An Adolescent Case of Citrin Deficiency With Severe Anorexia Mimicking Anorexia Nervosa

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abstract

We report a 12-year-old female citrin-deficient patient presenting with severe anorexia and body weight loss, mimicking the restricting type of anorexia nervosa (AN). She showed normal development until age 10 years when she started to play volleyball at school. She then became gradually anorexic, and her growth was stunted. At age 12, she was admitted to hospital because of severe anorexia and thinness. She was first thought to have AN, and drip infusion of glucose solution and high-calorie drinks were given, but her condition deteriorated further. She had a history of neonatal hepatitis and was therefore suspected to have citrin deficiency (CD). Genetic analysis of \textit{SLC25A13} revealed that she was compound heterozygous for 851del4 and IVS16ins3kb, and a diagnosis of CD was made. A low-carbohydrate diet with oral intake of arginine and ursodeoxycholic acid was started, and her condition gradually improved. The clinical features in our patient were similar to those of AN, and therefore AN may also be an important clinical sign in adolescent patients with CD.

Citrin deficiency (CD) is an autosomal recessive disorder caused by biallelic mutations of the \textit{SLC25A13} gene encoding citrin, a liver-type aspartate/glutamate carrier (AGC) on mitochondria.\textsuperscript{1,2} AGC provides aspartate for the synthesis of urea, protein, and nucleotides, in addition to participating in gluconeogenesis from lactate and transporting cytosolic dihydronicotinamide adenine dinucleotide-reducing equivalents into mitochondria as part of the malate-aspartate shuttle.\textsuperscript{3} Hence, citrin deficiency results in accumulation of cytosolic dihydronicotinamide adenine dinucleotide during glycolysis, and citrin-deficient patients avoid excessive carbohydrate in the diet.\textsuperscript{3}

NICCD has been reported as a self-limiting condition, with clinical presentation resolving in $<1$ year.\textsuperscript{3,4} Usually, citrin-deficient patients become apparently healthy without obvious clinical symptoms, but several studies have indicated that some CD patients at this stage can also show several clinical symptoms, such as pallor, drowsiness, fatigue, and headache.\textsuperscript{3} Here, we report a unique adolescent CD patient who presented with severe anorexia and thinness, mimicking the restricting type of anorexia nervosa (AN).

CASE REPORT

The patient was a 12-year-old Japanese girl who was born from nonconsanguineous parents, at 41 weeks' gestation, weighing 2886 g. At age 1 month, she was admitted to Nagano Red Cross Hospital because of...
severe jaundice, failure to thrive (FTT) and white stool. Raised levels of serum total bilirubin, transaminases, alkaline phosphatase, and γ-glutamyl transpeptidase (γ-GTP) were detected (Table 1), and therefore, she was thought to have biliary atresia (BA). Liver biopsy demonstrated fibrosis with lymphocytic infiltration in the portal area (Fig 1). The possibility of BA was excluded, but the etiology of her hepatitis remained unknown. Her abnormal liver function spontaneously ameliorated, and she had been healthy since age 1 year. During infancy, she consumed little sweets or rice but liked milk and beans. In this period, growth retardation was unremarkable, and her breast development and growth spurt began normally at the age of 10 (Fig 2). Her personality was well behaved, and she had always eaten the school lunch containing high levels of carbohydrates with dietary energy ratio >50%. She was fond of sports and started to play volleyball at age 10 years, which she practiced every other day after school. Only rice balls were permitted as snacks during volleyball practice, but she disliked them. She asked her coach if she could bring other foods, but this was not allowed. In addition, she was bullied at school, and her food intake gradually decreased. Her body weight decreased from 33 kg to 26 kg over 1 year from age 11, but she was highly active with exercise and playing volleyball, without any body image distortion. Despite normal development of secondary sexual characteristics, she had not yet had her first menstrual period. Subsequently, her food intake further decreased, and she could not even drink milk. At age 12, she took little food or drink and was admitted to our hospital.

On admission, she was thin and looked unwell. Her height was 142 cm and weight was 25 kg (BMI 12.4) (Fig 2). Downy hair was seen on the arms and legs, and her pulse rate was 50 beats per minute. Laboratory data are summarized in Table 1. She was initially diagnosed with the restricting type of AN, associated with

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient’s Neonatal and Adolescent Laboratory Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 mo, 3–10 kg</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>10.9</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>6.1</td>
</tr>
<tr>
<td>Total bile acid (µmol/L)</td>
<td>331</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>107</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>48</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>3526</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>203</td>
</tr>
<tr>
<td>α-fetoprotein (ng/mL)</td>
<td>194 350</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>4.6</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.1</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>278</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>186</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.7</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>4830</td>
</tr>
<tr>
<td>Citrulline (nmol/mL)</td>
<td>ND</td>
</tr>
<tr>
<td>Threonine/serin</td>
<td>ND</td>
</tr>
<tr>
<td>Ammonia (µmol/L)</td>
<td>102</td>
</tr>
<tr>
<td>PSTI (ng/mL)</td>
<td>ND</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; γ-GTP, γ-glutamyl transpeptidase; ND, no data; PSTI, pancreatic secretory trypsin inhibitor.

* Neonatal hepatitis period.

* On admission for anorexia.

* The ratio of hepatic ALP isozyme (ALP2) was raised to 75% (normal 36%–74%), and ALP1 was also detected (11%). In contrast, the ratio of ALP3 decreased to 13% (normal 25%–59%).

FIGURE 1
Histologic findings of liver tissue at the age of 1 month. A. Hematoxylin and eosin staining, ×200. B, Azan-Mallory staining, ×100. C, Periodic acid–Schiff staining, ×200. D, Berlin blue staining, ×200. Lymphocytic infiltration and fibrosis in the portal area were noted. In addition, ballooning of hepatocytes with glycogen granules and accumulation of hemosiderin (arrows) were seen.
some mental stress. Because she could not take food, a drip infusion containing 5% glucose was administered. Four days after admission, she was provided a high-calorie drink containing high levels of carbohydrate. She became slightly pale and showed no vigor the following day. Enteral nutrition containing 85% carbohydrate was given via a nasal-gastric tube. Twenty-five days after admission, she could take 1500 kcal a day by drip infusion and hospital diet. She still looked very ill, and white stools and dark urine were noted. Her mother remembered that she showed similar symptoms in her neonatal period.

Serum level showed γ-GTP and the percentage of hepatic alkaline phosphatase isozymes were elevated, and raised plasma levels of ammonia and citrulline were also detected (Table 1). Abdominal computed tomography revealed no fatty liver or malignant mass, but periportal collar sign was recognized. Because serum pancreatic secretory trypsin inhibitor, a diagnostic marker of CTLN2,5 was also high, she was suspected of having CD. After obtaining informed consent, genetic analysis of SLC25A13 was carried out, confirming that she was a compound heterozygote of 851del4 and IVS16ins3kb, both of which are common mutations in Japan,1,6 and a diagnosis of CD was made. The effective treatment of CTLN2 has been performed to this CD patient with anorexia. A high-protein, low-carbohydrate diet (protein/fat/carbohydrate energy ratio 20%/40%/40%) was begun,7 and urso-deoxycholic acid (40–80 mg/day) and arginine granules8 (5 g/day) were also provided. In addition, oral administration of sodium-pyruvate (1–5 g/day)9,10 was started with approval by Institutional Review Board of Shinshu University, and medium-chain triglyceride was begun,11 but they were soon stopped because she disliked taking them. However, low-carbohydrate diet therapy with oral intake of arginine and urso-deoxycholic acid was effective, and her abnormal data including serum biliary enzymes, albumin, and plasma ammonia improved 90 days after admission (Table 1).

Dyslipidemia was not detected at first, but subsequently serum level of total cholesterol was elevated to 279 mg/dL. Fasting plasma levels of acyl ghrelin and des-acyl ghrelin, which are peptides associated with appetite,12 were 41.59 fmol/mL (control: 22.30 ± 2.16 fmol/mL) and 400.84 fmol/mL (control; 230.8 ± 20.01 fmol/mL), respectively.

Although her weight dropped to 22.5 kg, it again increased to 27 kg at age 13 years, which was still below the mean weight for her age (Fig 2). She was discharged and returned to home and school taking urso-deoxycholic acid and arginine granules.

**DISCUSSION**

In this patient, analysis of the SLC25A13 gene confirmed the diagnosis, and therefore her neonatal hepatitis was attributable to NICCD. Until age 10, she had been well without any clinical symptoms and had attained average height and weight. Puberty also started at age 10 years (Fig 2). However, after
starting to play volleyball, her growth was retarded with decreased food intake, mimicking the restricting type of AN, which is characterized by severe emaciation with chronic food restriction secondary to an strong desire for thinness and fear of obesity. As our patient seemed to have neither desire for thinness nor fear of obesity, she did not completely meet the diagnostic criteria of AN (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Although the pathophysiological mechanism of AN is not fully understood, it is known that plasma ghrelin level is usually elevated in patients with the restricting type of AN. Ghrelin is an orexigenic hormone and is involved in stimulating gastrointestinal motility and emptying. In particular, a fasting plasma level of des-acyl ghrelin, which is des-acylated form of acylated ghrelin, has been reported to be significantly elevated in restricting type of AN patients, compared with control subjects. In our patient, the fasting plasma level of the des-acyl ghrelin was markedly elevated, and therefore the patient’s pathophysiological condition may have been similar to that in AN patients.

The clinical picture and pathophysiology of pre-CTLN2 and post-NICCD stage in CD patients has remained largely unclear. This period has been considered “an apparently healthy period” in which patients with CD would have no clinical symptoms. However, recent studies have revealed that patients in this stage can show diverse clinical symptoms. In particular, most CD patients in this period feel more fatigue compared with healthy children. In addition, high levels of oxidative stress were observed in patients with CD during this period, and these data suggest that this stage is by no means a dormant stage of the disease. FTT or FTT and dyslipidemia have also been reported as a cardinal feature of CD during the NICCD state and the following “healthy” state, from age 1 to 5 years. However, no cases of CD presenting with severe anorexia and thinness, similar to AN, have been reported. Our patient thrived until age 10 when she started to play volleyball (Fig 2); before school age and after the NICCD state, FTT had not been observed in our patient. Our patient always ate her school lunch and was forced to eat rice balls during volleyball practice. After changing dietary habits, she seemed gradually to lose her appetite and weight. A previous study indicated that carbohydrate intake was selectively reduced in the diet of most subjects with CD, compared with that of the general population. Whereas the protein/fat/carbohydrate ratio of the general Japanese population is 14% to 15%, 25% to 30%, and 54% to 58%, respectively, that of the CD subjects is 19% ± 2%, 44% ± 5%, and 37% ± 7%, respectively. This carbohydrate aversion in CD is unique in contrast to the protein aversion in other urea cycle enzyme deficiencies and is assumed to be directly linked to CD. Lee et al reported 2 teenage CD siblings with FTT, which started after dietary change to a low-fat or a low-protein diet to control dyslipidemia or hyperammonemia. Hence, in our patient, in addition to mental stress, a dietary change to a high-carbohydrate diet may have resulted in worsening of CD, inducing development of severe anorexia with loss of body weight, mimicking AN. In our patient, abnormal serum lipid level was seen 3 months after admission (age 12 years 4 months in Table 1), and therefore, the clinical picture may be similar to FTT and dyslipidemia, which developed in adolescence. Together with 2 teenage CD patients with FTT and dyslipidemia described by Lee et al, the diagnosis of this adolescent with CD suggests that FTT and dyslipidemia may also be one of the cardinal clinical features in teenage CD patients. Finally, the unique dietary characteristics in CD patients should be more widely understood because a forced change in their dietary habits can result in aggravation of the pathophysiology in CD. In addition, we emphasize that the possibility of CD should always be considered in adolescent patients suffering from AN, especially those with unique food preferences and/or a history of neonatal hepatitis, because alimentation with high-calorie solutions containing glucose can cause further deterioration of their condition.

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ABBREVIATIONS

AN: anorexia nervosa
CD: citrin deficiency
CTLN2: adult-onset type II citrullinemia
FTT: failure to thrive
NICCD: neonatal intrahepatic cholestasis caused by citrin deficiency
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