

Lysinuric Protein Intolerance: A Treatable Cause of Developmental Delay with Multiple Complications

Tanjung C¹, Watkinson J², Olpin S² and Yap S^{3*}

¹Department of pediatric, Pantai Indah Kapuk Hospital, Jakarta

²Department of Clinical Chemistry, Sheffield Children's Hospital, United Kingdom

³Department of Inherited Metabolic Medicine, Sheffield Children's Hospital, United Kingdom

Case Report

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***Corresponding author:** Sufin Yap, Department of Inherited Metabolic Medicine, Sheffield Children's Hospital, NHS Foundation Trust, Sheffield, United Kingdom, Email: Sufin.Yap@sch.nhs.uk, sufinyap@gmail.com

Abstract

Background: Lysinuric protein intolerance (LPI) is a multi systemic disease with a variety of clinical symptoms. Early and aggressive treatment can significantly reduce the number of hyperammonaemic episodes and prevent mental disability.

Case series: We report a case series from two siblings with LPI: The eldest boy presented at three and a half years of age with short stature, global developmental delay & a history of recurrent infections. His younger brother was identified in the newborn period with lethargy and weight loss. Basic metabolic screening showed hyperammonaemia, gross urinary excretion of lysine & to a lesser degree increased excretion of arginine, ornithine and orotic acid. Plasma amino acids showed either low or low normal lysine, arginine and ornithine.

Results: Both cases were treated with protein restriction, nitrogen scavengers, citrulline and L-carnitine. They were provided with an appropriate oral and intravenous emergency regimen for use when unwell. At the last follow-up the eldest boy showed a marked improvement in his development, whilst the youngest infant has normal physical & mental development for age.

Conclusions: Marked improvement in LPI patients can be achieved by strict diet and medication with early identification & treatment likely to lead to the best possible intellectual outcomes.

Introduction

Lysinuric protein intolerance (LPI, OMIM #222700) is a rare autosomal recessive inherited disease caused by defective cationic amino acid (lysine, arginine and ornithine) transport with mutations in the *SLC7A7* gene

[1-3]. The transporter protein ybLAT-1 is located on the basolateral membrane of epithelial cells in the intestine and kidney. LPI is a multi-systemic disease with a variety of clinical symptoms. Here we report a case series of two siblings with LPI presenting with global developmental delay in the elder brother and lethargy in the youngest.

Case Report

Index case

A three and a half-year-old boy were investigated for global developmental delay, hyperactivity and short stature. He is the first of three siblings from consanguineous parents. The second son is unaffected and the third boy was diagnosed with LPI soon after birth.

The index case attended a community developmental clinic where he was evaluated for global developmental delay. Following evaluation, a basic metabolic screening was undertaken which included plasma and urinary amino acids, organic acid and glycosaminoglycan. The plasma amino acids showed low lysine, ornithine, arginine and elevated glutamine (Table 1), with gross increased excretion of urinary lysine (Figure 1A). He was referred to a metabolic physician.

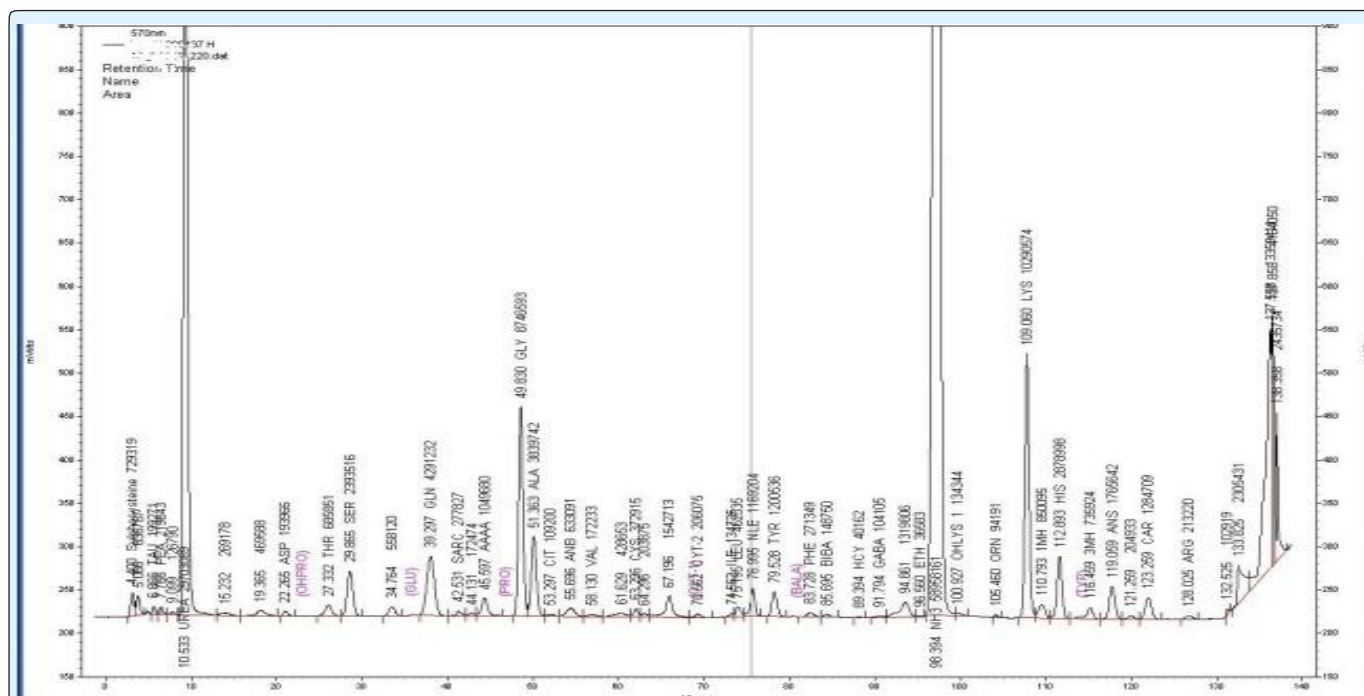


Figure 1: (A) Index Case - Biochromatography of plasma amino acids from pre-treatment sample.

(B) Index Case- Biochromatography of pre-treatment urine amino acids, showing increased excretion of lysine only.

On examination, his weight was 12kgs (2nd percentile), height was 89.2cms (<0.4th percentile) and the occipito-frontal circumference 47.1cms (<0.4th percentile). He displayed marked hyperactivity with hepatomegaly.

Developmental history revealed evidence of global delay from the age of 3 months. He smiled at 3-4 months, babbled around 6 months, turned over on 7-8 months, sat without support around 9-10 months and walked unsupported at 19 months. He had only a few single words. He was a poor eater and tended to avoid high protein food, preferring to eat vegetables and fruits. He developed pneumonia at six months and had recurrent respiratory tract infections requiring anti-biotic treatment.

A full blood count, lymphocyte subsets, immunoglobulins, chest x-ray, DEXA scan and full biochemical evaluation was undertaken. Ammonia was 115 μ mol/L and there was gross urinary excretion of lysine. Urinary excretion of orotic acid was increased with plasma amino acids showing low lysine, arginine and ornithine (Table 1). Based on these result a diagnosis of lysinuric protein intolerance was made.

Treatment included protein restriction to 1.5g/kg/day, sodium phenylbutyrate 250mg/kg/day, L-citrulline 100mg/kg/day and L-carnitine 20mg/kg/day. Low protein products were prescribed to provide calorie and variety in the diet. He was provided with an appropriate oral and intravenous emergency regimen for use when unwell.

	Index Case		Second Case	
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment
Growth Parameters	12.5 (2nd centile)	14.2 (2nd centile)	2.75 (2 nd centile)	3.29 (2 nd centile)
Weight (kg)	89.0 (<0.4th centile)	99.7 (2nd centile)	45.0 (< 0.4 th centile)	
Height (cm)			33.0 (2 nd centile)	52.2 (2 nd centile)
Head Circumference	-	-		36.5 (9 th centile)
Laboratory Results				
Blood*				
Ammonia	115 (<50)	23	126 (<150)	23
Glutamine	1381 (550-830)	711	1612 (487-1031)	996
Lysine	39 (50-233)	59	186 (105-315)	133
Arginine	<5 (0-160)	16	28 (10-70)	13
Ornithine	<5 (40-160)	16	23 (25-225)	26
Urine§				
Lysine	396 (10-68)	-	1648 (22-171)	1878
Arginine	9 (0-9)	-	183 (0-14)	605
Ornithine	<5 (0-7)	-	84 (0-19)	135
Organic acid	2-ketoglutarate, glutarate	-	2-ketoglutarate, fumarate	-
Orotic acid	9.6 (<3.5)	1.0 – 3.3	10.8 (<3.5)	1.2

Table 1: Growth parameters and pre- and post-treatment sample results from both cases.

Number in brackets shows normal value. *Blood concentrations for amino acids are in $\mu\text{mol/L}$. §Urine concentrations are in $\mu\text{mol/mmol creatinine}$.

Following three months of the treatment he showed marked clinical improvement. He was no longer hyperactive, could take verbal instruction and put several words together. He showed interest in food and had gained weight and height (Table 1). At five years and 10 months, he is attending a normal school with remedial help, interacts socially with his peers and understands verbal instructions.

Second case

This is the third son who was admitted on day 4 with weight loss (10%), poor feeding and lethargy. On admission ammonia was $126\mu\text{mol/L}$. Pre-treatment samples showed elevated urinary excretion of lysine, arginine, ornithine and elevated plasma glutamine. Urinary orotic acid was also increased.

On review of preliminary results the baby was immediately treated with oral sodium benzoate 250mg/kg/day , L-citrulline 100mg/kg/day and protein restriction. Natural protein, as breast milk or proprietary milk, was restricted to provide 1.5g/kg/day . A protein free product, Energivit ® (carbohydrate and fat formula)

was given to appetite to make up energy and volume requirements. Ammonia and plasma amino acids were all normal prior to discharge. At the age of two years, he was developmentally appropriate with growth parameters along the 2nd percentiles.

Diagnostic confirmation by molecular analysis of the *SLC7A7* gene showed both boys to be homozygous for c. [722G>A]; p.[(Gly241Asp)]. Both parents have been shown to be carriers of this mutation.

Discussion

Lysinuric protein intolerance (LPI, OMIM # 222700) is frequently under or misdiagnosed due to its highly variable, often nonspecific phenotype and often subtle biochemical abnormalities [2]. LPI is relatively common in Finland, with a prevalence of 1/60,000. It is also found in Southern Italy, Northern Japan and sporadically all over the world [2-5]. It is caused by mutations in the *SLC7A7* gene, which encodes the ybLAT-1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family [1-4]. The reduced activity of the transporter (*SLC7A7*) leads to

reduced absorption of arginine, ornithine and lysine in the kidney and intestine [5,6].

LPI is a multi organ disease with a variety of clinical symptoms. Protein malnutrition and lysine deficiency contribute to the patient's failure to thrive, as deficiency of arginine and ornithine result in dysfunction of the urea cycle with resultant hyperammonaemia and its developmental sequelae [2,5]. On weaning, patients usually display an aversion to high-protein foods and show delayed bone growth, osteoporosis, hepatosplenomegaly and muscle hypotonia [2,4,5]. These clinical features were all present in the index case. Some patients experience chronic congenital diarrhoea due to the osmotic effect of high concentration of amino acids in the intestine [7].

Immune dysfunction attributable to nitric oxide (NO) overproduction secondary to intracellular trapping of arginine (due to defective efflux from the cell) is also a major feature. This may be a crucial Pathophysiological explanation for many LPI complications including severe lung disease with pulmonary alveolar proteinosis, renal disease, hemophagocytic lymphohistiocytosis (HLH) with subsequent activation of macrophages (MAS), various auto-immune disorders and an incompletely characterized immune deficiency [2,3,5,8]. The index case experienced pneumonia at a young age and frequent respiratory tract infections.

The diagnosis of LPI is based on the combination of increased urinary excretion and low plasma concentrations of the cationic amino acids [2,5,6]. It is vital that both urine & plasma amino acids are quantitated so as not to miss the diagnosis. This is illustrated in the sibling of the index case where plasma arginine and lysine were within the normal range with only ornithine mildly reduced. However the urine amino acids showed marked excretion of lysine, arginine and ornithine.

Patients are treated with low-protein diet and supplementation of L-citrulline, which is absorbed by neutral amino acid transporters and serves to correct the urea cycle dysfunction. Citrulline is partially converted to arginine and ornithine. It is proposed that citrulline increases the intracellular synthesis of arginine and may further stimulate the immune cascade in renal tubular, glomerular and mesangial cells, alveolar macrophages and pulmonary epithelial cells and the reticular endothelial system. Thus regularly monitoring of plasma ammonia, glutamine and urinary orotic acid should be undertaken. If hyperammonemia develops, more severe

protein restriction with or without nitrogen scavengers must be used [2,5]. By giving early and aggressive treatment, the number of hyperammonaemic episodes can be reduced significantly thereby preventing intellectual disability [1,2,6,8]. Given the multi-systemic nature of this disorder, care should be taken to monitor for, and to treat early, manifestation of HLH, MAS, nephropathy and immune dysfunction. A multi-disciplinary team approach is required in order to treat these patients successfully [2,3].

In summary, we described a case series of LPI patients with a range of non-specific symptoms. In order to avoid missing the diagnosis we recommend careful quantitative evaluation of both plasma and urine amino acids. Marked clinical improvement can be achieved by diet and medication which is best achieved through early detection and treatment. Surveillance for other LPI associated complications should be part of the management of these patients.

References

1. Font-Llitjos M, Rodriguez-Santiago B, Espino M, Sillue R, Manas S, et al. (2009) Novel *SLC7A7* large rearrangements in lysinuric protein intolerance patients involving the same AluY repeat. *Eur J Hum Genet* 17(1): 71-79.
2. De Baulny HO, Schiff M, Dionisi-Vici C (2012) Lysinuric protein intolerance (LPI): a multi organ disease by far more complex than a classic urea cycle disorder. *Mol Genet Metab* 106(1): 12-17.
3. Barilli A, Rotoli BM, Visigalli R, Dall'Asta V (2013) Alterations of arginine in Lysinuric Protein Intolerance (LPI) macrophages. *FASEB Journal* 27: 1b475.
4. Santamaria F, Mirra V, De Stefano S, Andria G, Parenti G (2013) Respiratory manifestations in patients with inherited metabolic diseases. *Eur Respir Rev* 22(130): 437-453.
5. Nanto-Salonen K, Niinikiski H, Simel OG (2012) Transport defects of amino acids at the cell membrane: cystinuria, lysinuric protein intolerance and Hartnup disorder. In: Saudubray JM, et al. (Eds.), *Inborn metabolic diseases Heidelberg: Springer Medizin*, p. 366-368.
6. Mikolajek-Bedner W, Torbe A, Kwiatkowski S, Michalezyk M, Gizewka M, et al. (2013) Pregnancy

- delivery and puerperium in patient with lysinuric protein intolerance-a case report. *Ginekol Pol* 84(7): 654-656.
7. Terrin G, Tomaiuolo R, Passariello A, Elce A, Amato F, et al. (2012) Congenital Diarrheal Disorders: An Updated Diagnostic Approach. *Int J Mol Sci* 13(4): 4168-4185.
 8. Mannucci L, Emma F, Markert M, Bachmann C, Boulat O, et al. (2005) Increased NO production in lysinuric protein intolerance. *J Inherit Metab Dis* 28(2): 123-129.