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Ties IJzermans, MD, Wilbert van der Meijden, MD, Marlijn Hoeks, MD, PhD, Marleen Huigen, MD, PhD, Alexander Rennings, MD, PhD, Tom Nijenhuis, MD, PhD

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Improving a Rare Metabolic Disorder Through Kidney Transplantation: A Case Report of a Patient With Lysinuric Protein Intolerance

Ties IJzermans[1] MD, Wilbert van der Meijden[1] MD, Marlijn Hoeks[2] MD, PhD, Marleen Huigen[3] MD, PhD, Alexander Rennings[4] MD, PhD, Tom Nijenhuis[1] MD, PhD

[1] Department of Nephrology, Radboud University Medical Center, Nijmegen, the Netherlands.

[2] Department of Haematology, Radboud University Medical Center, Nijmegen, the Netherlands.

[3]Translational Metabolic Laboratory, Department of Laboratory Medicine, Radboud University Medical Center, Nijmegen, the Netherlands

[4]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.

Corresponding author:
Drs. Ties Ijzermans
Department of Nephrology, Radboudumc
Nijmegen, The Netherlands
ties.ijzermans@radboudumc.nl

Abstract

Lysinuric protein intolerance (LPI) is a rare metabolic disorder with reduced renal and intestinal reabsorption of ornithine, lysine and arginine, due to mutations in the *SLC7A7* gene encoding the y+LAT1 transporter, leading to urea cycle defects with protein intolerance. Furthermore, chronic kidney disease (CKD) in LPI is common and can progress to end stage kidney disease requiring renal replacement therapy. Kidney transplantation could in theory improve urine levels and consequently plasma levels of these amino acids and therefore improve clinical symptoms as well as protein intolerance in LPI patients. However data on kidney transplantation in LPI patients is limited and up till now no data on clinical and biochemical improvement after kidney transplantation has been reported. In this case report we describe a rare case of kidney transplantation in a LPI patient with significant improvement in protein tolerance, plasma and urine levels of ornithine, lysine and arginine and on LPI symptoms.

Index words: Lysinuric protein intolerance, kidney transplantation, amino acids, metabolic disorder, whole exome sequencing.

Introduction

Lysinuric protein intolerance (LPI) is a rare autosomal recessive metabolic disease, caused by mutations in the *SLC7A7* gene encoding the y+LAT1 transporter [1-3]. Impaired absorption in the intestine and decreased reabsorption in the tubules of the kidney of cationic amino acids causes low plasma levels of ornithine, lysine and arginine [4 5]. Symptoms most often present in childhood and mimic primary urea cycle defects consisting of protein intolerance, delayed growth, osteoporosis, hepatosplenomegaly, muscle hypotonia, macrophage activation, pulmonary fibrosis and chronic hemophagocytic lymphohistiocytosis (Box 1) [6-8]. These symptoms may occur secondary to arginine deficiency, hyperammonemia and/or immune disorders caused by the primary membrane transport defect for dibasic amino acids in the kidneys, intestine and lymphoid cells [8].

Renal involvement in LPI is common and can lead to progressive chronic kidney disease (CKD) and end stage kidney disease (ESKD) [9]. Findings in renal biopsies of LPI patients are non-specific and can vary from tubulointerstitial involvement to heterogeneous glomerular lesions and even amyloidosis [10].

Because increased urinary excretion of amino acids plays an important role in LPI pathogenesis, a kidney transplant with normal dibasic amino acid transport might be expected to improve the symptoms of LPI. To our knowledge kidney transplantation has been described in five LPI patients, however no data is available on symptoms, protein tolerance or amino acid levels after kidney transplantation [9 11]. Furthermore, no data is available on increasing protein intake after kidney transplantation or on attempts to taper treatment. In this case report we present a remarkable case of LPI with severe renal involvement and describe the course of LPI symptoms, protein tolerance and biochemical parameters after kidney transplantation.

Case report

A 37 year-old Caucasian female with a history including high ferritin with a compound heterozygous mutation for hemochromatosis and osteopenia was referred with CKD, proteinuria, tubular dysfunction with a high urinary output of alpha-1-microglobulin and beta-2-microglobulin, and erythrocyturia in 2004. A kidney biopsy at that time did not provide a

classifying diagnosis. In 2006 a repeat biopsy was obtained because of progressive loss of kidney function. Light microscopy revealed signs of glomerular infiltration and ischemia with concurrent signs of interstitial infiltration and fibrosis around the affected glomeruli. Erythrocyte casts were found as well as hemosiderin suggesting hemolysis. There were no signs of thrombotic microangiopathy. Immunofluorescence showed deposits of IgG, IgA, C3, kappa, lambda and fibrine, all in low quantities. Electron microscopy revealed podocyte injury and subendothelial as well as mesangial 15 nanometer fibrils. A diagnosis of fibrillary glomerulonephritis was assumed. Due to the advanced stage of CKD, no additional treatment was started. Patient progressed to ESKD and was started on peritoneal dialysis in 2019.

Thereafter she was again referred to our hospital because of preparation for kidney transplantation. In the interim, the patient had developed splenomegaly of unknown cause. Diuresis was 2300 ml/24h while on peritoneal dialysis. Laboratory examinations revealed a Hemoglobin level of 6.4 mmol/L, platelets 110 $x10^9$/L, leucocytes 5.3 $x10^9$/L, ferritin 270 µg/L, haptoglobin <0.10 g/L and a LDH of 587 U/L. Additionally, a monoclonal gammopathy IgM type kappa <2 g/L was found. Biopsy revealed a normocellular bone marrow with some lymphocyte aggregates and a remarkable histiocytosis without an increase of plasma cells or monotypic cells. Because of the cytopenias, hemolytic anemia, monoclonal gammopathy and splenomegaly, a genetic cause was suspected and a whole exome sequencing (WES) filtered for genes involved in clotting disorders, immunodeficiencies and kidney disease was performed. These analyses showed two heterozygous variants in each of the *SLC7A7* genes, a missense variant (SLC7A7: Chr14(GRCh37):g.23248023T>A; NM001126105.2:c.749A>T; p.(Glu250Val); heterozygote (class 4)) and a splice site variant SLC7A7: Chr14(GRCh37):g.23245041C>A; NM001126105.2:c.998+1G>T; heterozygote (Class 5) in an evolutionary conserved sequence, raising the suspicion of LPI.

Additional history showed that the patient had experienced symptoms after protein intake for all her life, consisting of nausea, vomiting and dizziness. She had also experienced recurrent viral and urinary tract infections during childhood and suffered from unexplained anorexia. There was no history of seizures or coma. However, she had apparently coped with these symptoms by changing her diet to a low protein intake. During peritoneal dialysis a high-protein diet was prescribed, however protein targets had to be consistently lowered due to intolerance. Metabolic

testing revealed low plasma levels of ornithine, lysine and arginine (Table 1) which have been described to be normal in patients on peritoneal dialysis[12]. Urine analysis showed elevated excretion of ornithine, lysine, arginine and tetraglucoside. These findings confirmed the diagnosis of LPI in our patient. She was started on a low-protein diet and was prescribed citrulline, which prevents the amino nitrogen and ammonia-induced hyperammonemia in LPI patients [13]. Sodium benzoate was omitted because of ESKD, as this acts by forming substance with glycine that can be renally excreted.

After establishing the diagnosis of LPI, the diagnosis of hemochromatosis was reconsidered, because LPI can cause high ferritin levels due to excess macrophage activation. Furthermore the patient had compound heterozygous HFE gene mutations (Cys282Tyr and His63Asp) with a very low described penetrance of only 0.5-2%, therefore a diagnosis of hemochromatosis was improbable [14]. The ESKD in the patient was presumably also due to LPI. Kidney involvement is common in LPI and kidney biopsies did not suggest a specific primary or secondary kidney disease. that resulted in ESKD. She was accepted for potential kidney transplantation. Possible anticipated complications during and after surgery were excessive bleeding due to thrombocytopenia and thrombocytopathy, a catabolic state or hyperammonemia. To prevent bleeding shortly before surgery a platelet transfusion was administered as well as tranexamic acid which both would be repeated if necessary. In order to prevent a catabolic state a glucose 10% infusion of two liters per 24h was administered and ammonia levels were monitored regularly during and after surgery. In the event that ammonia levels were elevated during surgery, the plan was to administer sodium benzoate and arginine hydrochloride, as supplementation for the urea cycle. Citrulline was continued after transplantation.

Kidney transplantation was performed in 2021 from a non-heart beating donor. No excessive bleeding, catabolic state or high levels of ammonia were observed under the aforementioned precautionary measures. After kidney transplantation protein tolerance increased significantly. Protein intake could be increased from 0.5 g/kg/day to the normal range of 1.0 g//kg/day without increasing symptoms. Three months after transplantation citrulline treatment was tapered and eventually could be stopped at 6 months. As of now, the patient experiences no symptoms after protein intake. Plasma levels as well as urinary excretion of ornithine, lysine and arginine normalized after transplantation and remained normal after the cessation of citrulline (Table 1).

Ferritin levels after transplantation significantly decreased, demonstrating an impact on hematological parameters as well.

Discussion

Renal involvement with progression to ESKD is a severe complication of LPI [9 10 15]. Our case demonstrates several interesting insights in this rare metabolic disorder and the value of kidney transplantation in this patient.

First, a kidney transplant at least partially normalized the metabolic profile in this patient with LPI. Due to the defect of the y+LAT1 transporter in LPI patients, reabsorption of ornithine, lysine and arginine in the proximal tubule is compromised, leading to loss of these amino acids via the urine [5]. This renal wasting of amino acids could be attenuated in CKD, however plasma ornithine, lysine and arginine in our patient were still lower than in other PD patients [12]. After kidney transplantation renal losses likely dissipates because the y+LAT1 transporter is functioning normally in the transplant kidney. This was evident in our patient who could increase her protein intake to normal levels and could stop taking citrulline. Amino acid plasma tests after kidney transplantation showed normal values for ornithine, lysine and arginine as well as normal urinary excretion of these amino acids, suggesting that the persisting gastrointestinal defect in amino acid absorption is overcome by correcting the renal defect. Tubular proteinuria along with a partial Fanconi has been described in LPI, probably due to excessive urinary loss of lysine which inhibits tubular protein uptake [16].

Secondly, it shows how heterogeneous the phenotype and, therefore, difficult the diagnosis of a rare disease like LPI can be and emphasizes the potential benefit of performing genetic analysis (e.g. WES) in a patient with unexplained disease [17]. Our patient experienced symptoms from the start of life, however the diagnosis was never considered until the age of 52. Furthermore, the symptoms she experienced because of protein intolerance went unnoticed, through years of visiting medical specialists, until she was referred to a metabolic expert after the genetic diagnosis had been established. Performing a WES could have helped diagnose this disease earlier. This can be especially important in patients with longstanding unexplained symptoms where genetic testing was not available earlier in their disease course. Furthermore it is important to establish a definitive diagnosis comprising more than a phenotypical or pathological description. In our patient a presumed diagnoses of fibrillary glomerulonephritis was made based

on kidney biopsy. However this is not a kidney disease in itself, and no disorder known to cause glomerular fibril deposits had been diagnosed.

To our knowledge, this is the first report of a case of improvement in LPI symptoms and protein tolerance after kidney transplantation. Two Finnish case series described a total of five patients with LPI in whom a kidney transplantation was performed [9 11]. However, dietary intake of protein was kept unchanged after transplantation, nor was the dose of citrulline tapered, and amino acid levels after kidney transplantation were not reported.

In summary, we describe a rare case of kidney transplantation in a patient with LPI where transplantation was associated with improvement in LPI symptoms. In addition, after transplantation, the patient's protein intake could be increased and the dose of citrulline tapered and discontinued. Further studies are required to generalize these findings to other LPI patients.

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Box 1. Main clinical features of Lysinuric Protein Intolerance

First symptoms after weaning from breast milk or formula
Postprandial hyperammonemia with stupor and/or coma after protein ingestion
Aversion to protein meals
Recurrent episodes of vomiting and diarrhea
Short stature because of malnutrition and failure to thrive
Recurrent viral infections
Hepatosplenomegaly
Muscle hypotonia
Osteoporosis
Pulmonary involvement with fibrosis, interstitial pneumonia and pulmonary alveolar proteinosis
Chronic hemophagocytic lymphohistiocytosis
Renal involvement, mostly tubular lesions often progressing to CKD

Table 1**:** Relevant amino acids, ammonia, renal function and ferritin as measured in plasma and urine before and after kidney transplantation.

Plasma	1 year before kidney transplantation*	1 month after kidney transplantation	8 months after kidney transplantation. After cessation of citrulline	Reference range
Ornithine (µmol/l)	29	129	23**	24 - 168
Lysine (µmol/l)	63	198	237	69 - 252
Arginine (µmol/l)	20	78	44	16 - 125
Citrulline (µmol/l)	119	121	30	11 - 46
Glutamine (µmol/l)	1067	703	909	304 - 750
Glutamic acid	90	116	59	22 - 196
Ammonia (µmol/l)	32	34	19	<50
Creatinine (µmol/l)	***	76	72	> 90
CKD-EPI (ml/min/1,73m^2)	***	77	82	> 90
Ferritin (µg/L)	631	998	161	20 - 300
Urine				
Ornithine (µmol/mmol creatinine)	25	2	0	0 - 4
Lysine (µmol/mmol creatinine)	77	10	4	1 - 40
Arginine (µmol/mmol creatinine)	33	4	0	0 - 7
Citrulline (µmol/mmol creatinine)	147	6	0	0 - 2
Glutamine (µmol/mmol creatinine)	1064	47	31	6 - 90
Glutamic acid (µmol/mmol creatinine)	6	2	1	1 - 10
Tetraglucoside (µmol/mmol creatinine)	53.9	-	0.8	0 - 2
Orotic acid (µmol/mmol creatinine)	1	2	-	0 - 3

*Without citrulline supplements, these were ceased 4 months after kidney transplantation.

**Plasma ornithine was 33 umol/L 7 days before the measurement 8 months after kidney transplantation.

*** Patient on peritoneal dialysis, normal diuresis.