinosis [Sperandeo et al 2008].

In 35 individuals with LPI of Japanese ancestry, no correlation between genotype and phenotype was observed [Noguchi et al 2016].

Nomenclature

Lysinuric protein intolerance has also been referred to as cationic aminoaciduria.

Prevalence

More than 200 individuals with LPI have been reported; one third are of Finnish origin [Sperandeo et al 2008, Font-Llitjós et al 2009, Carpentieri et al 2015]. Isolated clusters of affected individuals have also been identified in southern Italy and Japan.

The disorder is found worldwide: individuals with LPI originate from at least 25 countries [Sperandeo et al 2008, Font-Llitjós et al 2009]. A founder effect for specific alleles underlies the observed occurrence of LPI in Finland (c.895-2A>T) and in Japan (c.1228C>T). Surprisingly, the variant c.1228C>T was also found in a Moroccan individual [Font-Llitjós et al 2009].

The incidence of LPI has been estimated at 1:60,000 newborns in Finland and 1:57,000 in Japan [Koizumi et al 2000].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SLC7A7*.

Differential Diagnosis

The phenotypic variability of lysinuric protein intolerance (LPI) has resulted in various misdiagnoses.

Hyperammonemia. Hyperammonemia and clinical manifestations related to it are shared by other metabolic diseases, notably the urea cycle disorders (see Urea Cycle Disorders Overview). Increased orotic aciduria and hyperexcretion of cationic amino acids help to distinguish LPI from other hyperammonemic conditions.

Lysosomal storage diseases (LSDs). Hepatosplenomegaly, interstitial lung disease, and hematologic manifestation may suggest LSDs.

Malabsorptive diseases. The occurrence of gastrointestinal symptoms (e.g., vomiting, diarrhea) as well as of hypoproteinemia and failure to thrive suggests celiac disease. LPI should be included in the differential diagnosis of malabsorptive diseases.

Hemophagocytic lymphohistiocytosis/macrophagic activation syndrome. Failure to thrive, hepatosplenomegaly, fever, hypertriglyceridemia, increased serum ferritin concentration, anemia, and other blood abnormalities suggest acquired or familial hemophagocytic lymphohistiocytosis. See Familial Hemophagocytic Lymphohistiocytosis.

Autoimmune disorders. Clinical and biochemical findings consistent with diagnosis of an autoimmune disorder such as systemic lupus erythematosus (SLE) were reported in individuals with LPI and, in some cases, were the presenting features.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with lysinuric protein intolerance, the following evaluations are recommended if they have not already been completed:

- History for evidence of hyperammonemic crises with overt neurologic manifestations (vomiting, drowsiness, coma) and of respiratory involvement (cough, dyspnea, recurrent lower respiratory tract infections)
- Neurologic evaluation to detect secondary neurologic damage
- Respiratory evaluation including chest x-ray, pulmonary high-resolution computed tomography, and pulmonary function tests
- Evaluation and follow up of growth parameters
- Liver and spleen ultrasound examination to monitor liver structural changes and spleen enlargement
- Hematologic evaluation (bone marrow aspirate may be required)
- Immunologic assessment including plasma concentrations of immune globulins and, when clinically indicated, detection of autoimmune antibodies and immune complexes
- Renal function studies
- Bone density evaluation
- Consultation with a biochemical geneticist and/or genetic counselor

Treatment of Manifestations

The management of individuals with LPI is similar to that described in urea cycle disorders. In LPI, the severity of hyperammonemic crises rarely requires extreme treatments such as dialysis and hemofiltration. It is recommended that individuals with LPI be cared for by a specialized metabolic team.

Treatment of Acute Hyperammonemic Crises

Pharmacologic management. Blocking of ammonia production is accomplished by the intravenous administration of arginine chloride and of a combination of the nitrogen-scavenger drugs sodium phenylacetate and sodium benzoate. An intravenous loading dose is followed by an oral maintenance dose of nitrogen-scavenger drugs when the individual is stable. Depletion of branched chain amino acids (BCAAs) may occur as a consequence of the therapy with sodium phenylacetate [Scaglia 2010]. Persistence of BCAA deficiency hampers protein synthesis and induces catabolism. Therefore, careful evaluation of BCAA serum levels is recommended and specific supplementation may be required. Various detailed protocols for the treatment of intercurrent hyperammonemia in individuals with urea cycle disorders and (more generally) with hyperammonemia may be adopted [Häberle 2011].

Reducing the amount of excess nitrogen in the diet and reducing catabolism through the introduction of energy supplied by carbohydrates and fat. In acutely ill individuals, energy should be provided as carbohydrate and fat, either intravenously as glucose and Intralipid® or orally as protein-free formula.

Patients should be transitioned from parenteral to enteral feeds as soon as possible. Nasogastric tube feeding may be required to ensure adequate caloric and nutritional intake. Therapy with ondansetron can be started to decrease vomiting.

Complete restriction of protein for more than 24-48 hours is not recommended as the individual will become protein catabolic for essential amino acids.

Long-Term Treatment

Dietary protein restriction and citrulline supplementation. Current treatment consists of dietary protein restriction (0.8-1.5 g/kg/day in children and 0.5-0.8 g/kg/day in adults) and supplementation with citrulline (≤100 mg/kg/day, in 4 doses taken with meals). Nitrogen-scavenger drugs such as sodium benzoate (100-250 mg/kg/day in 4 divided doses) should be added to keep the lowest effective dosage of citrulline. As in the management of other inherited metabolic disorders, diet must be tailored on the basis of individual tolerance for the protein charge and carefully monitored to avoid disturbances of both growth and nutritional status.

Measurement of orotic aciduria appears to be a sensitive tool for adjustment of treatment.

Lysine supplementation. As lysine deficiency may contribute to the development of pathologic signs in LPI, oral supplementation with L-lysine-HCl should be attempted. Taking into account the defective intestinal absorption of lysine in LPI, small doses of L-lysine-HCl (20-30 mg/kg/day, in 3-4 doses per day) are given and may normalize plasma lysine concentrations [Tanner et al 2007].

Carnitine supplementation. In a survey of 37 affected individuals of Finnish ancestry, hypocarnitemia was found to be associated with female sex, renal insufficiency, and the use of ammonia-scavenging drugs. When documented, hypocarnitemia should be corrected (25-50 mg/kg/day) [Tanner et al 2008].

Additional therapies. In individuals with dyslipidemia, diet modification and fish oil supplementation should be tried before initiating pharmacologic treatment.

Treatment of Late Complications

While hyperammonemia can be efficiently prevented and treated, no effective therapy has been established for late complications.

Treatment of lung disease in LPI remains controversial: high-dose corticosteroid treatment was effective in a few patients when started early, whereas no response was noted in others.

In individuals with pulmonary alveolar proteinosis (PAP), treatment with granulocyte/monocyte colony-stimulating factor (GM-CSF) was shown to be ineffective or even to worsen the clinical course [Santamaria et al 2004]. However, in a Finnish study GM-CSF appeared to benefit two individuals with severe PAP [Tanner et al 2010]. Increased GM-CSF and decreased bioavailability of surfactant protein D have been proposed as a part of the mechanism underlying PAP in LPI [Douda et al 2009]. Whole-lung lavage remains the best therapeutic approach for PAP in LPI [Ceruti et al 2007]; however, relapses may require serial lavage.

Heart-lung transplantation was attempted with a temporary successful result, but it did not prevent a fatal return of the lung disease [Santamaria et al 2004].

Bone marrow transplantation has been discussed as a possible treatment for PAP in LPI. The rationale of this therapeutic approach would rely on the hypothesis of a defective function of lung macrophages [Barilli et al 2010, Sebastio et al 2011].

Treatment of renal disease in LPI should follow the standard guidelines under direction of the nephrologist.

Treatment of hemophagocytic lymphohistiocytosis / macrophagic activation syndrome in LPI should be formulated under the direction of a specialist.

Prevention of Primary Manifestations

The prevention of metabolic abnormality is the goal of treatment. Long-term management is based on protein-restricted diet and administration of citrulline (see Treatment of Manifestations).

Prevention of Secondary Complications

The onset and the clinical course of the secondary complications (e.g., lung and renal involvement) appear to be poorly responsive to early treatment.

Efforts to minimize the risk of respiratory infections should be promoted. Vaccination against influenza (and possibly pneumococci) is recommended.

An individual with LPI without previous history of chickenpox or varicella zoster should be vaccinated or, if exposed to varicella, treated as an immune-compromised person.

Some individuals with LPI may respond poorly to polysaccharide-containing vaccines. Therefore, revaccination may be required if specific antibody titers are non-protective.

Surveillance

Individuals with LPI should be referred for follow up to physicians with expertise in the treatment of inborn errors of metabolism. The age of the patient and the severity of the clinical features determine the frequency of clinical visits and monitoring.

Monitoring should include the following:

- Plasma concentrations of amino acids to identify deficiencies of essential amino acids induced by the protein-restricted diet (similar to that used in urea cycle disorders)
- Attention to early signs of hyperammonemia including lethargy, nausea, vomiting, and poor feeding in young children, and headache and mood changes in older children
- Fasting and postprandial blood ammonia concentrations
- Urinary orotic acid excretion
- Evaluation of renal function
- Attention to early clinical signs of lung involvement
- Serum concentrations of LDH and ferritin

The development of a multiorgan pathology in LPI requires careful surveillance of several complications including lung and renal diseases and osteoporosis. No specific guidelines have been proposed. Therefore, a tailored approach is necessary for the follow up of a specific complication.

Agents/Circumstances to Avoid

Large boluses of protein or amino acids should be avoided.

It is not clear whether prolonged fasting may trigger hyperammonemic crises.

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk sibs of a proband in order to reduce morbidity and mortality through early diagnosis and treatment:

- If the pathogenic variants in the family are known, molecular genetic testing of at-risk sibs should be performed. Plasma and urine amino acid and urinary orotic acid analyses are recommended in individuals with suspected LPI while awaiting molecular genetic results.

- If the pathogenic variants in the family are not known, early diagnosis of at-risk sibs relies on detailed clinical evaluation and determination of plasma and urinary amino acid concentrations and orotic acid urinary excretion.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy management should be performed in a center familiar with metabolic diseases. Frequent plasma amino acid and ammonia measurements are recommended as well as overall well-being of the mother and fetus. Most infants with LPI are born prematurely (between gestational weeks 31 and 39) [Tanner et al 2006]. Pregnant women with LPI are at risk of toxemia and bleeding complications during and after delivery.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

No treatment, including strict compliance with dietary regimen, citrulline supplementation, or high-dose corticosteroids, is effective in influencing the clinical course of the renal disease.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Lysinuric protein intolerance (LPI) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *SLC7A7* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with LPI are obligate heterozygotes (carriers) for a pathogenic variant in *SLC7A7*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *SLC7A7* pathogenic variant.

Carrier (Heterozygote) Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *SLC7A7* pathogenic variants in the family.

Note: Biochemical testing (e.g., plasma concentration of amino acids or urinary excretion of orotic acid) cannot distinguish carriers from controls.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *SLC7A7* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Biochemical testing cannot currently be used to distinguish between affected and unaffected fetuses.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Urea Cycle Disorders Foundation**
  Phone: 626-578-0833
  nucdf.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Urea Cycle Disorders Consortium**
  Phone: 202-306-6489
  Email: jseminar@childrensnational.org
  ucdc.rarediseasesnetwork.org

- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml
- **Urea Cycle Disorders Consortium Registry**
  Children's National Medical Center
  RDCRN Contact Registry
- **Urea Cycle Disorders International Patient Registry**
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  www.ucdregistry.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Lysinuric Protein Intolerance: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC7A7	14q11.2	Y+L amino acid transporter 1	SLC7A7 @ LOVD	SLC7A7	SLC7A7

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Lysinuric Protein Intolerance (View All in OMIM)

222700	LYSINURIC PROTEIN INTOLERANCE; LPI
603593	SOLUTE CARRIER FAMILY 7 (CATIONIC AMINO ACID TRANSPORTER, y+ SYSTEM), MEMBER 7; SLC7A7

Gene structure. *SLC7A7* has ten exons and 11 introns and spans 46.5 kbp in length on chromosome 14. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, about 60 *SLC7A7* pathogenic variants have been identified as causative of lysinuric protein intolerance (LPI) [Borsani et al 1999, Torrents et al 1999, Shoji et al 2002, Sperandeo et al 2008, Font-Llitjós et al 2009, Carpentieri et al 2015]. Most pathogenic variants reported in these studies are private, except for the Finnish founder variant c.895-2A>T, found in 38 individuals; the variant c.726G>A, found in 13; and c.1228C>T, the most frequent pathogenic variant found in the Japanese population [Noguchi et al 2016] (and also found in an individual of Moroccan origin [Font-Llitjós et al 2009]).

All types of pathogenic variants have been observed: missense and nonsense variants account for 54.4% and 28.6%, respectively; deletions, insertions, splicing variants, and large genomic rearrangements together account for 3.6%) (varsome.com/gene/SLC7A9).

Table 2. Selected *SLC7A7* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.726G>A [2]	p.Trp242Ter	NM_003982.3 NP_003973.3
c.895-2A>T [3] (1181-2A>T or 1136-2A>T)		
c.1228C>T	p.Arg410Ter	
c.1381_1384dupATCA (1670insATCA or 1384_1385insATCA)	p.Arg462AsnfsTer7	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

2. Described in Italian and North African individuals; see Genotype-Phenotype Correlations.

3. Founder variant of Finnish population; previously reported as 1181-2A>T by Torrents et al [1999] and as 1136-2A>T by Borsani et al [1999]

Normal gene product. *SLC7A7* encodes the Y^+L amino acid transporter 1 (y^+LAT-1) protein; y^+LAT-1 is linked by a disulfide bond to solute carrier family 3 member 2 (SLC3A2, also known as 4F2hc), which represents the heavy chain subunit of the heterodimeric amino acid transporter defective in LPI. This transporter, located at the basolateral membrane of epithelial cells, induces a system y^+L activity.

Abnormal gene product. Expression studies in cell culture systems demonstrated that the tested *SLC7A7* pathogenic variants are functionally different from wild type and that most abolish y^+L activity [Mykkänen et al 2000, Sperandeo et al 2005].

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Chapter Notes

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