

Sodium taurocholate cotransporter polypeptide deficiency with α -Thalassemia and Coffin-Siris syndrome

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Abstract

NTCPD, α -Thalassemia and CSS are three hereditary diseases associated with autosome. Especially, NTCPD and CSS are rarely reported in children. However, the co-occurrence of the three hereditary diseases occurred in a child, and presented complex and diverse genotypes and phenotypes, which has never been described.

Introduction

Sodium taurocholate cotransporting polypeptide deficiency (NTCPD) is an inborn error of bile acid metabolism caused by the solute carrier family 10 member 1 (SLC10A1) gene variants, which diminishes the enterohepatic circulation of bile acids by impairing the NTCP function as the primary transporter of conjugated bile salts from the plasma into hepatocytes^[1]. In 2015, Vaz et al. described the first NTCPD patient^[2]. Since then, sporadic cases with diverse genotypes have been reported in succession, but non of them were NTCPD accompanied with other autosomal diseases. Here, we present a rare pediatric case of NTCPD with α -Thalassemia and Coffin-Siris syndrome (CSS).

CASE

A 2 months and 28 days old male, Han Nationality from the Jianshui County of Yunnan Province, was born full term at 38.5 weeks gestation with a birth weight of 3,200 g and a birth length 47 cm, who was not the product of a consanguineous marriage. He presented skin yellowing, mild anemia and feeding difficulty for 2 months. Physical examination revealed a body weight of 6.5 kg, height 58 cm and head circumference 41.5 cm. Obvious jaundice was observed in the skin and sclera. No stridor, crackles or crepitus was heard in the two lungs. There was no abdominal distention, liver was palpable under the right costal margin (2.0 cm), spleen was non-palpable. Echocardiography showed patent foramen ovale (PFO). Laboratory test revealed that the serum levels of total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), total bile acids (TBA), aspartate transaminase (AST) and alanine transaminase (ALT), thyroid stimulating hormone (TSH), and alkaline phosphatase (ALP) were all elevated; 25-hydroxy vitamin D (VD) was decreased (Table 1). Blood routine examination revealed that the mean corpuscular volume (MCV), corpuscular hemoglobin (MCH) and hemoglobin (HB) were decreased (Table 1). The baby was diagnosed to have hypercholesterolemia, hyperbilirubinemia, mild anemia, abnormal liver and thyroid function, and high suspicion of NTCPD. Sanger sequencing revealed that the patient was a compound heterozygous for the c.800C>T (p.Ser267Phe) and c.263T>C (p.Ile88Thr) SLC10A1 mutations, which was inherited from the mother and father, respectively (Figures 1A-F); moreover, the patient and his mother were both heterozygous missense mutation of c.2698G>A (p.Ala900Thr) in AT-rich interaction domain 1A (ARID1A) gene (Figure 1G and H), and heterozygous deletion type α -Thalassemia ($-\text{SEA}/\alpha\alpha$), while his father was normal (Figure 1I). A diagnosis of NTCPD with heterozygous missense mutations in c.800C>T

and c.263T>C, ARID1A gene with a heterozygous missense mutation in c.2698G>A, and heterozygous deletion type α -Thalassemia ($-^{SEA}/\alpha\alpha$) was confirmed. Considering that the genotype of ARID1A is related to the phenotype of CSS, we did a detailed physical examination for the child again. However, except for feeding difficulties and PFO, we did not find any typical characteristics of CSS, such as developmental delay (DD), mental retardation, hypo/aplasia of the fifth digit phalanges/nails, coarse facial features, or body hypertrichosis and so on, which may be due to the baby was too young. The baby was started on symptomatic and supportive treatment including phototherapy for neonatal indirect hyperbilirubinemia, intravenous ademetionine1,4-butanedisulfonate, oral ursodeoxycholic acid capsules, fat-soluble vitamin D and clostridium butyricum powder. His transaminase, bilirubin, TSH, ALP, VD and foramen ovale gradually returned to normal, but the levels of TBA remained high, and mild anemia, which could only be continuously observed. After two years of close clinic follow-up, the baby grew well and had no other special clinical signs except mild hyperbilirubinemia and anemia (Table1, Figure 1J). We will continue to follow up and observe the patient. Written informed consent was obtained from the child's parents.

Discussion

Since NTCP was cloned in 1994, its function has been studied extensively, while a number of SLC10A1 genetic variants have been identified in humans^[3], such as c.800C>T (p. Ser267Phe), c.263T>C (p. Ile88Thr), c.595A>C (p. Ser199Arg), c.755G>A (p.Arg252His), c.615-618del (p.Ser206Profs*12), c.776G>A/p.G259E, c.374dupG (p. Cys125TrpfsTer23) and c.682-683delCT (p. Leu228AspfsTer49), which were commonly homozygous mutations. Among these mutations, c.800C>T (p. Ser267Phe) as a predominant variant accounting for 94.50% of all mutated alleles^[4], and c.263T>C (p. Ile88Thr) as a secondary one. In addition, SLC10A1 genetic variants could also be composed of compound heterozygotes, such as c.800C>T (p.S267 Phe) and c.263T>C (p.I88T), which were rarely reported. According to the literature and the case we provided, no matter the homozygous or heterozygous mutation of c.800C>T (p.S267 Phe) and/or c.263T>C (p.I88T) in SLC10A1 gene, it will lead to NTCPD and induce the phenotype of persistent hypercholesterolemia. However, knowledge about the laboratory and clinical presentations of patients with NTCPD remains rather limited, and the co-occurrence of several autosomal hereditary diseases in one case is unusual. To date, there has been no report of NTCPD complicated with other autosomal diseases, such as Thalassemia or/and CSS.

Thalassemia is a group of inherited autosomal recessive hemolytic anemia disease with varied phenotype, which is caused by human globin gene synthesis disorders^[5], including α -Thalassemia and β -Thalassemia. In Chinese populations, α -Thalassemia is mainly caused by three types of genotypes: Southeast Asian deletion ($-^{SEA}$ deletion), the right deletion ($-\alpha^{3.7}$), and the left deletion ($-\alpha^{4.2}$). Southeast Asian deletion is the main α -Thalassemia genotype, and the heterozygous deletion ($-^{SEA}/\alpha\alpha$) genotype accounts for approximately 66.0 of all the α -Thalassemia mutation carriers^[6].

The clinical features of patient with heterozygous deletion α -Thalassemia are asymptomatic carrier or mild anemia. In our case, the patient and his mother were heterozygous carriers for the Southeast Asian α -Thalassemia mutation, and both presented mild anemia.

ARID1A harbors an Nterminal DNA-binding ARID domain and a C-terminal folded region, and as one of the six genes (ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1), encodes for the BRG1/BRM-associated factor chromatin remodeling complex^[7]. As a subunit of the evolutionarily, ARID1A plays an important role in the maintenance of cell identity and the determination of cell fate, and is associated with a wide array of developmental disorders and cancers, such as CSS and hepatoblastoma. Approximately 5–7% of molecularly-confirmed CSS was caused by the heterozygous missense variants of ARID1A^[8], such as c.5954C>G (p.Ser1985Cys), c.6314C>T (p.Thr2105Ile), c.6334C>T (p.Leu2112Phe), and c.6843G>T (p.Leu2281Phe). The case we reported, accompanied by a de novo heterozygous missense variant ARID1A, which has not been described in large population cohorts.

It is worth noting that the clinical features of CSS, especially facial features, there is a wider degree of variation in patients with mutations in ARID1A and ARID1B. Some scholars even divided CSS into two

groups: “classic” group with coarse facies, and “variant” group with less coarse, more refined features, including thinner eyebrows and thin vermilion border of the lips^[9]. In our case, the patient and his mother were heterozygous missense mutation in ARID1A, but only the baby had feeding difficulties and PFO at birth, and neither the child nor his mother had any other clinical features of CSS during the 2-year follow-up. Therefore, we summarize some problems. First, changing phenotypes according to age, especially craniofacial features and physical or intellectual development. There was a report that patient had only feeding difficulties at birth and other symptoms gradually presented, but our patient still lacked typical symptoms during his growth. Should we consider it as “variant” CSS? Perhaps as a result of a selection bias for the diagnosis, all reports displayed DD, coarse facial appearance and hypo/aplasia of the fifth digit phalanges/nails. Because of this, these features were considered prerequisite for clinical diagnosis of CSS. Second, NTCPD, Thalassemia and CSS are three hereditary diseases associated with autosome. Due to the early onset age, their clinical symptoms are mild or may be similar to some newborn physiological manifestations, such as jaundice. Even some symptoms of the three diseases overlap with each other, such as development disorders. Therefore, it is difficult to diagnose any of the autosomal inherited diseases based on the atypical symptoms, and requires a high level of suspicion for a comprehensive evaluation. In recent years, genetic testing plays an important role in the diagnosis of hereditary diseases. However, it is difficult to find other coexisting hereditary diseases by detecting only one gene mutation site, and hard to carry out whole-gene screening for most patients. Third, due to reports of CSS probands with or without a mildly affected parent, both autosomal recessive and autosomal dominant inheritance have been suggested. But the recessive carrier of ARID1A genetic mutation, like our patient’s mother, has not been reported. The main reasons are attributed to the small number of cases with ARID1A mutations and the incomplete clinical assessment and examinations.

At present, as three genetic diseases, there are no good cure, mainly rely on symptomatic and supportive treatment. Thus, can we learn from the prevention and control strategy of Thalassemia to intervene with NTCPD and CSS? Primary prevention is to reduce the occurrence of congenital disorders and fetus’s disabilities, through health education and genetic screening before pregnancy and in the early stage of pregnancy. Secondary prevention is the treatment of birth defects diagnosed as intermedia or major at an early stage^[10].

In summary, the co-occurrence of three autosome hereditary diseases in a child is unusual. We presented an exceptionally rare male baby with complex and diverse genotypes and phenotypes. Further research is needed to provide more clues and comprehensive insights into this disease.

Data Availability Statement

All data, models, and code generated or used during the study appear in the submitted article.

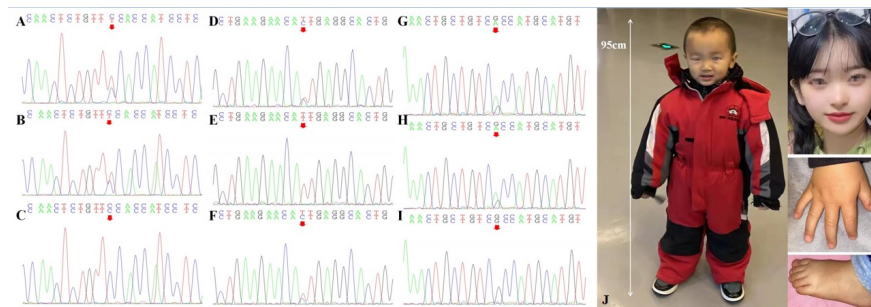
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Table 1. The 2-year follow-up records of physical, blood routine and serology examination of the child.

Figure 1. A-C Sanger sequencing of exon 4 in SLC10A1 gene with the heterozygous c.800C>T (p.Ser267Phe) mutation in the heterozygous state in the proband and his mother (Red arrow). D-F Sanger sequencing of exon 1 in SLC10A1 gene with the heterozygous c.263T>C (p.Ile88Thr) mutation in the heterozygous state in the proband and his father (Red arrow). G-I Sanger sequencing of exon 8 in ARID1A gene with the heterozygous c.2698G>A (p.Ala900Thr) mutation in the heterozygous state in the proband and his mother (Red arrow). J The 2-year follow-up records of growth and development, facial and the fifth digit phalanges/nails features of the child and his mother.



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