CASE REPORT

Lysinuric Protein Intolerance Presenting with Recurrent Hyperammonemic Encephalopathy

SUNITA BIJARNIA-MAHAY, [*]VIVEK JAIN, [*]RAJIV KUMAR BANSAL, [#]GUMMADI MAHESHWAR REDDY AND [‡]JOHANNES HÄBERLE

From Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, [*]Department of Pediatrics, Santokba Durlabhji Memorial Hospital, Jaipur; and Department of Biochemical Genetics, Sandor Lifesciences Pvt. Ltd., Hyderabad; India; and [‡]Division of Metabolism, University Children's Hospital Zurich, Switzerland

Correspondence to: Dr Sunita Bijarnia-Mahay, Senior Consultant, Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110 060. bijarnia@gmail.com
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Background: Lysinuric protein intolerance is an inherited disorder of transport of cationic amino acids, causing amino aciduria. **Case characteristics**: A 3-year-old boy with 12 month history of episodic change in behavior (decreased sleep, poor interaction), stunted growth and hyperammonemia. **Outcome**: Genetic analysis revealed a homozygous mutation, c.158C>T (p.Ser53Leu) in exon 1 of *SLC7A7* gene.With appropriate management of hyperammonemia episodes, his neurodevelopmental outcome is normal. **Message:** Lysinusic protein intolerance is a potentially treatable disorder and should not to be missed.

Keywords: *Behavioral problems, Neurometabolic disorder, Urea cycle disorder.*

Lysinuric protein intolerance (MIM #222700) (LPI) is an autosomal recessive inborn error of metabolism caused by mutations in the *SLC7A7* gene disrupting absorption and reabsorption of cationic amino acids, arginine, lysine and ornithine, across the intestinal and renal tubular membranes, respectively [1]. Infants with this disorder usually present after weaning with recurrent diarrhea, failure to thrive and episodes of stupor. As the disease can show varying multisystem presentations, it is likely to be misdiagnosed [2]. Pulmonary alveolar proteinosis, renal disease, hemophagocytic lymphohistiocytosis, osteo-porosis and various auto-immune and immunodeficiency disorders have been described in patients with LPI [2,3]. Recurrent hyperammonemic encephalopathy occurs frequently, and is due to deficiency of arginine and ornithine causing disruption of the urea cycle [3].

We report a child with LPI who presented with recurrent episodes of encephalopathy due to hyper-ammonemia.

CASE REPORT

A 3-and-a-half-year-old boy, born to a consanguineous couple, presented with episodes of difficulty in falling to sleep lasting several days, excessive crying and decreased oral intake over the last 18 months. This episodic change in behavior usually followed acute illness, especially gastroenteritis, though most episodes never required hospital admission. Except these episodes, the child was well, with the exception that parents had noted gradual regression of speech with poor eye contact and interaction with family members. This episodic mild encephalopathy was mistaken for epilepsy and treatment given. However, multiple anti-convulsants proved ineffective.

On examination, his height and weight were low - Weight 10.5 kg (<1st centile), height 90 cm (on 3rd centile) and head circumference of 47.5 cm (3rd centile) according to WHO charts. Child was pale and had mild hepatosplenomegaly. He was also restless, with limited speech and poor eye contact. Unsteadiness of gait was also noted. Routine investigations of blood counts, electrolytes, blood gas analysis, liver and renal functions did not show any abnormality except mild anemia (hemoglobin 11.2 g/dL) (***Table* I**). His plasma ammonia level was 840 µmol/L (normal range < 50); serum ferritin and LDH were also raised. Amino acids analysis revealed decreased levels of lysine, arginine and ornithine in plasma, and marked elevation of the same amino acids in the urine. Urine organic acids analysis by GC-MS (Gas Chromatography-Mass Spectrometry) demonstrated elevated levels of orotic acid (460-fold). EEG showed mild diffuse slowing of electrical activity, and MRI of brain revealed subtle symmetrical periventricular T2 hyper-intensities. Based on the finding of hyperammonemia along with unusual high excretion of cationic amino acids (lysine, arginine and ornithine) in urine, and deficient levels in plasma, a diagnosis of LPI was made.

Mutation analysis of *SLC7A7* gene using sequencing

TABLE I LABORATORY PARAMETERS IN THE PATIENT

Investigations	*Result*
ALT (SGPT)	30 IU/L(0-60)
ALP	513 IU/L(250-770)
Blood urea	6 mg/dL,
Serum Creatinine	0.3 mg/dL
Serum Ferritin ng/mL	572 (17.9 - 464)
LDH	2254 U/L (normal 313-464)
Plasma amino acids (nmol/mL)	
Lysine	16.7 (48-284)
Ornithine undetectable Arginine	12.8 (10-140)
Urine amino acids	(10-163) (nmol/mg of creatinine)
Lysine	3912 (34-894)
Arginine	292.5 (7-133)
Ornithine	32.8 (2-91)

showed homozygous, previously reported mutation, c.158C>T (p.Ser53Leu) in exon 1. Computational analysis of the variation revealed likely pathogenic by Mutationtaster, Polyphen 2, SIFT and Provean softwares.

After start of sodium benzoate, L-carnitine, low dose citrulline supplements and a protein-restricted diet, the child showed a marked improvement in symptoms. On follow-up at two years after diagnosis, his episodic behavioral symptoms had completely resolved. His interaction with parents and peer group was normal, there was good eye-to-eye contact and resolution of hyperactivity. He was in grade one at school, with no concerns about his academic performance. His physical growth was low (3rd centile), but tracking along the same centile, splenomegaly had resolved and mild hepatomegaly was present. Since start of specific treatment, he has had two further episodes of intercurrent illness, which could be managed with extra non-protein calories and sodium benzoate averting signs of encephalopathy. The most recent plasma amino acids analysis showed normal arginine, but low lysine and ornithine. Urinalysis for proteinuria and a chest radiograph showed normal findings.

DISCUSSION

LPI is characterized by a complex pathophysiology extending beyond merely a disruption of ureagenesis [3,4]. A defect in the *SLC7A7* gene is responsible for this disorder. Although more than 50 mutations have been detected in patients across the world, none has been described in Indian patient.

This unique multi-systemic disorder occurs due to defective intestinal absorption and renal reabsorption of amino acids – lysine, arginine and ornithine, leading to low levels of these amino acids in plasma and high levels in urine. While these cationic amino acids are essential for various biochemical pathways and bodily functions, the urea cycle is affected secondarily due to depletion of its metabolites, arginine and ornithine, leading to hyperammonemia. Other complications are thought to be related to the derangement in arginine metabolism [2]. Excess intracellular arginine, because of trapping (due to block in transport) may trigger an overproduction of nitric oxide, leading to monocytes and macrophages dysfunction [2,3]. This explains the association of this disorder with many immunodeficiency syndromes, hemophagocytic lymphohistiocytosis, pulmonary alveolar proteinosis and renal disease seen in older untreated patients with LPI. The elevation of LDH and ferritin in our case is also a known feature and a biomarker, along with ammonia, in LPI.

Misdiagnosis in patients of LPI, with either milk protein intolerance causing enterocolitis, malabsorptive syndrome or autoimmune disorders have been reported in literature [1,5]. It is thus important to recognize and treat the hyperammonemia early enough to be able to prevent further neurological damage and other complications. A close follow-up of patients is unnecessary. A bone densitometry has not been done on follow-up for this child due to logistic reasons, but is planned.

The standard treatment for hyperammonemia in LPI involves low protein diet, ammonia lowering nitrogen scavengers like sodium benzoate (100-250 mg/kg/day in 3 divided doses), carnitine (100 mg/kg/day in three divided doses) and low-dose citrulline supplementation.

Arginine supplementation is unhelpful as oral arginine is not absorbed from intestinal mucosa. Care has to be taken in supplementing with citrulline as higher doses may elevate the intracellular arginine levels paradoxically leading to harmful effects [3].

Another Indian patient was previously reported, suspected on clinical and biochemical grounds [6]. As LPI is an autosomal recessive trait, parents of probands have a 25% risk of recurrence in their subsequent pregnancies. Thus, genetic counseling is extremely important, as it opens the possibility of prenatal diagnosis once the disease-causing mutation is detected in the family.

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