CASE REPORT

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# Lysinuric protein intolerance with novel mutations in solute carrier family 7A member 7 in a Chinese family

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**ABSTRACT**

**Introduction:** Lysinuric protein intolerance (LPI) is a rare genetic disorder caused by mutations in the solute carrier family 7A member 7 (*SLC7A7*) gene.

**Case presentation:** We presented two siblings with LPI, carrying novel mutations of c.776delT (p.L259Rfs*18) and c.155G>T (p.G52V) in *SLC7A7*. The younger sibling, preferring protein-rich foods, showed severe symptoms, including alveolar proteinosis, macrophage activation syndrome, severe diarrhea, and disturbance of consciousness with involuntary movements. In contrast, the elder sibling only had mild symptoms, likely due to aversion to protein-rich food since toddler age.

**Conclusion:** LPI is a congenital genetic metabolic disease with multisystem involvement. Initiating appropriate protein-restricted diet therapy as soon as possible could help prevent the progression of LPI.

**KEYWORDS**

Diet, Lysinuric protein intolerance, Pulmonary alveolar proteinosis, SLC7A7

## INTRODUCTION

Lysinuric protein intolerance (LPI) is a rare autosomal recessive disorder caused by mutations in the solute carrier family 7A member 7 (*SLC7A7*) gene.[1] It is characterized by protein intolerance, secondary urea cycle disorders, and immune dysfunction after consuming protein-rich food in the post-weaning period.[2] Here, we report two siblings from a family with LPI who share the same genetic phenotype and exhibit similar clinical manifestations. However, the severity of their symptoms varies greatly due to differences in dietary intake.

## CASE REPORT

Patient 1: A previously healthy 23-month-old girl was admitted to the Emergency Intensive Care Unit of Beijing Children's Hospital with a history of fever for 26 days, shortness of breath for 15 days, and cyanosis for 1 day. Physical examination revealed rough skin, poor skin elasticity, non-itchy skin rash, dark skin on extremities with partial hyperpigmentation or depigmentation, nail fold telangiectasia, small limb muscle volume, abdominal distention, and hepatosplenomegaly. Chest high-resolution computed tomography (HRCT) showed diffuse pulmonary

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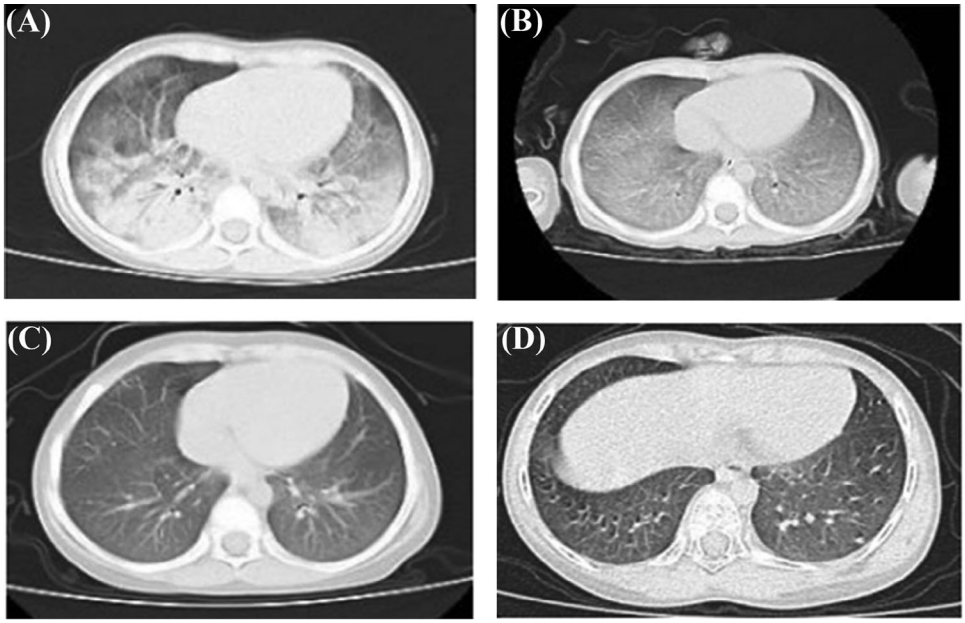


**FIGURE 1** The manifestations of chest HRCT in the two patients with lysinuric protein intolerance. (A) Patient 1, before admission, chest HRCT showed diffuse grid-like shadows and ground-glass opacity shadows in both lungs and large areas of consolidation in the dorsal lung segments. (B) Patient 1, after immunotherapy, consolidations in both lungs were absorbed, but diffuse interstitial lesions worsened. (C) Two months post-discharge, after total diet therapy and alveolar lavage, bilateral diffuse grid-like shadows significantly improved for Patient 1. (D) Patient 2's initial chest HRCT showed decreased transmittance in bilateral lower lungs and faint dot shadow. HRCT, high-resolution computed tomography.

interstitial lesions with consolidations in the dorsal segments of both lungs (Figure 1A). Laboratory tests showed $PaO_2$ 59.3 mmHg ($FiO_2$ 60%), white blood cell count of $1.79\times10^9$/L. Her ferritin (1043.6 ng/ml), lactate dehydrogenase (LDH) (2126 U/L), triglyceride (3.36 mmol/L), sCD25 (12 413 pg/ml), and erythrocyte sedimentation rate (ESR) (86 mm/h) were all raised. Positive antinuclear antibodies and anti-extractable nuclear antigens (ENA) were observed (Table 1). The blood amino acid result was atypical. The patient was initially diagnosed with juvenile dermatomyositis (JDM) with interstitial pneumonia and macrophage activation syndrome (MAS) based on fever for more than 7 days, splenomegaly, hemocytopenia, hypertriglyceridemia, elevated serum ferritin, and elevated sCD25.[3] The initial treatment included invasive mechanical ventilation, bronchoscopy lavage, antibiotics, methylprednisolone, immunoglobulin, and cyclophosphamide. Although the patient's temperature, rash, and nailfold telangiectasia improved after the immunotherapy, her pulmonary interstitial lesions deteriorated (Figure 1B). The patient developed new symptoms, including abdominal distension, severe diarrhea, and neurological symptoms such as consciousness disorders and involuntary movements after fasting and total parenteral nutrition. On the 21st day of hospitalization, genetic testing confirmed the diagnosis of LPI based on novel compound heterozygous mutations in *SLC7A7*, inherited from her mother [c.776delT (p.L259Rfs*18)] and her father [c.155G>T (p.G52V)], respectively. According to ACMG guidelines, c.776delT (p.L259Rfs*18) was predicted to be 'Likely pathogenic', while c.155G>T (p.G52V) to be 'Uncertain'. We traced the blood amino acid level at admission, and found elevated alanine, with arginine, ornithine and citrulline at the lower limit of the normal range, and glycine and proline at the upper limit of normal range. The urine analysis, collected after parenteral nutrition and before citrulline intake, showed that elevated levels of arginine, ornithine, and citrulline (Table 1). The treatment was adjusted to a protein-restricted diet (1–1.5 g/kg per day), supplemented with citrulline (100 mg/kg per day) and L-carnitine (100 mg/kg per day). The patient also underwent whole-lung lavage, further confirming the presence of pulmonary alveolar proteinosis (PAP). After adjusting treatment, the patient's gastrointestinal and neurological symptoms gradually improved, and oxygen support was withdrawn. Two months after discharge, a follow-up chest HRCT showed significant improvement in the pulmonary interstitial lesions (Figure 1C). In the latest follow-up, after 18 months dietary treatment, the patient showed no other obvious clinical symptoms except for short stature.

Patient 2: A 5-year-old girl, the elder sister of Patient 1, has refused to eat any protein-rich foods since she was a toddler. She exhibited some similar symptoms to her younger sister, including short stature, malnutrition, small muscle volume, skin hyperpigmentation, and depigmentation, as well as hepatosplenomegaly. Laboratory examination results also showed leukopenia, neutropenia, elevated ferritin, and LDH

**TABLE 1** Clinical manifestations and auxiliary examinations of the two patients with lysinuric protein intolerance

| Characteristic | Patient 1 | Patient 2 |
|---|---|---|
| Age at presentation | 23 m | 5 y |
| Diet | Protein-rich foods | Aversion to protein-rich foods |
| Weight, kg (%) | 10 (5.3)† | 13 (0.1)† |
| | 13.5 (14.4)‡ | 15.8 (0.7)‡ |
| Length, cm (%) | 82 (6.8)† | 100 (0.5)† |
| | 91 (1.1)‡ | 105 (0.1)‡ |
| Skin | Rough and stiff skin, poor elasticity; dark skin on extremities; hyperpigmentation and depigmentation; nailfold telangiectasia, systemic congestive rash | Rough skin, poor elasticity; dark skin on extremities; hyperpigmentation and depigmentation |
| Muscle | Small muscle volume on extremities; myogenic lesions of biceps, tibialis anterior, quadriceps | Small muscle volume on extremities |
| Respiration system | Alveolar proteinosis; severe respiratory failure | Mild subclinical pulmonary interstitial changes |
| Digestion system | Bloating; diarrhea; hepatosplenomegaly | Hepatosplenomegaly |
| Nerve system | Consciousness disturbance; involuntary movement of extremities | Normal |
| Blood test | | |
| White blood cell ($\times10^9$/L) | 1.79 ↓ | 2.9 ↓ |
| Neutrophils ($\times10^9$/L) | 0.62 ↓ | 1.42 ↓ |
| Hemoglobin (g/L) | 71 ↓ | 106 ↓ |
| Platelet ($\times10^9$/L) | 263 | 190 |
| Erythrocyte sedimentation rate (mm/h) | 86 ↑ | 17 |
| Ferritin (ng/ml) | 1043.6 ↑ | 386.6 ↑ |
| Fibrinogen (g/L) | 1.49 ↓ | 2.44 |
| Cholesterol (mmol/L) | 6.43 ↑ | 4.83 |
| Triglycerides (mmol/L) | 3.36 ↑ | 1.66 |
| Lactate dehydrogenase (U/L) | 2126 ↑ | 561 ↑ |
| NH3 (μmol/L) | 59 | 63 |
| Bone marrow | Active myeloproliferation | NA |
| Autoantibody | ANAs 1:160; ENA (+++); SSA (+); Ro52 (+++); ds-DNA (±); AnuA (±); CENPB (±); AMA-M2 (±); Jo-1 (-); c-ANCA (-); p-ANCA (-) | ANAs (-); ENA (±); SSA (±) |
| Metabolism | | NA |
| Blood amino acid (μmol/L) | Arginine 7.47 (Ref. 1.00–70.00) | |
| | Ornithine 8.88 (Ref. 7.00–120.00) | |
| | Citrulline 9.30 (Ref. 1.79–45.00) | |
| | Alanine 490.20 (Ref. 50.00–450.00) ↑ | |
| | Glycine 394.90 (Ref. 65.00–450.00) | |
| | Proline 2426.00 (Ref. 250.00–2500.00) | |
| | Glutamine 85.34 (Ref. 8.40–92.70) | |

(Continues)

**TABLE 1** (Continued)

| Characteristic | Patient 1 | Patient 2 |
|---|---|---|
| Urine amino acid (μmol/L)[§] | Arginine 21.18 (Ref. 0.45–7.47) ↑ | |
| | Ornithine 6.78 (Ref. 0.30–5.50) ↑ | |
| | Citrulline 14.85 (Ref. 1.28–13.00) ↑ | |
| | Glutamine 264.10 (Ref. 2.39–41.90) ↑ | |

[†]The weight or height percentile in children of the same age and gender at presentation.
[‡]The weight or height percentile in children of the same age and gender 18 months after treatment.
[§]Results after total parenteral nutrition.
Abbreviations: ANAs, antinuclear antibodies; AnuA, anti-nucleosome antibody; AMA-M2, anti-mitochondrial M2 antibody; CENPB, anti-centromere protein B antibody; c-ANCA, classic antineutrophil cytoplasmic antibody; ENA, extractable nuclear antigen antibodies; Jo-1, anti-histidyl transfer RNA synthetase antibody; m, month; NA, not applicable; p-ANCA, perinuclear ANCA; Ro52, SSA-52 kDa; SSA, anti-Sjogren's syndrome-related antigen A; y, year.

levels, and positive ENA and SSA antibodies (Table 1). However, she had no signs or symptoms of rash, nail fold telangiectasia, neurological abnormalities, dyspnea, or hypoxemia. Chest HRCT showed mild subclinical pulmonary interstitial changes (Figure 1D). Genetic testing revealed the same compound heterozygous mutations in *SLC7A7* as observed in Patient 1, confirming the diagnosis of LPI. She was also treated with a protein-restricted diet.

## DISCUSSION

The *SLC7A7* gene is located on chromosome 14q11.2, which encodes the light chain of the $y^+$L-type basic amino acid transporter 1 ($y^+$LAT1).[4] Here, we report two novel variants in the *SLC7A7* gene in two siblings with LPI. Both girls displayed identical genetic phenotypes and similar clinical manifestations, but the severity of their symptoms varied greatly, likely due to the difference in dietary intake.

PAP is one of the main and life-threatening pulmonary complications of LPI.[5,6] Patient 1 presented with severe PAP, whereas Patient 2 exhibited only mild subclinical pulmonary interstitial changes, which could indicate an early stage of PAP. PAP primarily arises from the increased secretion or clearance issue of pulmonary surfactant (PS), resulting in the accumulation of lipoprotein PS in the alveoli.[7] The pathogenesis of PAP secondary to LPI is not fully understood. Granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling may be involved in the pathological process of LPI.[8–10] However, *in vitro* experiments have shown that the presence of *SLC7A7* mutations did not interfere with the GM-CSF-induced macrophage phenotypes and differentiation process.[10,11] The initial administration of parenteral nutrition increased the intake of amino acids in Patient 1, leading to acute exacerbation of pulmonary interstitial lesions. However significant improvement was observed after using a protein-restricted diet and whole-lung lavage treatment. Patient 2, who has been refusing to eat protein-rich foods such as meat and eggs since toddler age, showed less severe pulmonary lesions compared to Patient 1. Therefore, it is speculated that the accumulation of lipoprotein PS caused by amino acid metabolism disorder may be the primary cause of PAP in LPI.

Autoimmune disease is another serious complication in LPI patients. The most common clinical manifestations include MAS/hemophagocytic lymphohistiocytosis (HLH) and systemic lupus erythematosus.[12,13] The pathological mechanism of LPI-related MAS/HLH remains inconclusive. It is speculated that this may be associated with the interference of the *SLC7A7* gene with macrophage function, as well as the direct involvement of $y^+$LAT1 in cytokines recruitment.[11,14,15] The manifestations of Patient 1 were consistent with those of MAS, accompanied by positive autoantibodies, muscle and skin changes, and hepatosplenomegaly. She was initially diagnosed with JDM. After immunotherapy, the ferritin, LDH, triglyceride, and ESR levels significantly decreased, suggesting that immunotherapy may be effective for LPI-related MAS/HLH. Previous studies on LPI have not reported similar skin manifestations. Her skin changes improved after immunotherapy and dietary adjustments. Thus, we speculate that skin changes may also be related to LPI.

Neurological symptoms, such as drowsiness and coma, are common in LPI patients and are usually caused by secondary urea cycle disorders after protein-rich food intake.[16] In Patient 1, neurological symptoms were not accompanied by elevated blood ammonia and spontaneously improved after diet adjustment. During admission, her head MRI showed brain atrophy, while lumbar puncture, electroencephalogram, and visual evoked potential were all normal. These transient neurological symptoms have not been reported before.

In LPI, typical amino acid changes involve reduced levels of basic amino acids (lysine, arginine, ornithine) in blood, while neutral amino acids may increase. Given the involvement of arginine and ornithine in the urea cycle, citrulline levels in the blood may decrease, and the excretion of basic amino acids in urine should increase.[3,17]

However, in Patient 1, blood amino acid analysis did not provide sufficient clues for early diagnosis. Due to the inability to quantitatively analyze lysine, lysine levels in these two patients remain unclear. For most LPI patients, changes in amino acid metabolism levels are often atypical, contributing to the delayed diagnosis of LPI.

Currently, there is no specific medication for LPI, and treatment primarily involves dietary therapy and managing symptomatic complications.[18] However, in 2019, the first allogeneic hematopoietic stem cell transplantation performed for an LPI patient showed promise as a therapeutic approach.[19] Further understanding of the pathological mechanism of LPI, as well as optimization and updating treatment regimens, may improve the quality of life for LPI patients.

## CONSENT FOR PUBLICATION

The patients' guardians provided informed consent for publication.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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