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Lysinuric protein intolerance: an overlooked diagnosis

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Abstract

Background: Lysinuric protein intolerance (LPI) is an autosomal recessively inherited inborn error of metabolism (IEM) caused by the defect in the dibasic cationic amino acid transporter found on the basolateral membrane of the lung, small intestine, and kidney due to mutations in the *SLC7A7* gene, which encodes the y^+LAT1 protein. LPI may present as an acute hyperammonemic episode or as chronic symptoms. Major clinical symptoms are feeding problems, vomiting and diarrhea, failure to thrive, hepatosplenomegaly, and cytopenia. We present a delayed diagnosis of symptomatic LPI with a homozygous mutation in the *SLC7A7* gene.

Case presentation: A 15-year-old girl was referred to our clinic due to growth retardation and diarrhea. Physical examination showed short stature, retarded puberty, and hepatosplenomegaly. Laboratory tests showed normal complete blood count and biochemical analyses except elevated aspartate aminotransferase, triglyceride, total cholesterol, and ferritin. Peripheral blood smear and hemoglobin electrophoresis were within normal limits. Bone marrow analysis showed hemophagocytic cells. Postprandial ammonium level was found elevated. Low lysine, arginine, and ornithine and elevated glycine and alanine in plasma amino acid analysis and high amount of lysine and slightly elevated arginine and ornithine excretion in urine were detected. Molecular genetic analysis of the *SLC7A7* gene showed a previously reported homozygous mutation. Low protein diet, sodium benzoate, L-carnitine, low-dose L-citrulline, and calcium replacement were initiated. The patient is now in good condition still being followed up in our department.

Conclusions: LPI is a metabolic disorder with multi-systemic involvement that may have severe consequences if left untreated. Initiation of early treatment is essential for the prevention of severe chronic complications. Also, confirmation of the genetic defect may provide the parents to have healthy offsprings in the future with the help of genetic counselling and preimplantation genetics.

Keywords: Lysinuric protein intolerance, Short stature, Hemophagocytic lymphohistiocytosis

Background

Lysinuric protein intolerance (LPI) is an autosomal recessively inherited inborn error of metabolism (IEM) caused by the defect in the dibasic cationic amino acid (CAA) transporter found on the basolateral membrane of the lung, small intestine, and kidney. The dysfunction of this transporter occurs due to mutations in the *SLC7A7* gene. LPI may present as an acute hyperammonemic episode or as chronic symptoms. Clinical symptoms are feeding problems, vomiting and diarrhea, failure to thrive, hepatosplenomegaly (HSM), and cytopenia. Long-term complications include retarded puberty, short stature, interstitial lung disease, renal disease, hemophagocytic lymphohistiocytosis, and osteoporosis [1, 2].

We present a delayed diagnosis of symptomatic LPI with a homozygous mutation in the *SLC7A7 gene*.

Case presentation

ES is a 15-year-old girl who was followed up in an external clinic due to short stature and diarrhea. She is the

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eldest child of consanguineous parents (first degree cousins) with a healthy brother and was born full-term after an uneventful pregnancy. During early childhood, there were no health problems until age 7 when growth retardation was first noticed and was evaluated for elevated transaminases and ferritin levels. γ-Glutamyl transferase, coagulation parameters, lactate, viral and autoimmune markers, alpha-1-antitrypsine, ceruloplasmine, thyroid function tests, coeliac markers, somatomedin C, insulin-like growth factor binding protein-3, and sweat test were detected within normal limits. Plasma and urine amino acid analyses showed normal results. Abdominal ultrasonography showed HSM and grade I hepatosteatosis. Liver biopsy, gastric, and small bowel biopsy showed nonspecific findings. She had a seizure 3 years ago where electroencephalography showed focal epileptic activity on the temporal lobe, and simple partial epilepsy was diagnosed.

The patient was referred to our clinic for further evaluation. On admission, she was pale and had growth retardation. Her height and weight were 142.5 [− 2.8 standard deviation (SD); 2.4 SD below mid-parental height] and 36 kg [body mass index (BMI), 17.7 kg/m2, − 1.02 SD], according to World Health Organization reference values. Retarded puberty (Tanner stages were of G2, PH2) and HSM (the liver and spleen 3 cm below the costal margin) were noticed. Bone age was 4 years delayed (Greulich and Pyle). When medical history was deepened, it was found out that she rejected protein-rich foods since the time of weaning.

Laboratory tests showed normal complete blood count and biochemical analyses (including ammonium) except elevated aspartate amino transferase (55 U/L, normal range-NR 10–40), lactate dehydrogenase, (932 U/L, NR 70–250), triglyceride (325 mg/dL, NR < 130), total cholesterol (229 mg/dL, NR < 199), and ferritin 6180 ng/mL (7–140 ng/mL) levels. Peripheral blood smear and hemoglobin electrophoresis were within normal limits. Bone marrow analysis showed a few hemophagocytic cells (Figs. 1 and 2). Reducing substance of urine was negative. Abdominal ultrasonography showed HSM, grades I–II hepatosteatosis, and uterine hypoplasia. Severe osteoporosis was detected in the bone mineral density analysis (*Z* score − 6.1). Due to the history of protein aversion, postprandial ammonium level was checked that was found elevated (71 umol/L, NR 15–45). Acylcarnitine profile and urine organic acid analyses showed normal results. Low lysine (21 umol/L, normal range 105–214), arginine (6.68 umol/L, normal range 45–125), and ornithine (11.7 umol/L, normal range 105–500) and elevated glycine (363 umol/L, NR 148–324) and alanine (1187, NR 192–508) in plasma and high amount of lysine (532.4 umol/g cr, normal range 7–58) and slightly elevated arginine (29.61, NR 0–5) and ornithine (11.99, NR 0–5) excretion in urine were detected.

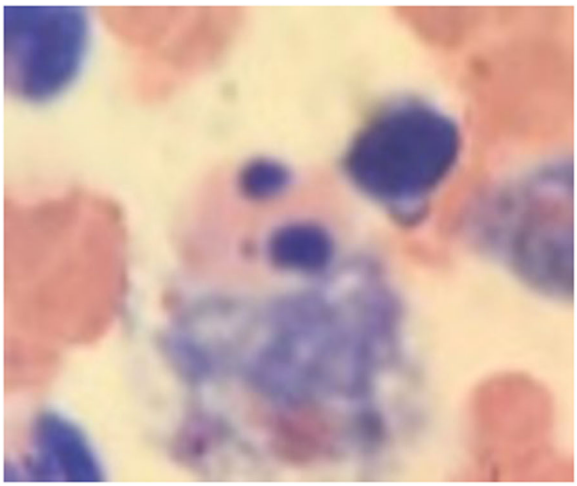

Fig. 1 Hemophagocytic cells detected in bone marrow aspirate

Since the metabolic test were suggestive of lysinuric protein intolerance, all coding and exon-intron boundaries of the *SLC7A7* gene were analyzed, which resulted a previously reported c.344_347delTTGC; p.Leu115fsX53 homozygous mutation. Low protein diet, sodium benzoate, L-carnitine, low-dose L-citrulline, and calcium replacement were initiated. The patient is now in good condition still being followed up in our department.

Discussion

LPI is a metabolic disorder with multi-systemic involvement that may have severe consequences if left untreated. Due to the defect of CAA transport, intestinal absorption and renal reabsorption are mainly affected, leading to shortage of lysine, arginine, and ornithine and dysfunction of the urea cycle, causing hyperammonemia.

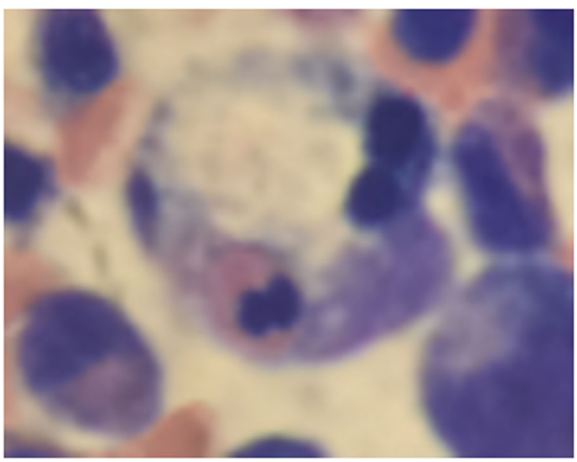

Fig. 2 Hemophagocytic cells detected in bone marrow aspirate

Other complications are thought to be related to the derangement in arginine metabolism. To date, 51 different mutations have been defined in the responsible *SLC7A7* gene, most of them consisting of single base substitutions or small deletions [1–4]. Although the underlying pathogenic mechanisms are not completely understood, intracellular l-arginine accumulation due to defective arginine efflux and increased nitric oxide (NO) production from l-arginine by NO synthases is one of the suggested factors.

The classical form of LPI begins in infancy after weaning, with feeding problems, refusal of protein rich foods, vomiting and diarrhea, failure to thrive, hypotonia, HSM, and cytopenia. Neurological problems, especially after protein-rich meals, including hypotonia, lethargy, ataxia, behavioral disorders, seizures, and coma due to hyperammonemia, may occur. Recurrent attacks of hyperammonemia may cause mental retardation. Osteoporosis can present due to malnutrition [1–3]. Long-term complications are retarded puberty, short stature, interstitial lung disease, (pulmonary alveolar proteinosis), renal disease, hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and osteoporosis [4, 5]. Impaired secretion of growth hormone has been described in a few patients [6]. Final height in treated LPI patients may be low normal due to prolonged growth and delayed bone age [7]. Liver failure may occur during severe MAS [1].

The biochemical findings are postprandial hyperammonemia, subclinical signs of macrophage activation (anemia, thrombocytopenia, or pancytopenia with hypofibrinogenemia, low levels of haptoglobin, high LDH, ferritin, and triglycerides) together with elevated transaminases. Abnormalities in plasma amino acid profile (low plasma levels of the cationic amino acids, arginine, ornithine, and lysine), high glutamine levels due to hyperammonemia, and hyperglycinemia due to malnutrition and increased urinary excretion of arginine, ornithine, lysine, and orotic aciduria are detected [1]. Permanent macrophage activation is responsible for the hematological abnormalities. Urine amino acid profile may be normal due to the malnutrition and become manifest after an oral loading test of citrulline [4]. Bone marrow smears may reveal erythroblastophagocytosis [1].

Misdiagnosis in patients of LPI (e.g. food allergies, celiac disease, enterocolitis, malabsorptive syndrome, autoimmune disorders) has been reported in the literature. It is thus important to recognize and treat the hyperammonemia early enough to be able to prevent further neurological damage and other complications [3].

The standard treatment for hyperammonemia in LPI involves low protein diet (0.7–1.2 g/kg/day), ammonia lowering nitrogen scavengers, and low-dose citrulline supplementation that controls hyperammonemia and improves nutritional status. Since large amount of citrulline may increase intracellular arginine synthesis, citrulline intake should be low (< 100 mg/kg/day). Hypolysinemia should be treated by oral lysine supplementation (20 mg/kg/day). L-Carnitine (due to carnitine depletion), vitamins, and micronutrients should be supplemented. Hyperlipidemia may require a specific treatment with HMG-CoA reductase inhibitors. Some patients may benefit form growth hormone supplementation [1–5].

The mutation detected in our patient, c.344_347delTTGC p.Leu115fsX53, was previously reported in a 15-year-old male patient with anorexia and vomiting, without any immunological abnormalities and apparent hemophagocytic syndrome. Similar to our patient, he also had growth retardation and severe osteoporosis [8].

Conclusion

LPI is a rare IEM with multi-systemic involvement and early recognition of symptoms, and initiation of treatment is essential for the prevention of severe chronic complications. Thus, the timing of diagnosis is extremely important, since the confirmation of the genetic defect may provide the parents to have healthy offsprings in the future with the help of genetic counselling and preimplantation genetics.

Abbreviations

LPI: Lysinuric protein intolerance; IEM: Inborn error of metabolism; CAA: Cationic amino acid; HSM: Hepatosplenomegaly; NO: Nitric oxide

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Authors' contributions

AO and LG prepared and checked the final draft of the manuscript. IY and RO collected laboratory data. GB has performed the metabolic test of the reported case and collected data. All authors have read and approved the manuscript entitled "Lysinuric protein intolerance: An overlooked diagnosis."

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Consent for publication

Written informed consent has been received from the mother of the patient for this case report and the figures to be presented.

Competing interests

None declared.

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