

CORRESPONDENCE

Lysinuric protein intolerance can be misdiagnosed as food protein-induced enterocolitis syndrome

DOI:10.1111/pai.12096

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a rising non-IgE-mediated food allergy triggered by specific food proteins (cow's milk, soy, and grains are the common offending foods). FPIES requires total elimination of the offending food from the diet and typically resolves by 3 yr of age (1). Metabolic disorders, such as lysinuric protein intolerance (LPI), are often underestimated in the differential diagnosis of FPIES. Although rare, these inherited conditions require different and life-long nutrition and dietary intervention to prevent impaired developments in infants. We present the case of an infant with LPI misdiagnosed as FPIES and discuss the similarities and differences between these two conditions.

A 12-month-old male infant, exclusively breastfed for the first 6 months of life, was admitted due to repetitive vomiting and diarrhea, commenced at 6 months after weaning began. These reactions typically occurred within 1–3 h after the consumption of the same foods—meat, chicken, fish, or eggs. None of these reactions were associated with bloody diarrhea, skin rash, angioedema, or dyspnea. Prior to our examination, the parents gradually eliminated these foods from his diet and reported an improvement in symptoms. The infant clinical and neurologic examinations were normal. A mild hepatosplenomegaly was revealed by an abdominal ultrasonography. Thyroid-stimulating hormone, free thyroxine, celiac serology, blood gases, ammonia, renal and liver functions, and urinalysis were all in the normal range. Only ferritin and LDH serum levels were very high (244 ng/ml and 1017 IU/l, respectively). A complete allergological work-up was performed, which came out negative for skin prick tests, patch

tests, and serum-specific IgE antibodies to the suspected foods (total IgE < 2 kU/l). A FPIES to solid food was diagnosed.

Due to the history of aversion to protein-rich foods associated with mild hepatosplenomegaly and very high ferritin and LDH serum levels, plasma and urinary amino acid analysis were carried out. The results showed in Table 1 led to a definitive diagnosis of LPI, which was confirmed by the molecular analysis of SLC7A7 gene (the patient was a homozygote with a missense mutation c. 1001T > G in SLC7A7 gene; his parents resulted heterozygous carriers of this mutation).

The child started a low-protein diet (1.5 g/Kg/day) and oral supplementation with citrulline (100 mg/kg/day), reporting no further gastrointestinal or neurologic symptoms after 6 months of good compliance with this therapy.

Lysinuric protein intolerance is a rare autosomal recessive defect of cationic amino acid (i.e. lysine, arginine, and ornithine) transport at the basolateral membrane of epithelial cells in intestine and kidney, which results in low activity of the urea cycle and possible episodes of hyperammonemia, particularly after ingesting protein-rich foods. The condition is caused by mutations in SLC7A7 gene (2, 3). Patients with LPI are usually asymptomatic while breast-feeding, but typically develop recurrent emesis and diarrhea during weaning, a few hours after being fed protein-rich foods. However, LPI can have a wide variability in its clinical manifestations, which range from aversion to protein-rich foods, failure to thrive and hepatosplenomegaly, to renal insufficiency, pulmonary alveolar proteinosis, and hematologic and immunologic abnormalities (4).

Table 1 Results of plasma and urinary amino acid analysis at diagnosis

Amino acids	Proband serum levels [†]	Reference range [†]	Proband urinary levels [‡]	Reference range [‡]
Lysine	62	115–278	247	10–56
Arginine	22.1	38–135	89.5	0–6
Ornithine	13.9	25–159	20.5	0–6
Cystine	38	25–62	6.7	4–12
Serine	247.6	92–181	82.3	23–69
Glycine	411.4	158–337	144.6	64–236
Citrulline	73.6	17–53	8.6	0–5
Glutamine	1025	399–823	190	20–112

[†]μmol/l.

[‡]mmol/mol of creatinine.

In less severe cases, the clinical presentation of LPI can mimic FPIES, which presents in the 1st yr of life with repetitive vomiting and/or diarrhea. These symptoms typically occur 2–6 h after ingesting proteins and tend to resolve after removal of the incriminated foods as well as to reoccur on re-exposure (5, 6). Both in FPIES and in LPI, skin prick tests and serum-specific IgE to the suspected foods are usually negative. In our opinion, the most important clinical feature that can help physicians distinguish these two conditions at onset is that LPI symptoms tend to develop after the consumption of any protein-rich food, whereas in FPIES, children typically react to a single or few foods (5). 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 (Table 1). Molecular confirmation of the condition via sequencing of the SLC7A7 gene is mandatory because long-term treatment for LPI requires protein-restricted diet, oral supplementation of citrulline, and life-long follow-up (2, 3). On the contrary, to date there are no *in vitro* tests capable of confirming FPIES. A diagnostic oral food challenge is the gold standard for FPIES. However, the diagnosis of FPIES can be also established on clinical grounds, if a small child or infant presents with repeated episodes of severe emesis upon ingestion of the same

foods and is well when the implicated food is eliminated from the diet (6).

In our case, the recurrence of emesis and diarrhea 1–3 h after consumption of the same foods misled the diagnosis toward FPIES. Moreover, the infant had no overt history of neurologic signs, or metabolic abnormalities. Nevertheless, the presence of hepatosplenomegaly, very high ferritin and LDH serum levels, and the aversion to protein-rich foods should have reinforced the suspicion of a metabolic disorder.

We suggest always considering metabolic disorders, such as LPI, in the differential diagnosis of repetitive vomiting and/or diarrhea which occur during weaning, 1–6 h after feeding, especially when solid foods are implicated.

Acknowledgment

The Authors are grateful to Ms Judyth Dillon for editing the English version of the manuscript.

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