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Trichohepatoenteric syndrome and cytomegalovirus infection: Case report and literature summary

Yumo Zhu[1,2], Yanyan Cao[2,3], Li Ma[1,2], Lili Fan[1,2], Weicong Pu[1,2] and Yaofang Xia[1,2]

Abstract

Trichohepatoenteric syndrome is a rare autosomal recessive genetic disease caused by *TTC37* (also known as *SKIC3*) or *SKIV2L* gene variant. We present a severely affected 2-month-old male infant with recurrent fever and unexplained diarrhea. Additionally, clinical data of 11 patients with trichohepatoenteric syndrome in China from 1 to 60 days of onset was presented. The infant's condition was not substantially relieved after cefotaxime sulbactam and meropenem treatment. Whole-exome sequencing revealed compound heterozygous variants (c.1708C>T and c.3342-9T>G) in *TTC37* of the child whose parents were heterozygous carriers of the corresponding locus. The c.3342-9T>G variant originated from his mother and was reported for the first time. Combined with the clinical manifestations, the infant was diagnosed with trichohepatoenteric syndrome and treated with ganciclovir antiviral, intravenous nutritional support, and liver function protection. The infant was discharged with no fever and high stool frequency, but his condition improved. Therefore, trichohepatoenteric syndrome should be considered for recurrent fever and unexplained diarrhea.

Keywords

Trichohepatoenteric syndrome, *TTC37*, cytomegalovirus, whole-exome sequencing

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Introduction

Trichohepatoenteric syndrome (THES) is a rare autosomal recessive disorder caused by variants in *TTC37* and *SKIV2L*. In 1997, Verloes et al.[1] named this disease THES. THES is stratified into type 1, which accounts for 2/3 of THES cases and is caused by the *TTC37* gene variant, and type 2, which accounts for 1/3 of THES cases and is caused by the *SKIV2L* gene variant.[2] THES is associated with five main manifestations: diarrhea, facial dysmorphism, hair abnormalities, immune disorders, and intrauterine growth restriction. In this study, we present a case of THES due to *TTC37* gene variant, combined with cytomegalovirus infection with neonatal onset, and summarize the reported cases in the last 10 years.

Case

A 2-month-old male infant with diarrhea was referred to the infection department of our hospital. He was born to a gravida 3, parity 3 mother at a gestational age of 37 weeks and 2 days via cesarean section due to a scarred uterus and intrauterine growth restriction, with a birth weight of 1800 g (<3%). The umbilical cord was short and thin, the placenta was small, and the amniotic fluid was clear. He was breastfed after birth and had yellow-green mucus stools with 10–15 bowel movements per day. Admission examination showed a weight of 2500 g, unresponsiveness, no positive cardiopulmonary signs, flat abdomen, no pressure pain, liver and spleen not palpable under the ribs, and normal

[1]Department of Neonatology, Children's Hospital of Hebei Province, Shijiazhuang, China
[2]Pediatric Clinical Research Centre of Hebei Province, Children's Hospital of Hebei Province, Shijiazhuang, China
[3]Institute of Pediatric Research, Children's Hospital of Hebei Province, Shijiazhuang, China

Corresponding Author:
Yaofang Xia, Department of Neonatology, Children's Hospital of Hebei Province, No.133, Jianhua South Street, Yuhua District, Shijiazhuang, Hebei 050031, China.
Email: yaofang75@163.com

bowel sounds. Blood cytomegalovirus Polymerase Chain Reaction (PCR) results showed 2.254×10^3 copies/mL; TORCH, liver and kidney function, total lymphocyte analysis, and immunoglobulin quantification were normal. Cefotaxime sulbactam and meropenem were sequentially administered. The patient was transferred to the neonatal department 2 months and 10 days after birth due to recurrent diarrhea and fever. At this time, his weight was 2830 g, his length was 49 cm, and his head circumference was 32 cm. The skin was pale and swollen, with little subcutaneous fat and thin yellow hair. Cytomegalovirus Immunoglobulin M (IgM) antibody was positive. Blood and urine cytomegalovirus PCR results were 9.801×10^4 and 5.516×10^5 copies/mL, respectively. Alanine aminotransferase, aspartate aminotransferase, and platelet results were 62 U/L, 136 U/L, and 46×10^9/L, respectively. Fecal calprotectin and *Clostridium difficile* were negative, and no abnormalities were found in the genetic metabolism screening for hematuria. The liver ultrasound showed that echogenic enhancement of liver parenchyma was not uniform, and lymph nodes in the hepatic hilum were visible. Immunoglobulin quantification and the total lymphocyte immunoassay showed no obvious abnormality. (Supplemental Table 1). Hearing screening, eyeground check, cranial Computerized Tomography (CT), and Magnetic Resonance Imaging(MRI) tests showed no abnormalities. Gastroduodenoscopy and mucosal biopsy could not be performed due to the infant's age and low weight. Intravenous nutritional support and powdered amino acid formula were administered. Meropenem was stopped after 3 days, and immunoglobulin (1.25 g) was infused for 3 days. Due to the presence of cytomegalovirus infection, growth retardation, liver function impairment, and diarrheal disease, the infant was given intravenous ganciclovir antiviral therapy (6 mg/kg q12h for 2 weeks, qd for 1 week), which was discontinued 3 weeks. After treatment, blood cells and alanine aminotransferase normalized. Stool characteristics also improved, but frequency was still high, and blood was occasionally seen. His parents and two siblings had no special appearance, no history of recurrent fever or diarrhea, and their body size and intelligence were normal. The mother's breast milk cytomegalovirus PCR result was 2.254×10^3 copies/mL. After the family provided informed consent, peripheral blood was drawn from the infant and his parents, and whole-exome sequencing was performed, which showed the presence of c.1708C > T (p.R570X; from the father) and c.3342-9T > G (from the mother) compound heterozygous variants in the *TTC37* gene of the infant. According to the American College of Medical Genetics(ACMG) variant rating guidelines and ClinGen expert recommendations, c.1708C>T (p.R570X) was rated as a pathogenic variant (PVS1 + PM2_ Supporting + PM3_Strong) and c.3342-9T>G was rated as a pathogenic variant (PM2_ Supporting+PM3 +PSV1 RNA) (Figure 1). In combination with the presence of difficult diarrhea, hair abnormalities, recurrent fever, and intrauterine growth restriction, the *TTC37* gene variant causing THES was diagnosed.

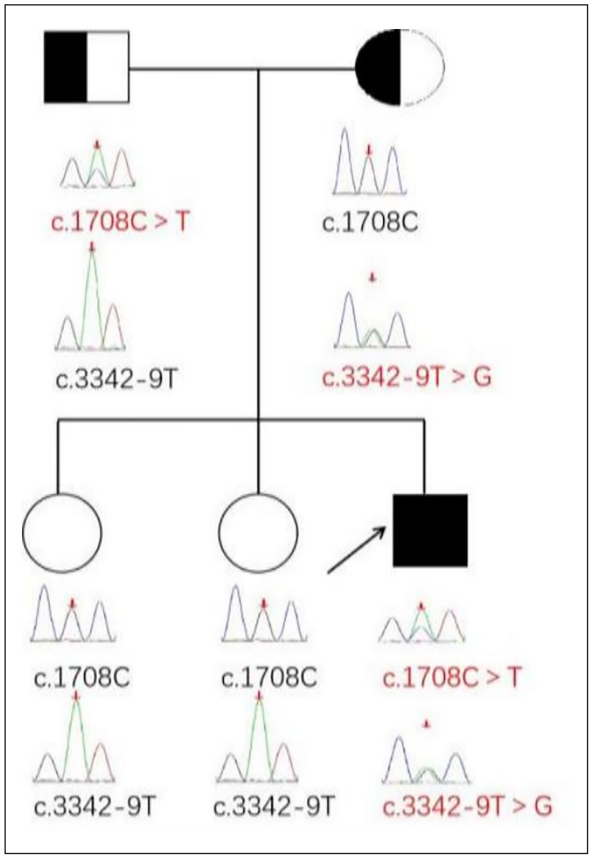

Figure 1. *TTC37* variations in this pedigree: The father carries a heterozygous variant of c.1708C>T. The mother has a c.3342-9T>G heterozygous variant. Two siblings are non-carriers. The patient has the compound heterozygous variations in *TTC37*: c.1708C>T and c.3342-9T>G.

The patient was discharged after 43 days of hospitalization with an improved response, no fever, weight of 2950 g, and weight gain rate of 4.19 g/kg d. The length and head circumference were significantly lower than those of the third percentile, and the patient still had frequent and yellow-green diluted stool, as well as a positive stool routine with occult blood.

After discharge from the hospital, an amino acid formula powder was given at 60–90 mL q3h, with no fever, defecation 3–4 times per day, or irregular characteristics. Three follow-up visits were conducted at 5 months and 12 days, 10 months and 13 days, and 11 months and 28 days after birth. Weight, length, and head circumference were consistently below the World Health Organization (WHO) growth curve. By 11 months and 28 days after birth, the patient's weight was 6800 g, length was 66 cm, and head circumference was 43 cm. T helper cells decreased (26.91%), suppressor T cells increased (35.67%), Natural Killer (NK) cells decreased (1.61%), and total B cells increased (32.78%). Cytomegalovirus IgM antibody was weakly positive, blood cytomegalovirus PCR was

negative, urine cytomegalovirus PCR decreased to 2.325×10^4 copies/mL, and liver function and immunoglobulin quantification showed no abnormalities.

Discussion

THES is an autosomal recessive disorder with an estimated incidence of 1 in 400,000–500,000. A total of 80 patients with THES were reported between 2010 and 2022, 53% were female, 47% were male, and 62% were relatives. The age of survival was 3 weeks to 32 years, the 15-year survival rate was 50.7%, and approximately 50% had mild mental retardation.[3–7] There were more than ten clinical manifestations of THES, all of which included refractory diarrhea, hair abnormalities, and facial deformities. Intrauterine growth retardation occurred in 86% of these cases, low serum immunoglobulin concentrations or lack of humoral immune response occurred in 77%, and chronic liver disease manifestations, such as elevated liver enzymes or cirrhosis, occurred in 51%.[8–10]

The Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php) currently contains 65 THES-related *TTC37* variants that had been reported as of September 2023, of which deletion (30.8%) and nonsense variants (26.2%) are the most common, followed by splice site variants (21.5%), missense variants (18.5%), complex rearrangements (1.5%), and in-frame deletions (1.5%).

TTC37 and *SKIV2L* encode the proteins SKI3 and SKI2, respectively. The SKI2, SKI3, and SKI8 proteins together form the SKI (superkiller) complex (SKIc). SKIc associates with disease, developmental processes, and antiviral responses by regulating mRNA metabolism. *TTC37* and *SKIV2L* variations may lead to SKI3 and SKI2 defects, thus affecting the normal function of SKIc and negatively regulating antiviral response.[11] In addition, when the immune system is immature (e.g., in newborns), cytomegalovirus can evade the host immune response and achieve an immune escape state.[12] Since pUL135 encoded by the human cytomegalovirus genome, can alter the actin cytoskeleton, thereby inhibiting the recognition and activation functions of NK cells, ultimately reducing the number of detected NK cells.[13] A report showed that two siblings matched the clinical features of THES, both with difficult diarrhea, cirrhosis, and microscopic hair structural abnormalities, and both died in infancy from fulminant cytomegalovirus pneumonia; however, THES was not definitively diagnosed.[14] The present case is the first report of THES combined with cytomegalovirus infection with immature immune function in the early postnatal period, which improved clinically after standardized antiviral treatment without further fever. With prolonged birth, the CD series showed a reduced number of T helper and NK cells at 11 months postnatally, suggesting a possible association with immunodeficiency.

TTC37 may be involved in the stability and intracellular localization of target proteins, resulting in abnormal expression or localization of intestinal epithelial cell apical transporter proteins and enterocyte brush border transporter proteins.[15] Almost all patients with *TTC37* variants develop diarrhea, which leads to growth restriction. The time of onset varies from 1 day to 7 months and often involves watery diarrhea with occasional bloody stools; rare cases present as very early onset inflammatory bowel disease. The intestinal pathology involves nonspecific villous atrophy with or without inflammatory cell infiltration. In this case, the infant presented early after birth with diarrhea and yellow watery stools with occasional blood loss accompanied by extrauterine growth restriction, consistent with the pathogenesis of THES. The whole-exome assay identified two compound heterozygous variants in the *TTC37* gene. The c.1708C>T (p.R570X), a known pathogenic variant, originated from the father. The splice variant c.3342-9T>G originated from the mother, and RT-PCR and cDNA sequencing confirmed this variant could result in exon 33 jumping of *TTC37*. (Supplemental Figure 1).

Notably, most of the 11 THES cases of Chinese ancestry (Table 1) were type 2 due to the *SKIV2L* variant (9/11, 82%), and only two cases were type 1 due to the *TTC37* gene variant, which differs from the worldwide distribution of disease types. The 11 cases of THES with Chinese ancestry did not show considerable ethnic or geographical differences. The c.1891G>A nonsense variant in *SKIV2L* was present in four cases, accounting for 21% of the reported alleles; therefore, the c.1891G>A variant may be a hotspot variant in Chinese patients with THES type 2. One of the two THES type 1 cases developed in the neonatal period, and the other developed in infancy, with relatively mild organ system damage. This suggests that patients with THES type 2 had earlier and more severe symptoms than those with THES type 1. The infant with THES type 1 caused by the *TTC37* gene variant exhibited early postnatal onset, with clinical manifestations, such as diarrhea, fever, and elevated liver enzyme levels, and their condition was relatively stable after treatment. The Gesell developmental diagnostic scale showed adaptive, borderline fine motor, mild developmental delays in gross motor, language, and personal-social functions, requiring continued follow-up for long-term prognosis.

There is no specific treatment for THES; the primary treatment is nutritional support. Antibiotics, steroids, immunosuppressants, and hematopoietic stem cell transplantation are not recommended as primary treatments. Malabsorption and growth retardation due to diarrhea usually require long-term parenteral nutrition, with treatment goals of maximizing weight gain and linear growth, reducing infections, and providing targeted intellectual management. In the current case, we achieved slow weight gain during hospitalization with long-term intravenous nutritional support; however, post-discharge follow-up suggested that weight, length, and head circumference were consistently below the WHO growth curve, and continued attention to growth and development is needed.

Table 1. Clinical phenotype and genotype of patients with trichohepatoenteric syndrome in China.

Patient	1[16]	2[17]	3 (this patient)	4[17]	5[17]	6[18]	7[19]	8[20]	9[21]	10[22]	11[23]	12[24]
Sex	Female	Male	Male	Male	Male	Female	Male	Male	Female	Female	Male	Male
Age of onset (days)	30	60	1	17	30	1	30	47	1	28	28	1
First symptoms	Gastroenteritis; severe dehydration	Continuous diarrhea	Growth retardation; diarrhea; fever	Severe diarrhea	Continuous diarrhea	Continuous diarrhea	Diarrhea; fever	Diarrhea	Continuous diarrhea	Fever; vomiting; bloating	Diarrhea	Growth retardation; diarrhea; hematochezia
Difficult diarrhea	+	+	+	+	+	+	+	+	+	+	+	+
Paratrichosis	+	+	+	−	−	+	+	+	+	+	+	+
Difficult diarrhea	+	+	+	+	+	−	+	+	+	+	+	+
Intrauterine growth restriction	+	−	+	−	−	+	+	+	+	+	−	+
Immunodeficiency	+	−	−	−	−	+	+	−	−		−	−
Chronic liver	+	+	−	−	−	−	+	−	−	−	+	−
Parenteral alimentation	+	+	+	+	−	+	−	−	−	−	+	−
Other symptoms	Atrioseptal defect; eczema; psoriasis-like dermatitis		Mild dysgnosia; cytomegalovirus infection	Atrioseptal defect; bicuspid aortic valve; enterogastritis; pneumonia	Aortic stenosis; bicuspid aortic valve; dysgnosia; enterogastritis; pneumonia		Indirect inguinal hernia; ascites; lower respiratory infection; pleural effusion	Metabolic acidosis; anemia; growth retardation	Dysgnosia; osteoporosis; menostasis; premature ovarian failure	Atrioventricular septal defect; metabolic acidosis; acleistocardia; patent foramen ovale	Hypophosphatemia; inguinal hernia; lower respiratory infection; pleural effusion	Dysgnosia; bicuspid aortic valve; necrotizing enterocolitis
Follow-up age and outcome	2 years Alive	11 years Alive	1 year Alive	8.5 years Alive	2.8 years Alive	0.6 years Alive	2.9 years Alive	0.6 years Alive	32 years Alive	0.3 years Dead	6.25 years Alive	0.75 years Dead
Gene	TTC37	TTC37	TTC37	SKIV2L	SKIV2L	SKIV2L	SKIV2L	SKIV2L	SKIV2L	SKIV2L	SKIV2L	SKIV2L
Genetic variant locus	c.3507T>G c.3601C>T	c.3426dupA (homozygote)	c.1708C>T c.3342-9T>G	c.1891G>A c.3187C>T	c.1891G>A c.3187C>T	c.3602_3609delAGCGCCTG; c.1990A>G	c.1891G>A c.1120C>T	c.2446G>T IVS22-1G>A	c.12_13del (homozygote)	c.2344delC (homozygote)	c.1891G>A c.1120C>T	c.2164C>T 6p21.33

Conclusion

THES caused by the *TTC37* variant is rare in the Chinese population. In this case, the diagnosis of THES type 1 was confirmed through coinfection with cytomegalovirus, and the parents were carriers of the pathogenic variant of *TTC37*. Prenatal or preimplantation genetic testing should be performed in future pregnancies. Genetic testing should be performed as early as possible to clarify the diagnosis in children with intrauterine growth retardation, refractory diarrhea, hair abnormalities, unusual facial features, and liver lesions and to alert for coinfection with cytomegalovirus.

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Ethics approval

Ethical approval to report this case was obtained from Ethics Committee of Children's Hospital of Hebei Province. (202136).

Informed consent

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

ORCID iD

Yumo Zhu https://orcid.org/0009-0007-0797-3322

Supplemental material

Supplemental material for this article is available online.

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