Clinical and histopathologic features of sodium taurocholate cotransporting polypeptide deficiency in pediatric patients

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Abstract
Until now, the recognition of sodium taurocholate cotransporting polypeptide (NTCP) deficiency has been mainly based on sporadic case reports. It was previously believed to be mildly symptomatic and resulting in mild liver dysfunction. However, to our knowledge, there have been no reports about the histopathologic and ultrastructural pathologic characteristics of the disease. The aim of the study was to analyze the clinical, histopathologic and ultrastructural pathologic characteristics of NTCP deficiency in 13 pediatric patients.

From August 2012 to October 2018, this retrospective study conducted in the Department of Pediatrics of Tongji Hospital, China analyzed the data of 13 NTCP deficient patients with an SLC10A1 gene mutation. Except for NTCP deficiency, no other liver diseases were present in the patients, which was determined by both a genetic testing panel for jaundice and by reviewing medical records. The laboratory results, imaging, histopathologic, and ultrastructural pathologic information were recorded for analysis.

The serum level of total bile acid was high in all 13 patients. All patients had adequate growth and development. Eight of the patients (8/13) presented with visible jaundice and 12 (12/13) were found to have hyperbilirubinemia. A needle liver biopsy was performed in 11 cases, which revealed slightly chronic inflammation in all 11 patients. One of the patients (1/13) was found to be suffering from gallstones.

The data showed that although NTCP deficiency was often asymptomatic, some of the patients showed obvious clinical expressions, such as jaundice. Among the 13 pediatric patients with NTCP deficiency, both the biochemical and histopathologic features were similar to those of mild hepatocellular jaundice. In addition, it was determined that the clinical features in the patient with gallstones may have been caused by NTCP deficiency.

Abbreviations: 5'NT = 5'-ribonucleotide, ALB = albumin, ALT = glutamic-pyruvic, AST = aspartic transaminase, DB = direct bilirubin, GGT = gamma-glutamyltransferase, HBV = hepatitis B virus, NTCP = sodium taurocholate cotransporting polypeptide, TB = total bilirubin, TBA = total bile acid.

Keywords: hyperbileacidemia, hyperbilirubinemia, sodium taurocholate cotransporting polypeptide

1. Introduction
Bile acid is an important ingredient in bile, which is mainly found in enterohepatic circulation. The circulation repeats itself 6 to 15 times every day. Approximately 95% of the bile acid is reabsorbed into the liver and recycled.[1,2] Under normal physiological conditions, bile acid maintains a constant internal environment and has anti-inflammatory properties. However, accumulation of bile acids causes liver inflammation and injury.
Therefore, it is very important to maintain a relatively low level of bile acid in both blood circulation and the liver. Sodium taurocholate cotransporting polypeptide (NTCP) is encoded by the SLC10A1 gene, which is located on human chromosome 14. It is a type of solute carrier protein, consisting of 349 amino acids. NTCP, which is considered to be the main receptor for the hepatitis B virus (HBV), plays an important role in the basolateral membrane of the liver in the above process. It transports the vast majority of bile acids from the portal vein to the hepatocytes.

Therefore, it could be inferred that NTCP deficiency may cause hyperbilirubinemia. However, because it is a rare genetic disorder, and most of the previous case reports suggested that the disease was characterized by mild symptom and liver dysfunction, larger studies are needed to confirm whether this characterization is true for all patients. In addition, it is necessary to find out the histopathologic and ultrastructural pathologic characteristics of the disease, as there have been no reports on this to date. Therefore, the aim of this study was to analyze the clinical, histopathologic, and ultrastructural pathologic characteristics of NTCP deficiency in 13 pediatric patients. It is believed that these findings may help in the identification and treatment of NTCP deficiency, especially in pediatric patients.

2. Methods

This retrospective, observational study was approved by the institutional ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology and was conducted in the Department of Pediatrics from August 2012 to October 2018, according to the principles expressed in the Declaration of Helsinki. The study involved a retrospective analysis of data of 13 NTCP deficient patients with SLC10A1 gene mutation. Differing opinions about the clinical features, laboratory results, image characteristics, and histopathologic findings of the disease were put forward. Informed consent in writing was obtained from each patient’s legal guardian.

2.1. Patients

Clinical, laboratory, imaging, and pathological data of 13 pediatric NTCP patients with SLC10A1 gene mutation in the Department of Pediatrics of Tongji Hospital, China from August 2012 to October 2018 were collected and analyzed. None of the 13 patients had other cholestatic liver diseases, except for NTCP deficiency, which was determined by a genetic testing panel for jaundice and by reviewing medical records. The patients with available results (including gene detection, clinical presentations, laboratory results, and transabdominal ultrasound results) were enrolled in the study to reduce information bias and selection bias. Thirteen patients were enrolled into the study. The ratio of males to females was 2.25:1. The median diagnostic age of the patients was 1.36 years (range: 1 month–5.5 years).

2.2. Gene detection

The Online Mendelian Inheritance in Man (OMIM, http://www.ncbi.nlm.nih.gov/omim/) and the Human Gene Mutation Database (HGMD, http://www.hgmd.org/) were referred, recruiting 60 genes associated with cholestatic jaundice. All mutations detected by the next generation sequencing (NGS) were confirmed by Sanger sequencing.

2.3. Clinical presentations

The patients’ general information (including age, sex, weight, height, family, and past history), clinical presentations (including the presence of jaundice, color of stools, and incidence of pruritus) were recorded according to the narratives of their parents or others living with the patients. The size of the liver and spleen were determined through the clinicians’ palpation.

2.4. Laboratory examination

Laboratory data, including the levels of glutamic-pyruvic (ALT), aspartic transaminase (AST), total bilirubin (TB), direct bilirubin (DB), total bile acid (TBA), albumin (ALB), gamma-glutamyl-transferase (GGT), 5’-ribonucleotide (5’NT), and the results of viral hepatitis tests (including hepatitis A, B, C, and E, and human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19) were recorded. In addition, the results of autoimmune hepatitis, as well as congenital metabolic diseases, were recorded.

2.5. Imaging examination

A fasted transabdominal ultrasound (US) was performed in the included patients.

2.6. Needle liver biopsy

After obtaining written informed consent from the parents, 11 patients underwent US-guided needle liver biopsy before treatment. Two pieces of tissue were collected from each patient before the start of the treatment. One was observed under light microscope after hematoxylin–eosin (H&E) staining by the same 2 pathologists in the pathology department of Tongji Hospital of the Huazhong University of Science and Technology. The other tissue piece was observed under an electron microscope by the same 2 pathologists in the electron microscope room of Tongji Medical College of Huazhong University of Science and Technology.

2.7. Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Continuous data were presented as mean ±SD. The rate was expressed as a percentage.

3. Results

3.1. Gene detection results

Among the patients, homozygous mutations of the SLC10A1 gene were identified in 12 patients. The last patient showed compound heterozygous mutations of c.800C>T (p. Ser267Phe) and c.812A>G (p. Asn271Ser) for the SLC10A1 gene (Table 1).

3.2. General information and clinical features

All 13 patients had a normal family and past medical history. According to the latest 2009 stature-for-age percentiles chart of Chinese children, the patients’ stature and weight were all between the 25th and 75th percentile of the same age and sex. Eight of the 13 patients (61.5%) presented with jaundice (yellowish eyes or skin). There were 3 patients (23.1%) who had hepatojugular. The livers of these 3 patients were palpable from
Each patient underwent a transabdominal US. Hepatomegaly was confirmed in 12 patients (92.3%) and splenomegaly was confirmed in 2 patients (15.4%). The ultrasonic diagnosis criteria for hepatomegaly are an enlarged liver with its lower edge ≥2 cm (<1 year old) or extended (≥1 year old) below the right costal margin. The ultrasonic diagnosis criteria for splenomegaly are a longitudinal spleen diameter ≥8 cm (0–3 years old) or ≥10 cm (4–10 years old). In addition, one of the patients (7.7%, male, 10 months old) was found to be suffering from gallstones.

3.3. Laboratory diagnostic results

The liver function results of the 13 patients before treatment are recorded in Table 2. According to the table, the serum level of TBA was high in all 13 patients. Serum TB levels were >34.2 μmol/L in 6/13 (46.15%) patients, although they were normal (<21 μmol/L) in 6 patients (46.15%). The serum TB level was <34.2 μmol/L and >21 μmol/L in the last patient. Seven patients had hyperbilirubinemia, among whom the direct/total bilirubin ratio of 5 patients was >50%. The average for the percentage of DB was 48.64%. In 12 of the 13 patients (92.3%), the percentages were >20%. In 6 of the 13 patients (46.15%), the percentages were >50%. In 12 of the 13 patients (92.3%), the DB level was above 1.0 mg/dL.

The viral hepatitis, autoimmune hepatitis, and congenital metabolic diseases tests of the 13 patients were all negative.

3.4. Imaging diagnostic examinations

Each patient underwent a transabdominal US. Hepatomegaly was confirmed in 12 patients (92.3%) and splenomegaly was confirmed in 2 patients (15.4%). The ultrasonic diagnosis criteria for hepatomegaly are an enlarged liver with its lower edge ≥2 cm (<1 year old) or extended (≥1 year old) below the right costal margin. The ultrasonic diagnosis criteria for splenomegaly are a longitudinal spleen diameter ≥8 cm (0–3 years old) or ≥10 cm (4–10 years old). In addition, one of the patients (7.7%, male, 10 months old) was found to be suffering from gallstones.

3.5. Histopathological results

After obtaining written informed consent from the parents, 11 patients underwent US-guided needle liver biopsy before treatment. Hepatic pathology changes are summarized in Table 3. Figure 1 shows the light microphotographs of H&E staining. Figure 2 shows the ultrastructural pathological photographs under an electronic microscope.

4. Discussion

NTCP deficiency was first reported as an inborn error with a relatively mild clinical phenotype in Hepatology.[18] In our study, 13 pediatric patients with NTCP deficiency were mainly characterized by mild cholestasis, similar to patients with hepatocellular jaundice in clinical manifestation, laboratory assay results, and pathological appearance.

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**Table 1**

The mutations in the SLC10A1 gene of 13 patients with sodium taurocholate cotransporting polypeptide deficiency.

| Patient | SLC10A1 genotypes | Father (Het/Homo) | Mother (Het/Homo) | Effects |
|---------|-------------------|------------------|------------------|---------|
| P1      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P2      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P3      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P4      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P5      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P6      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P7      | c.800C>T/c.812A>G (Het) | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe/p. Asn271Ser |
| P8      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P9      | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P10     | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P11     | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P12     | c.800C>T (Homo)   | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |
| P13     | c.800C>T/c.800C>T | c.800C>T/wild (Het) | c.800C>T/wild (Het) | p. Ser267Phe |

Het, heterozygous; Homo, homozygous.

"Wild" indicates the normal SLC10A1 allele.

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**Table 2**

Levels of liver function of 13 patients with sodium taurocholate cotransporting polypeptide deficiency.

| ID | P1 | P2 | P3 | P4 | P5 | P6 | P7 | P8 | P9 | P10 | P11 | P12 | P13 | Mean ± SD | Normal range |
|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|------------|-------------|
| Sex| M  | F  | M  | M  | M  | M  | M  | F  | M  | F   | M   | M   | M   | —         | —           |
| Age, mo | 1  | 12 | 12 | 10 | 10 | 66 | 42 | 3  | 3   | 15  | 3   | 36  | 36  | 54.47±18.62 | <33         |
| ALT*, U/L | 39 | 30 | 24 | 23 | 17 | 17 | 36 | 36 | 36  | 71  | 109 | 59.38±23.56 | <32         |
| AST*, U/L | 79 | 79 | 79 | 79 | 79 | 79 | 79 | 79 | 79  | 79  | 79  | 79  | 79  | 33.97±34.12 | <21         |
| TB*, μmol/L | 103.4 | 5.6 | 11.9 | 5.3 | 4.4 | 27.5 | 35.8 | 36.6 | 37.4 | 34 | 17.7 | 99.9 | 54.6 | 54.67±18.62 | <33         |
| DB*, μmol/L | 70.4 | 1.5 | 4.7 | 2.5 | 1  | 11.1 | 25.8 | 29.9 | 21.2 | 1.7 | 7  | 6.3  | 4.44 | 20.80±17.50 | <8.0        |
| TB/TB, % | 68.09 | 26.79 | 39.5 | 47.17 | 22.73 | 40.36 | 72.07 | 81.7 | 56.68 | 50 | 39.55 | 6.3  | 81.32 | 48.64±22.97 | —           |
| TBA*, μmol/L | 130.5 | 84.6 | 166 | 165.2 | 148.7 | 172.6 | 170 | 125.7 | 147.1 | 65.3 | 144.5 | 142.1 | 175.5 | 151.74±55.38 | <10.0       |
| ALB*, g/L | 36.8 | 45.9 | 44.5 | 49.4 | 49.8 | 40.1 | 40.6 | 40.9 | 46.4 | 43.6 | 40.9 | 43.5 | 43.5 | 42.64±4.94 | 38-54       |
| GGT*, U/L | 103 | 5 | 10 | 12 | 18 | 18 | 48 | 880 | 227 | 13 | 79 | 58 | 150 | 66.08±50.49 | 6-42        |
| 5'NT*, U/L | 0.1 | 4.6 | 5.7 | 5.2 | 5.8 | 4.4 | 3.4 | 10.1 | 3.1 | 5.3 | 3.1 | 3.9 | 4.59±2.25 | 0-10        |

*1) alanine aminotransferase 2) aspartate aminotransferase 3) total bilirubin 4) conjugated bilirubin 5) total bile acid 6) Albumin 7) gamma-glutamyltransferase 8) 5'-ribonucleotide.
As mentioned above, patients with NTCP deficiency may have hyperbileacidemia, which was verified in both the present and previous studies. In addition, no patient in our study had pruritus, which was similar to previous findings.\textsuperscript{[9–11]} It was also noted that all 13 patients had adequate growth and development. Nevertheless, there were some differences between the present study and those previously reported, which will be discussed below.

### Table 3
Pathological features of 11 patients with sodium taurocholate cotransporting polypeptide deficiency.

| Pathological features | Number (%) |
|-----------------------|------------|
| **Light microscope**  |            |
| 1. Normal structure of liver lobule | 11 (100) |
| 2. Cellular swelling of the hepatocytes | 11 (100) |
| 3. Fatty degeneration observed in hepatocytes | 6 (54.55) |
| 4. Mildly fibrous proliferation and small bile duct proliferation at portal areas | 7 (63.64) |
| 5. Portal lymphoplasmacytic infiltrate | 11 (100) |
| 6. Slight cholestasis in hepatocytes and small bile ducts | 6 (54.55) |
| **Electron microscope** |            |
| 1. Reduction of rough endoplasmic reticulum, dilation and hyperplasia of smooth endoplasmic reticulum | 10 (90.9) |
| 2. Hazy mitochondrial structures | 6 (54.55) |
| 3. Mildly increased lipid droplets in the cytoplasm | 11 (100) |
| 4. Aggregation of cholestatic pigment granules in most cytoplasm | 11 (100) |
| 5. Slightly diluted intercellular spaces | 10 (90.9) |
| 6. Slightly diluted bile capillaries | 8 (72.7) |
| 7. Slight cholestasis in bile capillaries | 8 (72.7) |
| 8. Hepatic stellate cells (HSCs) and deposit of collagen fibers arranged in fascicular clusters in Disse cavity | 8 (72.7) |
| 9. Kupffer cells common in hepatic sinusoid | 8 (72.7) |
| 10. Fibrous proliferation at portal areas | 8 (72.7) |

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**Figure 1.** Light microphotographs of H&E staining. (A) Normal structure of the liver lobule could be seen clearly. Mild fibrous proliferation and small bile duct proliferation were found at portal areas. (*100) (B) The cellular swelling and fatty degeneration were found in the hepatocytes. (*400) (C) Intrahepatocytic cholestasis could be seen. (*400) (D) Chronic inflammatory cells such as lymphocytes, aggregated at portal areas. (*400) (as depicted by the arrows).
A patient reported in Hepatology was clinically characterized by mild hypotonia, growth retardation, and delayed motor milestones without cholestatic jaundice, pruritis, or liver dysfunction.[8] Our study also found that some patients with NTCP deficiency were asymptomatic or mildly symptomatic; however, none of the 13 patients in the present study had growth retardation. Further, in our study, 8 of the patients (8/13) presented with visible jaundice, which was the reason they sought medical treatment. The high proportion of jaundice may be due to the fact that most patients with NTCP deficiency will not seek medical treatment unless obvious clinical expressions such as jaundice were present.

In addition, 2 pediatric patients reported in Oncotarget had slightly abnormal liver function with indirect hyperbilirubinemia.[15] In the present study, mild liver dysfunction was also found in the patients with NTCP deficiency. Unlike previous findings, among the 13 pediatric patients, the levels of both direct bilirubin and unconjugated bilirubin were elevated (Table 2), which was the same as hepatocellular jaundice.[12] A direct/total bilirubin ratio of >15% to 20% or a DB level above 1.0 mg/dL is collectively defined as direct hyperbilirubinemia.[11] Twelve of the patients (92.3%) in our study were defined as direct hyperbilirubinemia according to the diagnostic criteria. Furthermore, hepatocellular jaundice and cholestasis were also verified by histological examination in this study. The histopathology features included liver cell destruction, and periportal inflammation and fibrosis, which were similar to mild chronic viral hepatitis (Fig. 1, Fig. 2, and Table 3).[13-16]

It is important to identify NTCP deficiency as it can lead to damage of the hepatocytes and bile ducts if left undetected according to the results of the present study. It has been reported that several bile acid transporters are located on the hepatocytic membranes to absorb bile acids from the portal vein. In addition to NTCP, there is OATP1B1 and OATP1B3 (encoded by SLCO1B1 and SLCO1B3, respectively), which also have the function of bilirubin uptake into hepatocytes.[11] Therefore, the dysfunction of NTCP may cause the compensatory reabsorption of OATP1B1 and OATP1B3, leading to the deposition of bile.
pigment in liver cells. This is consistent with the pathological findings of aggradation of cholestatic pigment granules in most cytoplasm under an electron microscope. Over time, high levels of deposition of bile pigment lead to damage of and cholestasis in the hepatocytes, and even in the bile ducts.

It is noteworthy that one of the patients (P5 in Table 2) in the present study was found to be suffering from gallstones. Bile acid metabolism has been reported to be associated with gallstones, especially cholesterol gallstones. As mentioned above, NTCP plays an important role in the process of maintaining a relatively low level of bile acid. Relative reduction of bile acid content in bile would promote the formation of cholesterol crystals. A stable enterohepatic circulation may prevent cholesterol gallstone formation. Based on the above, we speculated that the formation of gallstones was closely correlated with NTCP deficiency.

Considering the above discussion points, the present study can be summarized as follows: most of the 13 pediatric patients with NTCP deficiency had similar clinical and histopathologic features with mild hepatocellular jaundice; an increased level of TBA found in regular medical examinations was the only indication of NTCP deficiency in some patients; NTCP deficiency may be the cause of mild hyperbilirubinemia in some pediatric patients, after the exclusion of other cholestatic liver diseases; and some pediatric patients with NTCP deficiency were at a high risk for gallstones.

Certainly, the present study had some limitations. First, there were a relatively small number of patients included, and therefore larger studies are needed to confirm the conclusions. Second, due to the retrospective nature of the study, there may be bias in patient-selection.

In conclusion, although some of the findings were in accordance with that of previous studies, the present study discovered novel characteristics of patients with NTCP deficiency. The findings of our study may help in the identification and treatment of NTCP deficiency, especially in pediatric patients.

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