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Original contribution

Renal involvement in lysinuric protein intolerance: contribution of pathology to assessment of heterogeneity of renal lesions

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Summary Lysinuric protein intolerance (LPI) is a rare autosomal recessive disease caused by mutations in the *SLC7A7* gene encoding the light subunit of a cationic amino acid transporter. Symptoms mimic primary urea cycle defects but dysimmune symptoms are also described. Renal involvement in LPI was first described in the 1980s. In 2007, it appeared that it could concern as much as 75% of LPI patients and could lead to end-stage renal disease. The most common feature is proximal tubular dysfunction and nephrocalcinosis but glomerular lesions are also reported. However, very little is known regarding histological lesions associated with LPI. We gathered every kidney biopsy of LPI-proven patients in our highly specialized pediatric and adult institution. Clinical, biological, and histological information was analyzed. Five LPI patients underwent kidney biopsy in our institution between 1986 and 2015. Clinically, 4/5 presented with proximal tubular dysfunction and 3/5 with nephrotic range proteinuria. Histology showed unspecific tubulointerstitial lesions and nephrocalcinosis in 3/5 biopsies and marked peritubular capillaritis in one child. Glomerular lesions were heterogeneous: lupus-like–full house membranoproliferative glomerulonephritis (MPGN) in one child evolved towards monotypic IgG1κ MPGN sensitive to immunomodulators. One

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patient presented with glomerular non-AA non-AL amyloidosis. Renal biopsy is particularly relevant in LPI presenting with glomerular symptoms for which variable histological lesions can be responsible, implying specific treatment and follow-up.

1. Introduction

Lysinuric protein intolerance (LPI) is a rare autosomal recessive inherited disease [1]. It is due to a defect in dibasic cationic amino acid (lysine, arginine, ornithine [y+]) transport. In 1999, positional candidate cloning approach identified causative mutation in the *SLC7A7* gene (MIM #603593; GenBank RefSeq:NM_00398) which encodes the protein y+ LAT1 (y+) L-type amino acid transporter 1). It is the catalytic light subunit of an heterodimeric amino acid transporter formed of y+ LAT1 and the heavy chain of the surface antigen 4F2. This transmembranous complex is able to exchange cationic amino acid with sodium [2-4]. It is mostly present at the basolateral membrane of lung, small intestine and kidney (mainly but not exclusively in the early proximal tubule) where it allows y+ efflux after their absorption in the lumen. Therefore, its defect in enterocyte and renal tubular cells accounts for low digestive y+ absorption and low renal y+ reabsorption [5]. More than 50 mutations leading to the protein malfunction have been identified. Most of them consist of single-base substitutions or small deletions. Larger deletions, insertions or splice-site mutations are unusual. Intracellular retention as well as loss of catalytic activity has been described. There are no phenotype–genotype correlations. Most patients are homozygous for a private mutation but founder effect is reported in restricted areas in Finland, Japan, and Southern Italy [6,7].

Clinical presentation often mimics urea cycle disorders, especially digestive and neurological symptoms (hypotonia, lethargy, ataxia, seizure, and hyperammoniemic coma after high protein intake). Malnutrition is often observed and is responsible for growth delay. Biologically, y+ LAT1 dysfunction is characterized by specific amino acid profiles in plasma and urine, showing hyperammonemia associated with low plasma levels of arginine, ornithine and lysine contrasting with their increased urinary excretion. These abnormalities are associated with secondary hypercitrullinemia, cystinuria, and orotic aciduria [6]. These symptoms are likely explained by the amino acid transport deficiency and the low amino acid availability for hepatocytes.

However, physiopathology of other symptoms remains unclear. Most patients present cytopenia, hepatosplenomegaly, high ferritinemia, and hypertriglycideremia attributed to chronic hemophagocytic lymphohistiocytosis [8]. Pulmonary alveolar proteinosis observed in up to 70% of the patients is pejorative [9]. Osteopenia and severe osteoporosis sometimes leading to pathological fractures can be observed, only partially explained by malnutrition [10]. Systemic lupus–like syndromes are also reported pointing towards immune dysfunction [11-15].

The first association of LPI with kidney disease was reported in a Finnish series: one of the 27 described patients presented proteinuria before she died from pulmonary involvement [16]. The first large clinical series describing kidney involvement in LPI was published in 2007: Tanner et al found that 74% of patients presented with constant proteinuria, and 38% had microscopic or macroscopic hematuria [17]. Serum creatinine was elevated in 38% of patients. Five patients presented with tubular dysfunction. End-stage renal disease (ESRD) occurred in 4 patients. More recently, Nicolas et al reported 6 pediatric LPI cases with renal impairment, showing potentially precocious renal involvement [18].

Little information regarding histology of LPI-associated kidney diseases can be found. In 1993, DiRocco et al reported renal histological findings in 1 LPI patient showing chronic tubulointerstitial nephritis and focal glomerulosclerosis [19]. Parto et al and McManus et al reported respectively 4 and 2 independent necropsy cases. They brought to light that mesangial (2/6), membranous (1/6), and lupus-like proliferative glomerulonephritis (3/6) can also be associated with LPI [12,20,21]. Nephrocalcinosis was also reported [18].

Two independent cases reported LPI-associated Fanconi syndrome. Both showed proximal tubular cells vacuolization and sloughing of the apical brush border. No ultrastructural mitochondrial abnormalities could be found [22,23].

We report renal histological data in a series of 5 patients with LPI and renal involvement. We found variable histological patterns, from tubulointerstitial to distinct glomerular lesions requiring different treatment and follow-up.

2. Materials and methods

2.1. Patients

We identified patients with renal involvement and histological data in the series of 15 LPI patients followed at the Reference Center for Inborn Metabolic Disease at Necker-Enfants Malades Hospital, Paris, France. LPI diagnosis was confirmed by the analysis of serum and urine amino acid chromatography showing low arginine, ornithine and lysine concentration and increased urinary excretion of these amino acids. We collected clinical and biological data in medical charts. Estimated glomerular filtration rate (eGFR) was determined with the Modification of Diet in Renal Disease formula for adults or with the Schwarz formula for children.

Molecular investigation was performed to identify mutations in the *SLC7A7* gene. Genomic DNAs were extracted from leukocytes. The nine coding exons and intron-exon