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Case Report

Primary carnitine deficiency with severe acute hepatitis following rotavirus gastroenteritis☆

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ABSTRACT

Rotavirus infection is a major cause of gastroenteritis, which occurs mainly in children. Liver dysfunction due to rotavirus gastroenteritis has been reported; however, acute hepatitis due to this disease is very rare. We present a rare case in which rotavirus gastroenteritis led to sequential diagnosis of acute hepatitis and systemic primary carnitine deficiency (CDSP) in a 1-year-old girl. The patient's symptoms (hypoglycemia, hepatomegaly, and elevated levels of serum transaminases and creatinine kinase) suggested a steatosis causing liver dysfunction. She was initially considered to have a beta oxygenation defect or secondary carnitine deficiency caused by pivalic acid-containing antibiotics; however, repetitive carnitine analysis and free carnitine clearance measurement confirmed primary carnitine deficiency (carnitine transporter deficiency). Children with severe liver dysfunction due to rotavirus infection and presenting with liver steatosis should undergo blood acyl carnitine analysis to detect potential carnitine or other beta oxidation deficiencies, especially if newborn screening for these diseases is not available.

1. Introduction

Rotavirus is a major causative agent of gastroenteritis, which occurs mainly in children. Liver dysfunction due to rotavirus gastroenteritis has been reported [1]; however, acute hepatitis due to this disease is very rare [2]. We present a case in which rotavirus gastroenteritis, caused acute hepatitis that led to a diagnosis of systemic primary carnitine deficiency (CDSP, also known as carnitine transporter deficiency) in a 1-year-old girl.

2. Case report

A previously healthy 1-year-old girl experienced recurrent vomiting and watery diarrhea for 5 days before hospitalization. Prior to hospitalization, she had received cefcapene pivoxil hydrochloride hydrate (CFPN-PI, 90 mg/kg per day for 4 days) and intravenous hydration with glucose (twice) at a clinic. Although her symptoms had transiently subsided, vomiting recurred the day before hospitalization, and she was admitted to our hospital for acute gastroenteritis with dehydration and liver dysfunction.

The patient was delivered at a gestational age of 38 weeks with a birth weight of 3210 g. She was the first-born child of non-consanguineous parents. The newborn screening performed for

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDSP, systemic primary carnitine deficiency; CDTR-PI, cefditoren pivoxil; CFPN-PI, cefcapene pivoxil; CPT-2, carnitine palmitoyl transferase 2; CT, computed tomography; OCTN-2, organic carnitine/carnitine transporter 2.

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her on day 5 was normal, but acylcarnitine profiling was not performed because she was born before the commencement of the expanded newborn tandem mass screening in Japan. Her growth rate and developmental history were normal. She only had an infectious history of exanthem subitum. There was no history of vomiting, diarrhea, or hypoglycemia until this episode. She had a documented history of vaccination with BCG, diphtheria-pertussis-tetanus, oral polio and measles-rubella vaccine. She did not have rotavirus vaccination. Her family history did not include any inheritable metabolic diseases.

On admission, her sensorium was clear; however, her general condition was poor, and she had generalized edema. Her vital signs were as follows: temperature, 37.2 °C; heart rate, 126 beats/min; blood pressure, 93/57 mmHg; and respiratory rate, 30 breaths/min. Neurological and chest examinations showed no abnormalities. Her abdomen was soft and distended, with hypoactive bowel sounds. Her liver was hard, enlarged, and palpable 7 cm under the right hypochondrium. Her spleen was not palpable.

Laboratory blood testing on admission (Table 1) showed a leukocyte count of 9.4 × 10^9/L; hemoglobin level, 10.8 g/dL; and platelet count, 190 × 10^9/L; C-reactive protein was negative. Her serum electrolytes were normal; however, she presented with a low serum calcium, 7.7 mg/dL. Though her creatinine level was normal, her blood urea nitrogen level was elevated to 24 mg/dL. Total protein, 5.2 g/dL and albumin, 3.7 g/dL testing indicated low levels. In addition, the following serum transaminases were elevated: aspartate aminotransferase (AST), 977 U/L; alanine aminotransferase (ALT), 748 U/L; and lactate dehydrogenase, 1142 U/L. Serum creatinine kinase was also elevated to 1033 mg/dL. However, total bilirubin, direct bilirubin, and ammonia were at normal levels. The patient also had hypoglycemia with a plasma glucose level of 57 mg/dL. Levels of serum ketone bodies were not measured. Urinalysis results were negative for sugar, protein, occult blood, and ketones. The rotavirus antigen was detected in a stool specimen. The patient tested negative for other viruses that could cause hepatic function disorders (e.g., hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus).

Table 1
Laboratory data on admission.

WBC count	9.4	(normal, 4–8)	×10^9/L
Neutrophils	43.8	(normal, 40–70)	%
Lymphocyte	48.3	(normal, 25–55)	%
RBC count	3.74	(normal, 3.5–5)	×10^{12}/L
Hb	10.4	(normal, 12–15)	g/dL
Ht	32.8	(normal, 35–45)	%
Platelet count	190	(normal, 150–350)	×10^9/L
PT	14.5	(normal, 11–14)	s
PT	52	(normal, ≤80)	%
aPTT	31	(normal, 22–37)	s
Fibrinogen	60	(normal, 150–400)	mg/dL
D-dimer	1.2	(normal, 1≥)	μg/mL
Na	134	(normal, 136–148)	mmoL/L
K	5.1	(normal, 3.6–5)	mmoL/L
CL	99	(normal, 98–109)	mmoL/L
Ca	7.7	(normal, 8.8–10.8)	mg/dL
TP	5.2	(normal, 6.5–8)	g/dL
Alb	3.7	(normal, 3.8–5.3)	g/dL
T-Bil	0.69	(normal, 0.3–1.2)	mg/dL
D-Bil	0.45	(normal, 0.05–0.4)	mg/dL
AST	977	(normal, 8–38)	U/L
ALT	748	(normal, 4–44)	U/L
LDH	1142	(normal, 106–220)	U/L
γGT	61	(normal, 12–73)	U/L
T-Chol	116	(normal, 140–239)	mg/dL
CK	1033	(normal, 40–182)	mg/dL
BUN	24	(normal, 8–19)	mg/dL
Cr	0.32	(normal, 0.5–0.9)	mg/dL
UA	7.8	(normal, 2.6–6)	mg/dL
NH_3	67	(normal, 20–80)	mg/dL
Glu	57	(normal, 70–110)	mg/dL
CRP	0.04	(normal, 0.2≥)	mg/dL

WBC indicates white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; PT, prothrombin time; aPTT, activated partial thromboplastin time; Na, sodium; K, potassium; CL, chloride; Ca, calcium; TP, total protein; Alb, albumin; T-Bil, total bilirubin; D-Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γGT, γ-glutamyltransferase; T-Chol, total cholesterol; CK, creatinine kinase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; NH3, ammonia; Glu, glucose; CRP, C-reactive protein.

The patient was diagnosed with rotavirus gastroenteritis and liver dysfunction for which she received isotonic fluid infusions with glucose and liver-supporting therapy. After treatment, the vomiting stopped, and her general condition improved; however, the generalized edema persisted. Moderately low albumin (3.7 g/dL), total cholesterol (116 mg/dL), and fibrinogen (60 mg/dL) levels at the initial blood examination indicated impaired protein synthesis in the liver. On abdominal plain computed tomography (CT), the liver was markedly enlarged, with diffuse low absorbance throughout (Fig. 1A). Acute hepatitis was diagnosed, and fatty liver disease was suspected.

The patient was placed on a low-fat diet with glucose infusion. Ammonia levels did not increase during this treatment, and there was no disturbance of consciousness. After treatment, total cholesterol and fibrinogen levels gradually normalized. Liver function improved (AST, 110 U/L; ALT, 178 U/L) on hospital day 12, and she was discharged on hospital day 14.

Consistent with fatty liver disease, the patient had hypoketotic hypoglycemia, hepatomegaly, and elevated serum transaminase and creatinine kinase levels. We suspected that a beta oxidation deficiency or secondary carnitine deficiency, perhaps due to the CFPN-PI she had received at the clinic, accounted for the fat accumulation in the liver. In support, tandem mass spectrometry at the time of hospitalization showed that the free carnitine level in plasma was extremely low (1.55 nmol/mL; cut off, <8.0 nmol/mL).

A blood examination 3 months after discharge did not reveal any abnormalities (e.g., blood counts and transaminase and creatine kinase levels were normal and plasmatic coagulopathy was not detected). Abdominal CT showed normal liver size and density (Fig. 1B). However, the free carnitine level was still low (1.50 mmol/L) and the free carnitine clearance rate was high (46.7%; normal range, <2%) despite the absence of any medications during this time. Hence, CDSP was diagnosed, which was confirmed by the low enzymatic activity of organic carnitine/carnitine transporter 2 (OCTN-2) in skin fibroblasts. Moreover, sequencing of the *SLC22A5* gene, which encodes OCTN-2, revealed a heterozygous C to T mutation in codon 1394 (protein, V465A) and an exon 1 deletion (Fig. 2). Oral levocarnitine (L-carnitine, 100 mg/kg per day) was administered, and the free carnitine level increased to 11.6 mmol/L.

The patient's parents provided informed consent for the publication of this case report.

3. Discussion

Carnitine carries long-chain fatty acids across mitochondrial membranes to the mitochondrial matrix, where they are broken down via beta oxidation. When carnitine levels are low, beta oxidation is restricted, resulting in energy depletion and hypoglycemia during prolonged starvation. CDSP is an autosomal recessive disorder in which carnitine transporters such as OCTN-2 are defective. It is typically characterized by hypoketotic hypoglycemia, hepatomegaly, elevated transaminase levels, and hyperammonemia in infants; skeletal myopathy, elevated creatine kinase levels, and cardiomyopathy in children; and fatigability in adults [3]. However, in many patients, it is asymptomatic. Carnitine deficiencies such as CDSP are often misdiagnosed as Reye syndrome

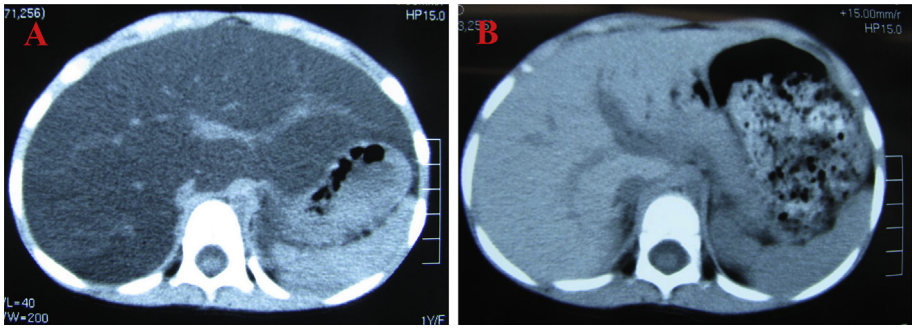

Fig. 1. Plain abdominal computed tomography (CT). A. At admission, the scan showed hepatic lobular enlargement and remarkably low absorbance throughout the liver, suggesting severe fatty liver disease. The biliary tract system was not expanded, and there were no abnormalities in the portal system, spleen, or kidney. B. Three months after discharge, the scans showed that the liver was normal sized with a normal absorption value.

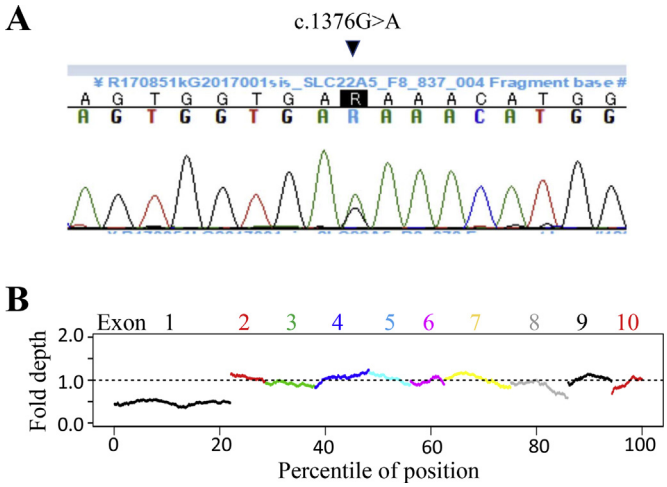

Fig. 2. Analysis of *SLC22A5*, encoding the organic carnitine/carnitine transporter 2 (OCTN-2). A. The mutation of c.1394C > T (p.V465A) was identified by direct sequencing by the Sanger method. B. Decreased copy number of exon 1 in *SLC22A5* was identified by next-generation sequencing. The horizontal axis showed the percentile position of 1874 bps *SLC22A5* coding region. The vertical axis showed the fold change of reads from the control average value.

because liver biopsies show fat degeneration in both diseases [4]. Although tandem mass spectrometry screening of newborns may reveal low free carnitine levels in plasma (<5 μM; normal, 25–50 μM), confirmation of CDSP also requires demonstration of reduced carnitine transport rates in fibroblasts (<10% of controls) and *SLC22A5* gene mutations [5].

Our patient was born before newborn screening via tandem mass spectrometry began in Japan. Therefore, CDSP was not suspected until acute hepatitis, fatty liver disease, and hypoketotic hypoglycemia had become apparent. We believe that the acute hepatitis was triggered by reduced glucose intake before and during the treatment for rotavirus enterocolitis (recurrent vomiting and no oral intake status after admission).

The incidence of CDSP varies depending on ethnicity. It is approximately 1/40,000 in Japan, 1/120,000 in Australia, and 1/20,000–70,000 in the United States and Europe [6]. In Japan, CDSP was not assessed in newborn screening programs until recently. CDSP should be considered when newborns with rotavirus gastroenteritis experience liver dysfunction, fatty liver disease, and hypoketotic hypoglycemia.

Our patient was initially considered to have secondary carnitine deficiency. Causes of secondary carnitine deficiency include metabolic disorders such as organic aciduria. It can also be iatrogenic, as seen in recipients of anti-epileptic agents [7], hypoallergenic formulas [8], and pivalic acid-containing antibiotics [9,10]. Pivalic acid combines with free carnitine to form pivaloylcarnitine, which is then excreted in the urine [9,10]. In almost all cases of secondary carnitine deficiency, pivalic acid-containing antibiotics had been administered for more than 1 week [11]. Jun et al. described a case of acute encephalopathy and severe hypoketotic hypoglycemia in 3-year-old girl with CDSP who had received CFPN-PI for 2 days [12]. Takahashi et al. described a case of sudden infant death of a 22-month-old boy with thermolabile *carnitine palmitoyl transferase 2 (CPT-2)* variant [13]. CPT-2 impairment is described as restricted mitochondrial β-oxidation (same as CDSP). He was infected with rotavirus 2 days earlier and was treated with cefditoren pivoxil (CDTR-PI). At autopsy, diffuse and severe liver steatosis was reported. Our patient had taken this pivalic acid-containing antibiotic for 4 days before hypoketotic hypoglycemia and liver dysfunction occurred. Until this episode, she had never had hypoglycemia, liver dysfunction, seizures, or encephalopathy. CFPN-PI administration may have caused metabolic compensatory events that triggered and exacerbated CDSP.

In conclusion, we presented a case in which a 1-year-old girl was diagnosed with CDSP after diagnosis of acute hepatitis and rotavirus gastroenteritis. CDSP should be considered in children with severe liver dysfunction and fatty liver disease due to rotavirus, other infections, or repeated attacks of hypoketotic hypoglycemia.

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Conflicts of interest

None.

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