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Minireview

Lysinuric protein intolerance (LPI): A multi organ disease by far more complex than a classic urea cycle disorder

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ABSTRACT

Lysinuric protein intolerance (LPI) is an inherited defect of cationic amino acid (lysine, arginine and ornithine) transport at the basolateral membrane of intestinal and renal tubular cells caused by mutations in *SLC7A7* encoding the y^+LAT1 protein. LPI has long been considered a relatively benign urea cycle disease, when appropriately treated with low-protein diet and L-citrulline supplementation. However, the severe clinical course of this disorder suggests that LPI should be regarded as a severe multisystem disease with uncertain outcome. Specifically, immune dysfunction potentially attributable to nitric oxide (NO) overproduction secondary to arginine intracellular trapping (due to defective efflux from the cell) might be a crucial pathophysiological route explaining many of LPI complications. The latter comprise severe lung disease with pulmonary alveolar proteinosis, renal disease, hemophagocytic lymphohistiocytosis with subsequent activation of macrophages, various auto-immune disorders and an incompletely characterized immune deficiency. These results have several therapeutic implications, among which lowering the L-citrulline dosage may be crucial, as excessive citrulline may worsen intracellular arginine accumulation.

Contents

1. Introduction

Lysinuric protein intolerance (LPI, MIM 222700) is a rare autosomal recessive disorder caused by defective cationic amino acid transport which mainly affects their intestinal absorption and renal reabsorption.

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The human gene *SLC7A7* [1,2], encodes the y^+LAT1 protein which heterodimerizes with 4F2hc to express system y^+L amino acid transport activity at the basolateral plasma membrane of epithelial cells [3–6]. So far, 50 different *SLC7A7*-specific mutations have been identified in 142 patients [7,8]. A founder effect mutation has been demonstrated in Finland, where the incidence of the disease is 1/60,000 births. Southern Italy and a northern part of Japan are other locations with high prevalence. Many patients diagnosed in Europe, originate from Mediterranean countries especially from North Africa and Turkey.

Most, but not all, of the symptoms of LPI have been linked to a secondary urea cycle derangement due to impaired transport of cationic amino acids. The disease has long been erroneously considered relatively benign when appropriately treated with low-protein diet and L-citrulline supplementation. During the past years, however, other manifestations have suggested that LPI is not only a urea cycle disorder but also a complex multisystem disease with uncertain outcome [9] thus considerably modifying the way to view this disorder. Finnish patients, all with the same homozygous mutation, exhibit a highly heterogeneous phenotype. This ranges from nearly normal growth with minimal protein intolerance to severe cases with full protein intolerance, failure to thrive, osteoporosis, hepatosplenomegaly, lung and renal involvement, and immune disorders (*e.g.* alveolar proteinosis, erythroblastophagocytosis, and glomerulonephritis) [10,11]. Such heterogeneity stresses the role of putative exogenous factors that could interfere with the course of the disease.

The aim of this review is to focus on clinical aspects of the disease in order to highlight the unusual aspects of its complications. Then, we will stress the speculative pathomechanisms and finally propose an adapted follow-up and treatment.

2. Diagnostic approach

LPI is most often under- and misdiagnosed due to its highly variable and nonspecific phenotype with undefined laboratory assessment. Therefore, based on data in the literature as well as on our personal experience, we propose the following diagnostic approach which should help to properly conduct the diagnostic evaluation.

2.1. Clinical symptoms

LPI patients may come to medical attention at any age, ranging from neonatal to adulthood. However, in most cases a thorough clinical history will include the majority of the classical clinical signs.

The classic form affects infants who exhibit neurodigestive signs that most often develop after weaning with poor feeding, recurrent episodes of vomiting and bouts of diarrhea that result in poor growth and hypotonia. Aversion for protein-rich food is particularly evident in these patients who can spontaneously tend to eat a mainly vegetarian diet. These nutritionally inadequate diets result in malnourished infants or children with pallor, poor muscle tone, osteopenia with delayed bone age and subsequently osteoporosis with pathologic fractures [12]. Patients progressively exhibit celiac disease-like phenotype with thin extremities, relatively enlarged abdomen, and sparse hair. Accordingly, many patients are evaluated in gastroenterology units for malabsorption. Hepatosplenomegaly typically develop within the first months of life and may lead to hematological or immunological investigations especially when anemia, thrombocytopenia or pancytopenia is associated. Growth failure may be severe leading to dwarfism (−2 to −6 SD). However the final height is usually subnormal due to delayed puberty and prolonged growth in mildest affected patients. Impaired secretion of growth hormone has been described in a few patients and has been attributed to arginine depletion [13].

After protein-rich meals patients may develop neurological signs such as hypotonia and lethargy in infants, ataxia and abnormal behavior in children. Coma and seizures with hyperammonemia may arise in case of forced high-protein intakes. In many situations (20%), these acute signs have led to metabolic investigations and appropriate diagnosis as they are reminiscent of signs encountered in urea cycle defects. Mental development is usually normal except for patients who have experienced severe or recurrent hyperammonemic episodes who are intellectually disabled. Pregnancies in affected women are associated with an increased risk for anemia, toxemia, intrauterine growth retardation, and excessive bleeding during delivery. However, children born after uncomplicated pregnancies are asymptomatic [14].

Treatment with a protein-controlled diet, L-citrulline supplementation and, nitrogen-scavenging drugs easily correct hyperammonemia and improve some nutritional aspects. However, despite these beneficial effects, many complications may arise. Each of them may be a presenting sign in older patients who may have been relatively protected by their protein aversion (see Section 3).

2.2. Biochemical diagnosis (Table 1)

Two main keys are needed to conduct the diagnosis. First, the LPI patients are affected with a secondary urea cycle defect and, second they have overt or at least, subclinical signs of macrophage activation.

This type of urea cycle defect is characterized by special amino acid profiles in plasma and urine: hyperammonemia is associated with low plasma levels of the cationic amino acids, arginine, ornithine and lysine that contrast with their increased urinary excretion. Regularly, these abnormalities are associated with hypercitrullinemia, cystinuria and orotic aciduria. Besides, there are high plasma glutamine levels due to hyperammonemia and often hyperglycinemia probably due to malnutrition. Low plasma level of lysine is peculiar in this context of hyperammonemia where hyperlysinemia would be expected. These abnormalities will be easily recognized during acute episodes while functional investigations would be required for chronic forms. For these functional tests, patients would first be investigated under their usual diet. Ammonia cycle comprising, along one day, measurements of plasma ammonia levels before and one hour after each meal may be sufficient to reveal postprandial hyperammonemia especially after dinner. In parallel, characteristic amino acid profiles and orotic aciduria will be easily recognized. This basal investigation may fail in malnourished patients. Indeed, plasma ammonia levels may be normal and/or amino acid profiles may reveal nonspecific and generalized hypo aminoacidemia with aminoaciduria. Still, orotic aciduria may be in the normal range. In such cases, normalization of protein intakes for one day associated with L-citrulline supplementation (150–200 mg/kg/d) in four divided dosages would be safe and sufficient to lead to the diagnosis. For such one patient, L-citrulline supplementation has resulted in characteristic amino acid profiles in both the plasma and urine (personal observation).

Table 1
Laboratory abnormalities in LPI patients.

Category of laboratory exams	Laboratory abnormalities in LPI patients
Blood cell count	Anemia Thrombocytopenia
Ferritin	Massively increased
LDH	Massively increased
TG	Massively increased
Transaminases	May be slightly above normal
Liver function tests (albumin, coagulation)	May be abnormal (liver failure in case of severe macrophage activation syndrome)
Plasma ammonia level	Usually elevated especially in the post-prandial state but may be normal
Plasma amino acids	Low concentrations of arginine, ornithine and lysine
Urinary amino acids	Increased excretion of arginine, ornithine and lysine
Orotic acid urinary excretion	Most often increased but may be normal