A 6-Year-Old Child With Citrin Deficiency and Advanced Hepatocellular Carcinoma

Limin Wang, MD, a,b Lifeng Wang, MD, PhD, c Shishu Zhu, MD, a Min Zhang, MD, a Yi Dong, MD, a Fu-Sheng Wang, MD, PhD d,e

We report the case of a 6-year-old boy with citrin deficiency and advanced hepatocellular carcinoma diagnosed by using imaging. He exhibited intrahepatic cholestasis 2 days after his birth and was misdiagnosed with inspissated bile syndrome at that time. The symptoms of jaundice spontaneously resolved when he was 5 months old. However, his transaminase levels remained elevated for ~6 years, for which he received no treatment. He preferred a high-protein, high-fat, low-carbohydrate diet, which has been observed in many patients with citrin deficiency, but no clinical features of adult-onset type II citrullinemia were observed. At the age of 6 years, he was admitted to our hospital with a nonviral infection and high α-fetoprotein level; results from an abdominal MRI and computed tomography revealed multiple tumors in the liver. Because of his history of intrahepatic cholestasis in the neonatal period, he was suspected to have citrin deficiency. A genetic analysis of solute carrier family 25, member 13 revealed the presence of a homozygous 851del4 mutation, and a diagnosis of citrin deficiency was made. The patient did not qualify for liver transplantation and died 2 months later, after discharge from our hospital. Thus, this case reveals that not all patients with neonatal intrahepatic cholestasis spontaneously and totally improve, and this case is used to emphasize that patients with neonatal intrahepatic cholestasis should be managed carefully, especially in the stage of failure to thrive and dyslipidemia caused by citrin deficiency, which may lead to advanced hepatocellular carcinoma.
Clinical diagnoses of citrin deficiency during this stage are difficult in the absence of a history of unique food preferences or molecular testing. Researchers in most case reports have found that CTLN2 is associated with hepatocellular carcinoma (HCC), and the incidence of HCC in patients with CTLN2 is estimated to be ∼8%. However, citrin deficiency complicated with HCC in other types of patients, such as those with NICCD or FTTDCD, has never been reported. Here we report the case of a 6-year-old boy with citrin deficiency at the FTTDCD stage who developed advanced HCC.

CASE REPORT

The boy was born via a normal delivery from nonconsanguineous parents at 40 weeks’ gestation and with a weight of 3200 g. He presented with jaundice, discolored stools, hepatosplenomegaly, and liver dysfunction 2 days after his birth. He underwent an exploratory laparotomy and gallbladder fistula surgery for suspected biliary atresia at 1 month of age at a local, tertiary hospital without a liver biopsy. However, biliary atresia was later excluded, and he was diagnosed with inspissated bile syndrome when he was discharged. The symptoms of jaundice spontaneously resolved when he was ∼5 months old, but his liver transaminase levels were persistently abnormal for 6 years (Fig 1). However, the etiology of his persistent elevations of liver transaminases remained unknown. During this period, regular ultrasonic examinations revealed no hepatic steatosis, fibrosis, or cirrhosis; his growth retardation was unremarkable, and he had no neurologic symptoms, such as disturbances of consciousness, tremors, seizures, or abnormal behavior. He had a preference for protein- and lipid-rich foods and an aversion to carbohydrate-rich foods. At 6 years of age, his α-fetoprotein (AFP) level rose to 2000 ng/mL, and computed tomography revealed multiple tumors in the right lobe of his liver. After this, he was admitted to our hospital for further treatment. His weight was 20 kg (−0.36 SD), and his height was 116 cm (−0.43 SD) on admission. His liver was palpable 4 cm below the right costal margin, and his spleen was palpable 4 cm below the left costal margin. Laboratory tests revealed elevated levels of alanine aminotransferase (74 U/L; normal: <40 U/L), aspartate aminotransferase (134 U/L; normal: <40 U/L), plasma ammonia (30.3 μmol/L; normal: 0–30 μmol/L), γ-glutamyl transpeptidase (221 IU/L; normal: 5–10 IU/L), and AFP (14 323 ng/mL; normal: 0–30 ng/mL). Normal values were observed for total bilirubin, albumin, prothrombin time, α1-antitrypsin, and ceruloplasmin. His γ globulin level was normal, and the results of tests for autoantibodies were all negative. The results of tests for markers of viral hepatitis infections A, B, C, and E were negative, and the results of tests for markers of immunoglobulin M antibodies to cytomegalovirus and Epstein-Barr virus were also negative. The results of urinary analysis by using gas chromatography–mass spectrometry and blood analysis by using liquid chromatography–tandem mass spectrometry were normal, respectively. He had a history of intrahepatic cholestasis in the neonatal period and was therefore...
suspected to have citrin deficiency. An analysis of the SLC25A13 gene was performed by using classic methods, with informed consent being gained from his parents. The patient was found to have a homozygous 851del4 mutation. Both parents were found to have heterozygous 851del4 mutations. However, his brother was healthy and lacked any mutations (Fig 2). Meanwhile, the mother was pregnant again, and the newborn infant girl was found to have a heterozygous 851del4 mutation. Enhanced computed tomography revealed multiple lesions in the right hepatic lobe, portal vein thrombosis, arterial portal fistula, liver cirrhosis, and splenomegaly. Consequently, enhanced MRI revealed multiple lesions in the right lobe of the liver with mild-to-moderate intensity, which is indicative of liver malignancy (Fig 3). After consultation with a hepatobiliary surgery expert, the patient was considered unsuitable for liver surgery or liver transplantation. The patient’s parents refused to have a liver biopsy or further treatment conducted. Hepatoblastoma and HCC are the most prevalent liver tumors in children. Hepatoblastoma usually occurs in children between 6 months and 3 years of age. The presence of underlying liver diseases, especially with a known risk factor, favors the diagnosis of HCC. Regarding this patient, the liver cirrhosis and malignancy occurred after he was 6 years old because of citrin deficiency. Combination with MRI, 3 independent hepatologists all favored a diagnosis of advanced HCC rather than hepatoblastoma. The patient died of hepatic failure combined with ruptured esophageal varices 2 months later, after his discharge.

DISCUSSION

Citrin deficiency affects individuals worldwide. FTTDCD was recently proposed as a novel post-NICCD phenotype before the onset of CTLN2. The clinical and laboratory features of FTTDCD remain largely unclear. During this apparently healthy period, some pediatric patients exhibit diverse clinical symptoms and laboratory abnormalities, including growth retardation, pancreatitis, fatigue, dyslipidemia, increased lactate/pyruvate ratios, elevated levels of urinary oxidative stress markers, and considerable deviations in tricarboxylic acid cycle metabolite levels. However, liver
transaminase levels are normal in most of these patients. In this case, the patient did not undergo genetic analysis or tandem mass spectrometry at his local hospital because his doctor did not consider citrin deficiency and misdiagnosed him as an infant with inspissated bile syndrome. His jaundice resolved spontaneously after a few months, but his transaminase levels remained abnormal for 6 years, ultimately leading to HCC. The patient did not undergo dietary management until he was diagnosed with citrin deficiency, after the detection of the homozygous 851del4 mutation at our hospital. In addition, on the basis of blood examinations, we ruled out the most common etiologies of abnormal transaminase levels in pediatric patients, such as viral infections (hepatitis viruses A, B, or C, Epstein-Barr virus; and cytomegalovirus), autoimmune liver diseases (primary biliary cholangitis, autoimmune hepatitis, primary sclerosing cholangitis, and overlap syndrome), and inherited metabolic disorders (Gilbert syndrome, Dubin-Johnson syndrome, Wilson disease, α1-antitrypsin deficiency, cystic fibrosis, and so on). Sadly, blood amino acids and lipids were not examined in this patient, so it is hard to say whether excessive citrulline or dyslipidemia caused his abnormal transaminase levels, as was previously reported.7

A high incidence of HCC is evident in patients with CTLN2, and most of the reported cases have occurred in Japan.18 To date, there have been no reports on the occurrence of HCC in patients with other types of citrin deficiency. Our patient was unique in that he had HCC during the FTTCDCD stage with constantly abnormal transaminase levels. Many mechanisms have been proposed to explain the origin of HCC in patients with CTLN2. Genetic mutations play an important role in the development of HCC. On the one hand, preneoplastic changes can result from alterations in gene expression conferred by factors such as loss of heterozygosity, which can inactivate tumor-suppressor genes or amplify oncogenes19; on the other hand, the odds ratio for carriers of SLC25A13 mutations among patients with nonviral HCC versus the general population is reportedly 6.6, indicating that SLC25A13 gene mutations may cause HCC with or without a secondary insult.20 In patients with citrin deficiency and excessive citrulline levels, the proliferation of hepatocytes is ultimately promoted, which may lead to hepatocarcinogenesis.21 Increasing evidence reveals that the development of HCC is a multistep process. HCC can appear in patients with a background of chronic hepatitis or cirrhosis after many years.9 In addition, oxidative stress and lipid peroxidation22 may also be among the factors that lead to hepatocarcinogenesis in patients with CTLN2. In this case, the patient had no history of hepatitis–related viral infection or exposure to substances known to induce HCC. His AFP level was >2000 ng/mL in the NICCD stage, but on the spontaneous resolution of his symptoms of jaundice, his AFP level remained normal until the occurrence of HCC in the FTTCDCD stage. The constantly abnormal transaminase levels and lack of diet management in this patient may also have contributed to hepatocarcinogenesis.

**CONCLUSIONS**

The findings in this case report reveal that FTTCDCD is not characteristic of an apparently healthy period in patients with citrin deficiency, which
is a concept that should be kept in mind by every physician. Persistent elevations of liver transaminases and advanced HCC can also occur at this stage, and careful monitoring and early detection are necessary. Misdiagnosis of the disease at a local hospital followed by long-term ignorance of the persistently abnormal transaminase levels reveals that citrin deficiency is a condition that is not totally understood by Chinese physicians, especially those in rural areas. The collaborative care models and distance-learning programs provided by administrators in large, academic medical centers will be used to greatly improve the standards of such medical services. In addition, citrin deficiency should be considered 1 of the etiologies of persistent elevations of liver transaminases in children, and genetic counseling and detection should be used to confirm the diagnosis.

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ABBREVIATIONS

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<th>Definition</th>
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<tr>
<td>α-fetoprotein</td>
<td>AFP</td>
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<td>Adult-onset type II citrullinemia</td>
<td>CTLN2</td>
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<td>Failure to thrive and dyslipidemia caused by citrin deficiency</td>
<td>FTTDCD</td>
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<td>Hepatocellular carcinoma</td>
<td>HCC</td>
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<td>Neonatal intrahepatic cholestasis</td>
<td>NICCD</td>
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