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Intrahepatic Cholestasis of Pregnancy as a Clinical Manifestation of Sodium-Taurocholate Cotransporting Polypeptide Deficiency

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Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. Although the etiology of ICP is not fully understood thus far, some genetic factors might contribute to the development of this condition. Sodium-taurocholate cotransporting polypeptide (NTCP), the protein encoded by the gene Solute Carrier Family 10, Member 1 (*SLC10A1*), is the primary transporter expressed in the basolateral membrane of the hepatocyte to uptake conjugated bile salts from the plasma. NTCP deficiency arises from biallelic *SLC10A1* mutations which impair the NTCP function and cause intractably elevated levels of total bile acids (TBA) in the plasma (hypercholanemia). In this study, all the *SLC10A1* exons and their flanking sequences were analyzed by Sanger sequencing to investigate the etiology for hypercholanemia in two male infants aged 2 and 20 months, respectively, from two unrelated families. As a result, both patients are homozygous for the reported pathogenic variant c.800C>T (p.Ser267Phe) that could impair the NTCP function to uptake bile acids, and the diagnosis of NTCP deficiency was thus made. Their mothers are also homozygotes of the same variant and both had been diagnosed to have ICP in the third trimester, with one of them undergoing cesarean section. The father of the first patient in this paper has the same *SLC10A1* genotype c.800C>T/c.800C>T, also exhibiting slight hypercholanemia with a plasma TBA level of 21.5 μmol/L. In conclusion, we suggest that with hypercholanemia being a common laboratory change, NTCP deficiency may be a genetic factor leading to ICP and even cesarean section in clinical practice.

Keywords: bile acid; hypercholanemia; intrahepatic cholestasis of pregnancy; SLC10A1; sodium taurocholate cotransporting polypeptide deficiency
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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. The ICP etiology was complex and not fully understood so far, but besides the cholestatic effects of reproductive hormones and their metabolites, genetic factors might also contribute to the development of this condition in some women, such as mutations of the genes ATP-Binding Cassette, Subfamily B, Member 11 (*ABCB11*) (Eloranta et al. 2003), ATP-Binding Cassette, Subfamily B, Member 4 (*ABCB4*) (Jacquemin et al. 1999), ATPase, Class I, Type 8B, Member 1 (*ATP8B1*) (Painter et al. 2005), as well as ATP-Binding Cassette, Subfamily C, Member 2 (*ABCC2*) (Sookoian et al. 2008).

Sodium-taurocholate cotransporting polypeptide (NTCP) is a carrier protein in the basolateral membrane of the hepatocyte to uptake conjugated bile salts from the plasma in a sodium-dependent manner. The human NTCP protein consists of 349 amino acid residues, with a calculated molecular mass of 38 kDa (Hagenbuch and Meier 1994). This protein is encoded by the gene Solute Carrier Family 10, Member 1 (*SLC10A1*), which spans approximately 23 kb distributed over five exons (Shiao et al. 2000). Pathogenic variants of *SLC10A1* gene impair NTCP function, giving rise to intractable elevated levels of plasma bile acids (hypercholanemia) (Vaz et al. 2015; Karpen and Dawson 2015). Although the gene *SLC10A1* was cloned as early as in 1994 (Hagenbuch and Meier 1994) while NTCP function has been studied extensively (Ho et al. 2004; Yan et al. 2012, 2014), the first patient with NTCP deficiency

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was just reported in 2015 as a homozygote of the *SLC10A1* variant c.755G>A(p.Arg252His) (Vaz et al. 2015). Thereafter, only a limited number of such patients harboring biallelic pathogenic *SLC10A1* variants including c.800C>T(p.Ser267Phe), c.263T>C(p.Ile88Thr) and c.615_618del (p.Ser206Profs*12) have been reported (Deng et al. 2016; Liu et al. 2017; Qiu et al. 2017; Song and Deng 2017; Van Herpe et al. 2017; Tan et al. 2018), while the clinical features of NTCP deficiency remained far from being well understood.

In this paper, five patients with NTCP deficiency were diagnosed via *SLC10A1* analysis in two unrelated families. Our findings suggest that with hypercholanemia being a common laboratory change, NTCP deficiency may be a genetic factor leading to ICP and even cesarean section in clinical practice.

Clinical Report

Patient 1 was a 2-month-old male referred to our hospital due to elevated serum levels of total bile acids (TBA) for 2 months. Soon after birth, the infant was admitted to the Neonatal Section in the local hospital as a high-risk baby due to ICP of his mother. On the first day after birth, jaundiced sclera and skin were noticed and increased serum bilirubin and TBA levels were revealed on biochemistry analysis (Table 1). His jaundice was alleviated soon in response to phototherapy, but the hypercholanemia persisted. The patient was then discharged at the age 9 days, and on subsequent clinic follow-up, the hyperbilirubinemia subsided gradually while hypercholanemia became increasingly prominent (Table 1). Hence, when aged 2 months, the baby was referred to our hospital for further investigation and management.

As the second child of a non-consanguineous couple, the infant was delivered with the birth weight 3.35 kg and body length 50 cm. The mother was found to have ICP at the gestational age (GA) 37 weeks and 2 days, with a TBA level of 25.93 μmol/L (Table 1), and then gave birth to the baby spontaneously one week later. No history of hepatitis or any genetic diseases in the family. The infant had a healthy brother who had been vaginally delivered as a full-term baby after an uneventful pregnancy.

Physical examination at his referral to our hospital revealed a body weight 5.92 kg (–0.33SD), height 60 cm (–0.17SD) and head circumference 39.2 cm (–0.38SD). No jaundice was observed in the skin and sclera, and no malformation in head, ears, nose, mouth, and eyes could be observed. No abnormal breath sounds, wheezes or rales were heard in the two lungs. No murmurs were noticed on heart auscultation. The liver and spleen were not enlarged.

Biochemistry analysis at referral revealed a markedly elevated TBA level as high as 225.1 μmol/L (0-10 μmol/L) in the infant. The mother and father also demonstrated slight hypercholanemia, with the TBA levels of 37.9 μmol/L and 21.5 μmol/L, respectively (Table 1). NTCP deficiency was highly suspected, and Sanger sequencing of the *SLC10A1* gene revealed that the infant and his parents are all homozygotes of the reported pathogenic variant c.800C>T (p.Ser267Phe) (Fig. 1A). Due to unavailable blood sample, *SLC10A1* genotyping was not carried out for the sibling brother of this child.

NTCP deficiency was thus definitely diagnosed for the infant as well as his parents. No specific suggestion other than close clinic follow up was given. When aged 98 days, his hypercholanemia was still unresolved, with the TBA level of 123.1 μmol/L.

Patient 2 was a 20-month-old male referred to our clinic due to high TBA levels for 20 months. The infant

Table 1. Biochemical alterations in Family 1.

Indices (reference range)	Patient 1							Mother			Father
								Gestational ages		Postpartum	
	1 D	4 D	12 D	41 D	56 D	2 M	98 D	37 + 2 W	38 + 2 W	2 M (Age 28 Y)	32 Y
ALT (5-40 U/L)	7	10	10	38	41	46	70	-	5	24	16
ALT (5-40 U/L)	43	31	19	50	-	45	54	-	17	25	21
GGT (8-50 U/L)	-	-	-	-	138	108	71	-	72.8	29	23
TP (60.0-83.0g/L)	50.7	52	51.3	52.9	51.4	53.5	59.4	-	37.3	83.8	73.7
ALB (35.0-55.0 g/L)	30	31.4	31	36	40.4	37.7	41.5	-	35.5	47.7	49.2
GLB (20.0-30.0 g/L)	20.7	20.6	20.3	16.9	11	15.8	17.9	-	-	36.1	24.5
Tbil (2-19 μmol/L)	123	137	71.1	56	24.1	20.8	12.9	-	-	14	14.7
Dbil (0-6 μmol/L)	8.2	13.4	11.9	13.4	6.1	8.3	3.4	-	-	2.4	2.7
Ibil (2.56-20.9 μmol/L)	114.8	123.6	59.2	42.6	18	12.5	9.5	-	-	11.6	12
TBA (0-10 μmol/L)	36.6	94.9	141.3	150	193	225.8	123.1	25.9	19.4	37.9	21.5

In full-term baby, the upper limit for Tbil level in the first 1-4 days were 85, 145, 190, and 215 μmol/L, respectively; and in the 5-7 days of life, 225 μmol/L.

D, days; W, weeks; Y, years; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; TP, total protein; ALB, albumin; GLB, globulin; Tbil, total bilirubin; Dbil, direct bilirubin; Ibil, indirect bilirubin; TBA, total bile acids; −, not tested.

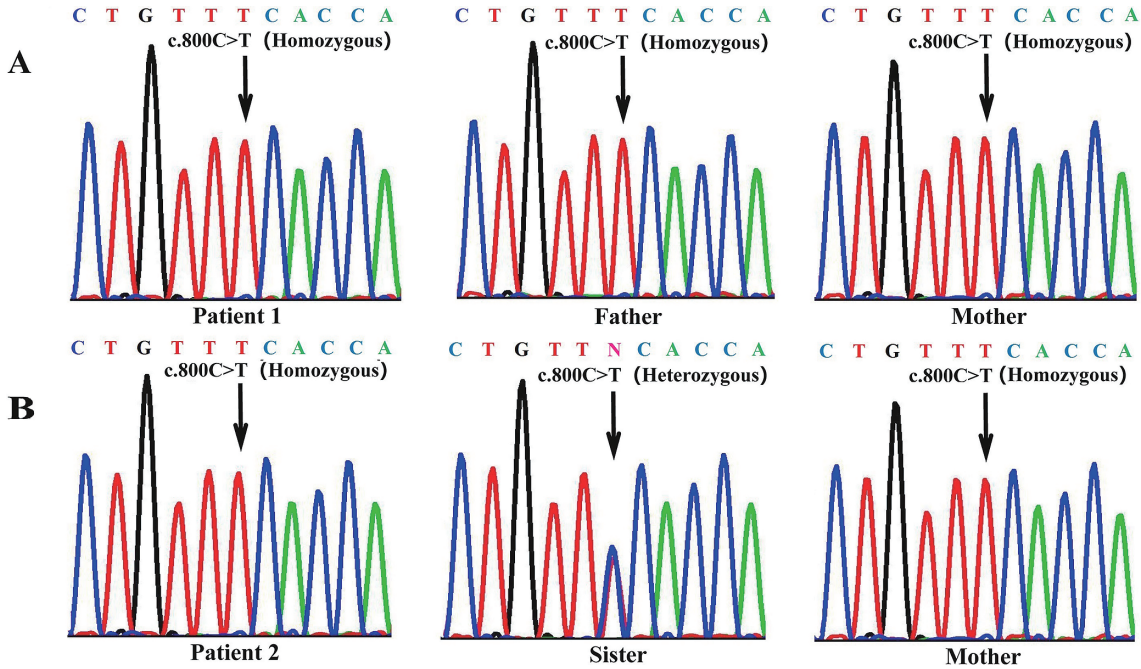

Fig. 1. *SLC10A1* genotypes of the 2 unrelated families on Sanger sequencing.
(A) Patient 1 and his parents are all homozygotes of the variant c.800C>T (p.Ser267Phe). (B) Patient 2 and his mother are both homozygous for, while his twin sister is a carrier of the same variant. The letter "N" stands for the heterozygous nucleotides of the variant c.800C>T.

Table 2. Biochemical alterations in Family 2.

Indices (reference range)	Patient 2								Mother						Sister	
									Gestational ages					Postpartum		
	1 D	3 D	6 D	21 D	2 M	2.7 M	12 M	20 M	30 + 1 W	31 + 6 W	32 + 6 W	33 + 5 W	34 + 4 W	20 M (Age 29 Y)	1 D	20 M
ALT (5-40 U/L)	5	-	10	9	16	22	28	31	30	35	36	26	-	12	7	20
ALT (5-40 U/L)	36	-	24	23	27	36	38	46	21	20	22	13	-	15	39	52
GGT (8-50 U/L)	212	-	-	130	-	-	11	10	-	-	-	-	-	14	-	7
TP (60.0-83.0g/L)	52.3	-	55.2	46.3	-	-	66	71.4	62	56.9	64.6	54.6	-	81.2	-	66.4
ALB (35.0-55.0 g/L)	35.3	-	32.4	31	-	-	44.2	44.6	55.1	32.3	35.3	29.4	-	44	-	44.7
GLB (20.0-30.0 g/L)	17	-	22.8	15.3	-	-	21.8	26.8	26.9	24.6	29.3	25.2	-	37.2	-	21.7
Tbil (2-19 μmol/L)	31.1	129.1	-	19.6	11.2	3.4	2.8	7.2	8.3	7.4	6.9	-	-	12	39	6.3
Dbil (0-6 μmol/L)	12.5	14.9	-	7.3	4.7	1.4	0.7	1.2	-	2.3	1.8	-	-	2.3	13.3	1.8
Ibil (2.56-20.9 μmol/L)	18.6	114.2	-	12.3	6.5	2	2.1	6	-	5.1	5.1	-	-	9.7	25.7	4.5
TBA (0-10 μmol/L)	30.2	-	54.5	141.7	178.7	57.3	48.4	60.3	25.4	22.6	12.9	35.6	28.5	14.5	24.5	16.2

D, days; W, weeks; Y, years; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; TP, total protein; ALB, albumin; GLB, globulin; Tbil, total bilirubin; Dbil, direct bilirubin; Ibil, indirect bilirubin; TBA, total bile acids; −, not tested.

had been admitted to the Third Affiliated Hospital, Sun Yat-Sen University as a premature baby born by cesarean section at the gestation age of 34 weeks and 4 days due to ICP of the mother. On day 1 after admission, a biochemistry test revealed elevated plasma levels of bilirubin and TBA (Table 2). In response to phototherapy, his jaundice subsided and he was discharged when aged 14 days. Thereafter, a series of clinic follow-up revealed refractory hypercholanemia (Table 2), and thus the parents referred the baby to our clinic for further investigation and treatment at his age 20 months.

The patient was one of the preterm twins with the birth weight 1.75 kg and body length 50 cm. The twin sister was apparently healthy, but also had slightly elevated serum TBA levels (Table 2). The mother had suffered from ICP since the GA 30 weeks and 1 day. Then oral ursodesoxycholic acid was given, but her hypercholanemia was intractable, eventually resulting in cesarean section at the GA 34 weeks and 4 days. However, even after delivery, her hypercholanemia persisted (Table 2). Family history of any genetic diseases was denied.

On physical examination at his referral to our clinic, the body length was 82 cm (–0.22SD), weight, 9 kg (–1.9SD), and head circumference, 45.5 cm (–1.75SD). No positive signs were found in the two lungs and heart. Abdomen was flat and soft, without liver or spleen enlarge-

ment. Physiological reflexes existed without any pathological ones.

Sanger sequencing of the *SLC10A1* gene demonstrated that the patient and his mother are both homozygous for the variant c.800C>T (p.Ser267Phe), and his twin sister, a carrier of the same variant (Fig. 1B). The genotype of the father was not analyzed because of unavailable blood sample. The infant and mother were hence diagnosed to have NTCP deficiency. No specific treatment was given, and clinic follow up was ongoing.

Ethical Approval

This research was carried out with written informed consents from the parents of the patients, and had been approved by the Committee for Medical Ethics, the First Affiliated Hospital, Jinan University in Guangzhou, China.

Discussion

By way of *SLC10A1* analysis, five new patients with NTCP deficiency were definitely diagnosed in this paper, including two infants and three adults all presenting with elevated plasma TBA levels. NTCP is highly expressed on the basolateral membrane of hepatocytes, and plays a key role in the enterohepatic circulation of bile salts as the major transporter of conjugated bile salts from the plasma compartment into the hepatocyte (Hagenbuch and Dawson 2004; Anwer and Stieger 2014). The c.800C>T(p.Ser267Phe) variant detected in all five patients in this paper had been reported to nearly eliminate the NTCP function for bile acid uptake, suggesting that this position may be part of a region in the transporter critical and specific for bile acid substrate recognition (Ho et al. 2004). There are sodium-independent bile acid transporters on the hepatocyte sinusoidal membrane such as OATP 1B1/1B3 as well as OSTα-OSTβ, but their effect on bile acid clearance is insufficient to compensate for loss of NTCP (Karpen and Dawson 2015). It was therefore not surprising that the five patients in this paper present with hypercholanemia as their common clinical characteristics.

As a carrier of the variant c.800C>T, the twin sister of Patient 2 also exhibited mild hypercholanemia. This finding, however, did not constitute a challenge against NTCP deficiency as an autosomal recessive condition. Due to immature hepatic function, transient elevation of serum TBA levels in normal neonates and infants represented a state of "physiologic cholestasis" (Balistreri et al. 1981) which had been reported repeatedly (Suchy et al. 1981; Polkowska et al. 2001). Particularly, in human beings, NTCP protein was gradually expressed on the plasma membrane of the hepatocyte in an age-dependent manner, and its glycosylation was not completed until approximately 1 year after birth (Sargiacomo et al. 2018). Consequently, the hypercholanemia in the preterm twin sister of Patient 2 might be a reflection of evolving maturation of liver function after birth. Of note, her hypercholanemia was not so prominent as in the five patients with NTCP deficiency (Tables 1 and 2), and might resolve spontaneously later in pace with their development and growth, as we observed previously (Li et al. 2018).

ICP diagnosis was based on otherwise unexplained pruritus and elevated serum bile acid concentrations ≥ 11 μmol/L; however, although uncommon, isolated elevation of bile acids may occur (European Association for the Study of the Liver 2009). In terms of the NTCP-deficient mothers in the two unrelated families, although without intense pruritus, their TBA levels were intractably elevated in the third trimester of pregnancy, and the ICP diagnosis led to cesarean section to terminate pregnancy in Family 2, giving birth to two premature babies. It was well known that ICP is a reversible condition with spontaneous relief after delivery within 4-6 weeks; however, this was not the case for the two women with NTCP deficiency in this paper (Tables 1 and 2). These findings suggested that NTCP deficiency might be a novel genetic factor leading to ICP diagnosis in clinical practice and should be considered in pregnant women presenting with persistent hypercholanemia in the third trimester of pregnancy, especially in those without spontaneous relief postpartum.

The finding of the two women with NTCP deficiency presenting as ICP raised a new question whether hypercholanemia from maternal NTCP deficiency will threaten the fetus as in traditional ICP cases. Van Herpe et al. (2017) reported a female who suffered from ICP and NTCP deficiency and lost her fetus in the third trimester. This important report excluded other common causes of late fetal loss, but to confirm a causal link, larger series of hypercholanemia due to NTCP deficiency and associated with late fetal loss are necessary (Van Herpe et al. 2017). In this paper, to avoid possible detrimental effect of maternal ICP on the fetuses, Family 2 chose cesarean section to terminate pregnancy. Although the resultant babies all demonstrated benign prognoses, the association remained uncertain between the favorable clinical outcomes with the interrupted effects of maternal NTCP deficiency on the fetuses. Overall, these sporadic maternal cases of NTCP deficiency were not enough to draw a conclusion for its negative effect on fetus health, but raised a new question worthy of further investigation.

In conclusion, five patients with NTCP deficiency in two unrelated families were diagnosed, including two women who had suffered from ICP, leading to cesarean section in one of them. The findings in this paper suggest that with hypercholanemia being a common laboratory change, NTCP deficiency may be a genetic factor leading to ICP and even cesarean section in clinical practice.

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Conflict of Interest

The authors declare no conflict of interest.

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