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CASE REPORT

Citrin deficiency presenting as acute liver failure in an eight-month-old infant

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Abstract

Citrin deficiency typically presents as neonatal intrahepatic cholestasis and resolves in late infancy. Here we report a case of citrin deficiency that presented as acute liver failure in late infancy in an apparently healthy child. The full-term male infant weighed 3400 g at birth, and exhibited normal development for eight months, at which time he contracted bronchial pneumonia. The infant developed jaundice and laboratory tests indicated elevated bilirubin and ammonia levels and an abnormal coagulation profile. Plasma amino acid analysis showed elevated levels of tyrosine, methionine, citrulline, and arginine. Citrin deficiency was suspected, and genomic DNA analysis revealed a mutation (IVS16ins3kb) in *SLC25A13*, which encodes a mitochondrial aspartate-glutamate carrier protein. The infant was immediately put on a lactose-free, medium-chain-triglyceride-enriched formula with ursodeoxycholic acid and lipid-soluble vitamins. However, cholestasis and abnormal laboratory indices persisted, and the infant died at the age of 11.5 mo, two days before a scheduled liver transplantation. This case demonstrates that citrin deficiency can present in late infancy as acute liver failure triggered by infection, and may require liver transplantation.

Key words: Citrin deficiency; Infant; Liver failure; Respiratory infection; *SLC25A13*

Core tip: Citrin deficiency typically presents as neonatal intrahepatic cholestasis in early infancy and resolves

spontaneously in late infancy. However, this case report demonstrates that citrin deficiency can also present as acute liver failure triggered by infection in apparently healthy late infancy. Thus, citrin deficiency should be considered in cases of acute liver failure in older infants. Dietary therapy may be ineffective, necessitating liver transplantation in such circumstances.

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INTRODUCTION

Citrin deficiency is an autosomal recessive disorder caused by *SLC25A13* mutations[1,2]. As citrin functions as a calcium-stimulated aspartate-glutamate carrier in the liver[3], a deficiency can induce a variety of biochemical and metabolomic alterations, leading to a series of clinical manifestations and laboratory abnormalities[4-6]. Mutations in *SLC25A13* produce three phenotypes: neonatal intrahepatic cholestasis, adult-onset citrullinemia type Ⅱ[7], and failure to thrive and dyslipidemia[8,9].

The first case of neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) was reported in 2001 in Japan[10]. The majority of NICCD cases that have since been diagnosed occur within the first months of life. The symptoms generally ameliorate by one year of age either spontaneously or with dietary adjustment[4], though progression to liver failure has been reported, requiring liver transplantation or resulting in death from liver cirrhosis or severe infections[4,8,11-16]. However, the presentation of citrin deficiency in late infancy is very rare. Herein, we report a case of citrin deficiency in an 8-mo-old infant who presented with acute liver failure following an infection, which ultimately resulted in death.

CASE REPORT

Patient history

An 8-mo-old male infant was initially referred to a local tertiary hospital for bronchial pneumonia and jaundice. The infant had been full-term at birth (*via* emergency caesarean section), weighing 3400 g, was formula-fed, and showed normal growth and development. Laboratory tests conducted at that time showed elevated liver enzymes and a prolonged coagulation time even after vitamin K1 injection. Hepatobiliary scintigraphy indicated that hepatic uptake was not impaired, and the isotope appeared in the bowel. The infant was given intravenous antibiotics and oral ursodeoxycholic acid for two weeks, and received a total of three fresh-frozen plasma and albumin transfusions. Respiratory symptoms disappeared but jaundice and prolonged prothrombin time were not improved. Tandem mass spectrometry analysis revealed elevated plasma levels of tyrosine, methionine, citrulline, arginine, and several acylcarnitines. Gas chromatography-mass spectrometry analysis of urine showed elevated 4-hydroxyphenyl lactic and pyruvic acids. Based on these results, a citrin deficiency was suspected and the patient was referred to our hospital for further evaluation.

Intake assessment

Jaundice was observed upon physical examination. The infant's height and weight were normal, at 74 cm and 10 kg, respectively. There were no obvious signs of spider angiomata or palmar erythema. The abdominal girth was 60 cm with noted abdominal distension. The superior epigastric vein was visible. The liver was palpable 3 cm below the right costal margin, and the spleen was palpable 4 cm below the left costal margin. The infant could stand for a moment on his own and call for his mother.

Laboratory tests on admission showed elevated alanine aminotransferase (63 U/L; normal: < 40 U/L), aspartate aminotransferase (210 U/L; normal: < 40 U/L), total bilirubin (709.5 μmol/L; normal: 2-20 μmol/L), direct bilirubin (409 μmol/L; normal: 0-6 μmol/L), and plasma ammonia (114 μmol/L; normal: 9-33 μmol/L). Normal values were observed for levels of gamma-glutamyl transpeptidase (30 IU/L) and albumin (37.1 g/L). However, the prothrombin time (39.1 s; normal: 9.0-14.5 s) and activated partial thromboplastin time (72.3 s; normal: 25-39 s) were elevated after intravenous administration of vitamin K1. The international normalized ratio was also elevated (4.08; normal: 0.77-1.25). Markers for active hepatitis A, B, C, and E infection were negative, as well as for IgM antibodies to toxoplasma, cytomegalovirus, herpes virus, and Epstein-Barr virus. An abdominal ultrasound revealed mild hepatosplenomegaly.

Management

The clinical manifestations and laboratory results indicated a diagnosis of acute liver failure, and citrin deficiency was highly suspected. The parents initially refused a liver transplantation, and the infant was given lactose-free, medium-chain-triglyceride-enriched formula (Alfare; Nestle, Vevey, Switzerland) and lipid-soluble vitamins and ursodeoxycholic acid (5 mg/kg *bid*). After two weeks, the cholestasis and laboratory indices did not improve, and the parents agreed to schedule a liver transplant. Unfortunately, the infant died two days before the scheduled operation at the age of 11.5 mo.

Mutation identification

With approval by the Ethics Committee on human research of the Jinshan Hospital of Fudan University

and informed consent of the parents, a 1.5 mL peripheral blood sample was obtained and *SLC25A13* mutations were tested as previously reported[5,17]. Briefly, DNA was extracted using the Tiangen Blood Genomic DNA Isolation Kit (Tiangen Biotech, Shanghai, China) according to the manufacturer's instructions. All the coding exons and adjacent intronic sequences of *SLC25A13* gene were amplified and sequenced. The known large insertion IVS16ins3Kb and deletion Ex16+74IVS17-32del1516 were tested by long-range PCR and electrophoresis directly. RefSeq NM_014251.2 was used as the SLC25A13 reference[12]. A homozygous known big insertion for IVS16ins3Kb was detected.

DISCUSSION

Citrin deficiency is a condition that affects individuals worldwide[10,14,18-23]. Adult-onset citrullinemia type Ⅱ presents as an acute hepatic and neurologic disorder in adolescents or adults (11-79 years of age)[7], whereas NICCD typically presents before three months of age with jaundice, discolored stools, hepatosplenomegaly and coagulopathy[4,5,10,14,17,23]. Here, we report a previously unreported presentation of citrin deficiency as acute liver failure triggered by respiratory tract infection in a child in late infancy. The patient was apparently healthy before the infection, as the parents did not observe any prior signs of jaundice, dark urine, or pale stool. Moreover, the growth and development of the infant were comparable to the national standard, suggesting that he was in good condition before the trigger infection.

Most NICCD patients recover spontaneously or after dietary adjustment. However, there are a few reported cases where end-stage liver disease developed, resulting in liver transplantation or death[4,8,11-13,15,16]. A case reported by Chew *et al*[14] presented at 10-wk-old as conjugated hyperbilirubinemia and progressed to liver failure precipitated by infection. In contrast, our case presented as acute liver failure precipitated by infection in an apparently healthy 8-mo-old infant. Given that the development of end-stage liver disease in NICCD patients is extremely rare in late infancy, we presume that the multiple hyperaminoacidemia and elevated acylcarnitines were secondary to severe liver dysfunction. As a definite diagnosis of citrin deficiency is determined by a mutation of *SLC25A13*, a genetic study was performed, confirming the diagnosis by detection of the IVS16ins3kb mutation, which is a known causative mutation that is common in East Asians[4,24].

In conclusion, this case demonstrates that citrin deficiency can present as infection-triggered acute liver failure in late infancy. Therefore, citrin deficiency should be taken into account in the differentiation of acute liver failure in patients within this age group. Furthermore, this case shows that dietary therapy alone may be ineffective, and liver transplantation may be needed in such circumstances.

COMMENTS

Case characteristics

An apparently healthy 8-mo-old infant presented with acute liver failure triggered by infection.

Clinical diagnosis

Acute liver failure, jaundice, abdominal distension, superior epigastric vein, and hepatosplenomegaly was observed; no obvious signs of spider angiomata or palmar erythema were observed.

Differential diagnosis

Acute viral hepatitis.

Laboratory diagnosis

Conjugated hyperbilirubinemia with significantly prolonged prothrombin time and hyperammonemia; a known IVS16ins3kb mutation of *SLC25A13* was detected upon genomic analysis; the patient was negative for infectious hepatitis strains.

Imaging diagnosis

Abdominal ultrasound revealed mild hepatosplenomegaly.

Treatment

The infant was administered a lactose-free, medium-chain-triglyceride-enriched formula supplemented with lipid-soluble vitamins and ursodeoxycholic acid.

Related reports

A few neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) cases have been reported developing end-stage liver disease, which resulted in liver transplantation or death. However, the case presented here is the first report of citrin deficiency presenting as acute liver failure in an apparently healthy late-stage infant.

Term explanation

Citrin deficiency is an autosomal recessive disorder caused by mutations in gene *SLC25A13*, which encodes a calcium-stimulated aspartate-glutamate carrier named citrin.

Experiences and lessons

Citrin deficiency typically presents with jaundice within the first three months after birth, but our case was apparently healthy for the first eight months; as citrin deficiency can present as acute liver failure in such a child after a common infection, it should be considered in differential diagnosis and liver transplantation should be considered in similar cases.

Peer-review

This article indicates that citrin deficiency cannot be excluded from the differential diagnosis of acute liver failure in healthy late-stage infants.

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