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Early Diagnosis of Lysinuric Protein Intolerance: A Case Report

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Abstract **Case Report**

Introduction: Lysinuric protein intolerance (LPI) is a metabolic disorder resulting from recessive inherited mutations involving the SLC7A7 gene that control the transport of urea cycle intermediates. ***Case report***: In this study we report a case of a kid who diagnosed with LPI at age of 18 month, he has recurrent vomiting and diarrhea with a break in the height-weight curve, the dosage of orotic acid in the urine which was increased, the chromatography of the amino acids which found a low level of lysine, ornithine and arginine in the blood and increased in the urine suggestive of LPI. ***Discussion***: The defects occur in the y+ LAT1 sub-unit of the cationic amino acids transporter localized in the kidney and also expressed in the lung, spleen and in circulating monocytes and macrophages, which explain that an LPI patient usually comes with hepatosplenomegaly, failure to thrive, aversion to protein rich food, and poor feeding.

Keywords: Arginine, dibasic, lysinuria, ornithine.

INTRODUCTION

Dibasic protein intolerance with lysinuria (IPD) is a rare disease of recessive autosomal transmission caused by an abnormality of the dibasic amino acid transporter (arginine, ornithine, and lysine). It is due to the mutation of the SLC7A7 gene located at 14q11.2.

CASE REPORT

Jad aged 16 months, born at term with a weight of 3400 g from non-consanguineous parents.

Its story begins with a break in the height-weight curve observed from the age of 3 months with vomiting, chronic diarrhea, aversion to proteins, anorexia and psychomotor retardation.

Clinical examination found failure to thrive (-3DS), malnutrition, axial hypotonia. The workup carried out showed hypochromic microcytic anemia. There is no hydro electrolytic or hepatic enzymatic abnormalities, renal function is normal. Vitamin B12 and B9, vitamin D, phosphocalcic and thyroid analysis are normal, amonemia and dose of lactate are also normal. The test for anti-transglutaminase IgA antibodies is negative. Esogastroduodenal fibroscopy revealed a small open heart disease with grade 1 esophagitis. With gastric and jejunal biopsy: chronic fundic gastritis of mild inactive intensity.

The abdominal ultrasound and the x-ray of the lung are normal. Cerebral MRI revealed discreet cortical atrophy predominantly temporal with a thin appearance of the corpus callosum.

The IPD diagnosis was taken at the age of 18 months after a break in the height-weight curve with aversion to proteins, anorexia, vomiting, chronic diarrhea episode, a delay in psychomotor development and the dosage of orotic acid in the urine which was increased, the chromatography of the amino acids which found a low level of lysine, ornithine and arginine in the blood and increased in the urine suggestive of LPI.

Therapeutically: a low protein diet associated with supplementation with citrulline and carnitine was started. The evolution was marked by weight gain and improvement in general condition.

DISCUSSION

Among the several metabolic-endocrine disorders causing short stature, especially in cases of aversion to protein-rich foods, LPI must always be considered.

Lysinuric protein intolerance (LPI), is a metabolic disorder resulting from recessive inherited mutations involving the SLC7A7 gene, that control the transport of urea cycle intermediates. LPI patients will usually present with recurrent episodes of vomiting and diarrhea. Most of the times, first symptoms manifest after weaning from breast milk. After a while, many complications involving multiple systems become apparent. Plasma ammonia levels may be normal in the fasting state and only rise after a protein-rich meal. Urinary excretion of cationic amino acids as seen in the reported older sibling supports the diagnosis [1].

Defects occur in the y+ LAT1 sub-unit of the cationic amino acids transporter localized at the basolateral membrane of the tubular kidney and small bowel cells, leading to the classical hallmarks of the disease: leakage of cationic amino-acids in the urine (arginine, ornithine, lysine) with associated normal to low plasma levels [2]. Y+ LAT1 is also expressed in the lung and spleen and in circulating monocytes and macrophages, which explain that an LPI patient usually comes with hepatosplenomegaly, failure to thrive, aversion to protein rich food, and poor feeding.

Since the first description of LPI, a great deal of clinical heterogeneity has been observed among patients. LPI is often revealed by the appearance of chronic digestive symptoms and failure to thrive after presumptive diagnoses of celiac disease, other causes of malabsorption or "food allergies" [3, 4]. Lysinuric protein intolerance (LPI) should be suspected in an infant who presents after weaning from breast milk or formula with the following features [9].

Early Clinical Features

Recurrent vomiting with episodes of diarrhea, Episodes of stupor and coma after a protein-rich meal, Poor feeding, Aversion to protein-rich food, Failure to thrive, Enlargement of the liver and spleen, Muscular hypotonia.

Later clinical features

In some individuals, the diagnosis is established in adulthood. Over time, additional clinical features appear like Poor growth, early (often severe) osteoporosis.

In a cohort analysis of the medical records of all patients identified at Necker Hospital (Paris, France) with a diagnosis of LPI from January 1977 to July 2015 concluded that patients from the same family can have entirely different evolution of symptoms, which may hinder the ability to provide a definitive prognosis [2].

In addition, inflammatory markers, namely ferritin and LDH, are commonly elevated in LPI. The diagnosis of LPI is highly supported by the presence of excessive amounts of cationic amino acid in the urine combined with their low serum levels. In order to confirm the diagnosis of LPI, mutation analysis of genomic DNA and cDNA extracted from peripheral blood samples, and of cultured lymphoblasts was carried out via polymerase chain reaction (PCR) amplification and the direct DNA sequencing method described previously [5].

For better prognosis earlier diagnosis is crucial, given that the LPI patients with earlier diagnosis had a lower prevalence of intellectual disability. Similarly, a study analysis suggests the importance of the prevention of hyperammonemia as an early treatment to protect against intellectual disability as well as other symptoms, as malnutrition and bone fractures [6]. But other several complications as immunological disorder, as well as renal and lung involvements are not preventable despite adequate control of serum ammonia and nutrition, which remains a subject for future investigation.

However, prenatal diagnosis by direct mutational analysis of LPI has been reported in a Tunisian Family on his third pregnancy pregnancy, an amniotic fluid sample was taken at 16 weeks of gestation. The 1471 delTTCT mutation at homozygous state was identified, indicating that the fetus was affected by LPI [7].

In our case the diagnosis was at the age of 18 month, the kid was symptomatic, a break in the height-weight curve with aversion to proteins, anorexia, vomiting, chronic diarrhea episode, a delay in psychomotor development, so the dosage of orotic acid in the urine which was increased, the chromatography of the amino acids which found a low level of lysine, ornithine and arginine in the blood and increased in the urine suggestive of LPI.

General therapeutic management remains empirical with 3 major axes: prevention of hyperammonemia, nutritional supplementation and prevention of specific complications. There is a general consensus that a hypoproteinemic regimen should be initiated with an objective of 1 g/kg/d. associated with L-citrulline supplementation, L-carnitine 20-50 mg/kg/d, vitamins and other nutritional supplementation, if necessary [3, 4]. Ammonia scavengers such as sodium benzoate or phenylbutyrate are used based on glutamine levels. L-citrulline is used to correct the intracellular defect of arginine through arginosuccinate-synthase and argininosuccinate-lyase.

CONCLUSION

We report a case of an infant who presents a typical LPI picture. LPI is a multisystem disease which could lead to late diagnosis.

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