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Integrated Traditional Chinese and Western Medicine in the Treatment of Biliary Cholestatic Liver Disease in an Infant with ABCB4 Gene Mutation: A Case Report

Aixia Peng[1], Yufeng Lu[2]

[1]Dongguan Polytechnic, Dongguan 523808, Guangdong, China
[2]Guangzhou Medical University, Guangzhou 511436, Guangdong, China

Abstract: *Objective:* To summarize the clinical manifestations, gene mutation type, treatment, and follow-up results of one admitted infant with biliary cholestatic liver disease caused by ABCB4 gene mutation, so as to improve the understanding of this rare disease. *Methods:* A retrospective analysis was conducted on the clinical manifestations, laboratory examinations, gene mutation type, treatment, and follow-up data of one infant with biliary cholestatic liver disease caused by ABCB4 gene mutation. *Results:* The patient was a 1 month 23-day old male infant. His main clinical manifestations included dark yellow skin, rash, and pruritus. The disease onset was early, and his serum gamma-glutamyl transpeptidase level was elevated. Genetic analysis revealed two newly identified point mutations in the ABCB4 gene, namely c.1576G > A and c.2596A > G heterozygotes, which were inherited from his father. The infant was cured after treatment with integrated traditional Chinese and Western medicine, and no recurrence was observed during a 6-month follow-up. *Conclusion:* This study reports a case of biliary cholestatic liver disease caused by ABCB4 gene mutation in an infant, which expands the mutation spectrum of the ABCB4 gene. It also provides a reference for the early diagnosis and treatment of this rare disease using integrated traditional Chinese and Western medicine.

Keywords: Cholestasis; Intrahepatic; ABCB4 gene; Infant; Integrated traditional Chinese and Western medicine

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1. Introduction

Infantile biliary cholestatic liver disease is the leading cause of hospitalization for pediatric liver diseases in China. Progressive Familial Intrahepatic Cholestasis (PFIC) is one of its etiologies. PFIC is a group of rare, heterogeneous liver diseases with autosomal recessive inheritance. Its estimated incidence is 1 in 50,000 to 100,000. It usually presents with manifestations of biliary cholestatic liver disease in infancy, accompanied by pruritus and malabsorption. The disease progresses rapidly and eventually leads to liver failure.

At present, there are 6 known subtypes of PFIC, namely PFIC type 1 (ATP8B1 deficiency), PFIC type 2 (ABCB11 deficiency), PFIC type 3 (ABCB4 deficiency), PFIC type 4 (TJP2 deficiency), PFIC type 5 (NR1H4 deficiency), and PFIC type 6 (MYO5B deficiency).

Case reports of PFIC type 3 are relatively few, and most cases are distributed among white populations in North Africa, Europe, and Western Asia [1,2]. In China, the first case was reported in 2012, followed by a small number of subsequent reports, especially rare reports of infant cases [3–8]. The epidemiological characteristics of this disease are unclear, and there is limited experience in its diagnosis and treatment.

Herein, this study has reported the clinical characteristics, gene mutation features, and therapeutic effect of integrated traditional Chinese and Western medicine in an infant with biliary cholestatic liver disease caused by ABCB4 (ATP-binding cassette, sub-family B, member 4) gene mutation.

2. Subjects and methods

2.1. Subject

One infant visited our hospital on September 28, 2021. The infant was male, aged 1 month and 23 days.

2.2. Methods

2.2.1. Genetic testing

A 2 mL sample of the infant's peripheral venous blood was collected and sent for testing (Guangzhou Sheng'an Medical Laboratory). Capture-based high-throughput sequencing technology was used. Genomic DNA was extracted from the blood sample, and then specific primers were used to amplify the exon regions of the target genes (including ABCB4) to be detected.

After the quality of the obtained products met the control standards, a sequencing library was constructed. A high-throughput sequencer was used to sequence the constructed library, with the reference genome version being GRCH/37hg19. After mutations were detected, 2 mL samples of peripheral venous blood were collected from each of the infant's parents and sent for testing. Sanger sequencing was used to verify the DNA in the parents' blood samples.

2.2.2. Medical history collection and condition at the time of consultation

The infant sought medical attention because skin jaundice had persisted since the neonatal period, and the skin color had turned dark yellow in the past more than 10 days. The infant was the first child of the first pregnancy, born at full term via normal vaginal delivery. Regular prenatal examinations were conducted, and there were no abnormalities during delivery. The birth weight was 3400 g. Jaundice appeared a few days after birth, initially bright yellow. The jaundice fluctuated but persisted without treatment. In the more than 10 days before consultation, the infant's skin color was found to turn dark yellow. The stool was pasty with a pale color, and the urine color was yellowish. A rash also appeared, which might have been accompanied by pruritus (manifested as head turning, twisting, and crying).

The infant's milk intake did not decrease. The infant was breastfed after birth, with good weight gain. The mother took loratadine for about 2 weeks due to "skin allergy" after delivery. At admission, the infant's weight was 4900 g, with normal crying and responsiveness. The skin was dark yellow, and fine granular, spine-like, densely distributed rashes were seen on the neck and upper chest. The rashes were slightly whiter than the dark yellow

base skin color, with a natural transition to normal skin and no obvious boundary. There were no petechiae. The sclera was slightly yellow, the lip color was pale, and the tongue coating was white and greasy. The abdomen was slightly distended and soft, with no visible veins.

The liver was palpable about 2 cm below the costal margin, with a blunt edge and moderate texture. The spleen was not palpable. Auxiliary examinations at admission (see **Table 1** for details): Liver function and color Doppler ultrasound of the liver, gallbladder, spleen, and pancreas were normal. The quantitative level of alpha-fetoprotein (AFP) was 340.8 ng/mL, total cholesterol was 3.24 mmol/L, and triglyceride was 1.91 mmol/L. Tests for TORCH infection-related IgM antibodies, hepatitis B, hepatitis C, syphilis, and AIDS were negative. Blood glucose, blood ammonia, activated partial thromboplastin time (APTT), prothrombin time (PT), blood routine, C-reactive protein (CRP), renal function, myocardial enzymes, electrolytes, and routine urine and stool tests were all normal.

Table 1. Laboratory tests, ultrasound findings, and symptoms at different ages

Indicator	1 Month 23 Days (At Admission)	2 Months 1 Day (At Discharge)	3 Months 8 Days	4 Months	6–7 Months	Normal Range
Tbil (umol/L)	74.19	19.46	5.18	4.3	1.64	3.40–17.0
Dbil (umol/L)	44.87	8.86	1.81	1.3	0.81	0–6.0
TBA (umol/L)	136.9	46.3	38.4	27.2	6.9	0–9.67
ALT (U/L)	59.1	63.8	22.10	19.4	30.1	7–40
AST (U/L)	73.8	81.8	33.30	36.0	43.3	8–40
GGT (U/L)	104.8	53.3	18.00	9.7	6.1	9–45
ALP (U/L)	529.70	376.7	297.44	-	229.33	20–220
ALB (g/L)	37.4	44.7	35.2	40.4	42.5	35.0–55.0
TP (g/L)	51.3	54.4	55.2	58.0	60.2	49–71
Blood Ammonia	17.4	23.50	-	-	-	10–47
CHOL	-	3.24	-	3.79	-	3.00–5.20
TG	-	1.91	-	0.73	-	0.40–1.70
AFP (ng/mL)	-	340.8	-	-	-	—
Four Coagulation Tests	Normal	-	-	-	-	—
Hepatobiliary Ultrasound	No Abnormality	Slightly Enhanced Biliary Echo	-	No Abnormality	No Abnormality	—
Skin Color	Obvious Dark Yellow	Slightly Dark Yellow	Normal	Normal	Normal	—
Spine-Like Rash	Neck and Upper Chest	Significantly Faded	None	None	None	—
Pruritus	Suspected	Suspected	None	None	None	—
Stool	Pale Yellow-Brown	Yellow-Brown	Normal	Normal	Normal	—

Tbil: Total Bilirubin, Dbil: Direct Bilirubin, TBA: Total Bile Acid, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transpeptidase, ALP: Alkaline Phosphatase, ALB: Albumin, TP: Total Protein, AFP: Alpha-Fetoprotein, CHOL: Cholesterol, TG: Triglyceride, -: Not Tested.

2.2.3. Diagnosis and treatment

(1) Admission diagnosis

Infantile biliary cholestatic liver disease. Traditional Chinese Medicine (TCM) diagnosis: Fetal Jaundice (Tai Huang Bing), syndrome of cold-dampness obstruction.

(2) Treatment

Lidan Mixture (concentrated granule formulation), containing Yinchen (*Artemisiae scopariae herba*), Lianqiao (*Forsythiae fructus*), Heshouwu (*Polygoni multiflori radix*), Rougui (*Cinnamomi cortex*), Chishao (*Paeoniae radix rubra*), Guizhi (*Cinnamomi ramulus*), Zhiqiao (*Aurantii fructus*), Baizhu (*Atractylodis macrocephalae rhizoma*), Wuweizi (*Schisandrae chinensis fructus*), Chuanshanjia (*Manitis squama*), and Gancao (*Glycyrrhizae radix et rhizoma*). One dose was administered daily, dissolved in 50 mL of water, and taken in 2 divided doses. A 2-week period constituted one course of treatment. Oral administration of ursodeoxycholic acid (UDCA) and glucuronolactone for choleretic and hepatoprotective therapy.

2.2.4. Efficacy evaluation

The TCM Syndrome Scoring Table for cholestatic hepatitis was developed with reference to the Guiding Principles for Clinical Research of New Chinese Medicines. The efficacy index was calculated using the formula: [(Pre-treatment score - Post-treatment score) / Pre-treatment score] × 100%.

(1) Clinical cure

Main symptoms and signs disappeared or basically disappeared, with an efficacy index ≥ 95%.

(2) Marked effect

Main symptoms and signs improved significantly, with an efficacy index ranging from 70% to < 95%.

(3) Effective

Main symptoms and signs improved obviously, with an efficacy index ranging from 30% to < 70%.

(4) Ineffective

Main symptoms and signs showed no significant improvement or even worsened, with an efficacy index < 30%.

3. Results

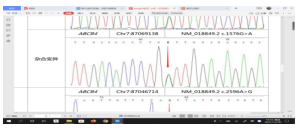
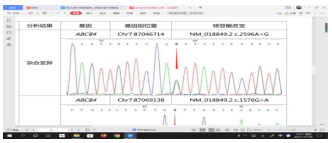
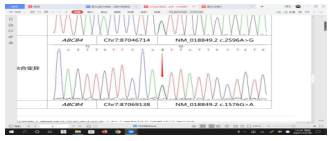
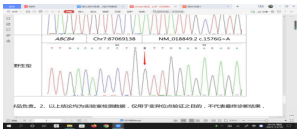
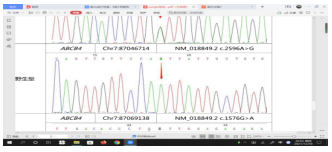
3.1. Genetic testing results

For the genetic testing of common hereditary diseases causing jaundice (Guangzhou Sheng'an Medical Laboratory), exon capture high-throughput sequencing detected two heterozygous mutations in the infant's ABCB4 gene. Both were missense mutations, namely c.1576G>A and c.2596A > G (see **Table 2**). Sanger sequencing verification confirmed that the infant carried the above two heterozygous mutations, both inherited from the father, while the mother had the wild-type genotype (see **Table 3**). In addition, one heterozygous insertion mutation (IVS16ins3KB) was detected in the infant's SLC25A13 gene, but no further Sanger sequencing verification was performed as blood samples from the parents were not collected. A search of the Wanfang, CNKI, VIP, PubMed, and HGMD databases showed that the above two ABCB4 gene mutations were newly identified types that had not been reported previously.

Table 2. ABCB4 gene detection results of the infant

Chromosomal location	Transcript	Nucleotide change	Amino Acid change	Genotype
Chr7:87069138	NM_018849.2	c.1576G > A	p.Val526Ile	Heterozygous
Chr7:87046714	NM_018849.2	c.2596A > G	p.Ile866Val	Heterozygous

Table 3. Sanger sequencing electropherograms of the proband and his parents

Subject	Analysis result	Chr7:87069138, c.1576G > A	Chr7:87046714, c.2596A > G
Proband (Infant)	Heterozygous		
Proband's father	Heterozygous		
Proband's mother	Wild type		

3.2. Results of blood and urine metabolite tests

Tandem mass spectrometry analysis of blood metabolites showed elevated levels of Arg (arginine), CO (carbon monoxide), C_2 (acetylcarnitine), C_3 (propionylcarnitine), Arg/Phe (arginine/phenylalanine), Met/Phe (methionine/phenylalanine), C_3/C_{16} (propionylcarnitine/palmitoylcarnitine), $CO/(C_{16}+C_{18})$ (carbon monoxide/(palmitoylcarnitine+stearoylcarnitine)), and Orn/Ala (ornithine/alanine).

It also showed decreased levels of C_{16}DC (hexadecenoylcarnitine), C_{14}/C_3 (myristoylcarnitine/propionylcarnitine), C_{16}/C_2 (palmitoylcarnitine/acetylcarnitine), C_{16}/C_3 (palmitoylcarnitine/propionylcarnitine), C_{18}/C_3 (stearoylcarnitine/propionylcarnitine), and $(C_{16}+C_{18:1})/C_2$ ((palmitoylcarnitine+oleoylcarnitine)/acetylcarnitine). No abnormalities were found in the urine GS-MS (gas chromatography-mass spectrometry) results.

3.3. Treatment and follow-up results

After one course of integrated Traditional Chinese and Western medicine treatment, the therapeutic effect was significant. Laboratory test results improved rapidly, and clinical symptoms gradually alleviated. The infant achieved clinical cure at discharge.

During the 3-month follow-up, no symptoms occurred. Ultrasound results and laboratory tests tended to be normal, and the infant had good growth and development. The clinical manifestations, laboratory data, and auxiliary examination results at different time points are shown in **Table 1**. The infant's father was in good health. His serum total bilirubin, direct bilirubin, total bile acid, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, albumin, alpha-fetoprotein, cholesterol, and triglyceride levels were all normal. He denied having pruritus, jaundice, or other liver disease histories, as well as such histories in his relatives.

4. Discussion

Among infantile biliary cholestatic liver diseases, Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of hereditary diseases mainly manifested as cholestatic hepatitis. PFIC type 3, caused by ABCB4 gene mutation, is one of its subtypes. The main clinical features of PFIC type 3 are as follows: it usually onsets in children or adolescents, with elevated gamma-glutamyl transpeptidase (GGT) levels; except for pruritus, there are few other extrahepatic manifestations. Pathologically, it is characterized by extensive bile duct proliferation and periportal fibrosis, and may eventually progress to cirrhosis and liver failure in early adulthood. The diagnosis of PFIC type 3 requires the exclusion of other causes of cholestasis, such as biliary atresia, Alagille syndrome, and alpha-1-antitrypsin deficiency. To date, there are no clinical or laboratory diagnostic criteria for PFIC type 3, and its confirmation relies on genetic diagnosis. Reports on genetic diagnosis of PFIC type 3 first appeared overseas, mostly involving white Europeans and North African Arabs. With the popularization of genetic testing, domestic reports have gradually emerged.

ABCB4 gene mutation can lead to decreased expression or absence of multidrug resistance protein 3 (MRP3). This results in phospholipid deficiency in bile, causing free bile salts to exert toxic detergent effects on the capillary bile duct membrane. Consequently, bile duct damage, proliferation, and inflammatory infiltration occur, which gradually develop into periportal fibrosis, cirrhosis, and portal hypertension [1]. The ABCB4 gene is located at chromosome 7q21.1, spanning 74 kb and containing 28 exons. More than 100 types of ABCB4 gene mutations have been reported so far, including missense mutations, nonsense mutations, deletion mutations, insertion mutations, and splice site mutations. Family members may carry homozygous mutations, heterozygous mutations, compound heterozygous mutations, or multiple heterozygous mutations. It is generally believed that the type of gene mutation is associated with the severity of the disease. Nonsense mutations, deletion mutations, and homozygous mutations in family members are more likely to cause severe clinical symptoms. A multicenter study in Europe defined ABCB4 gene mutations as disease-causing mutations (DCM) or benign substitution mutations by determining whether the mutation leads to premature termination of translation and using the PolyPhen algorithm [9]. Patients with severe ABCB4 genotypes usually show no response to ursodeoxycholic acid (UDCA) and often develop cirrhosis and end-stage liver disease within the first 20 years of life. Although children carrying a single ABCB4-related benign substitution mutation may remain asymptomatic for many years or only present with non-jaundiced pruritus, studies have found that even a single missense heterozygous point mutation in the ABCB4 gene can impair MDR3 function [10]. Patients with mild genotypes, including those with a single heterozygous mutation, may present with various liver disease manifestations. These manifestations may be influenced by comorbidities or triggering factors, or regulated by as-yet-unknown genetic modifiers [11,12]. Domestic literature has also reported that hepatitis B virus infection and cytomegalovirus infection may be comorbidities or triggering factors affecting MDR3 function in patients with ABCB4 gene mutations [8,13].

This study also detected a heterozygous mutation (IVS16ins3KB) in the infant's SLC25A13 gene. Mutations in the SLC25A13 gene can cause neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). IVS16ins3KB is the most common mutation type in patients, but heterozygous mutations do not cause the disease. NICCD usually onsets early, presenting with intrahepatic cholestasis, often accompanied by galactosemia, hypoproteinemia, bleeding tendency, hypoglycemia, and a significant increase in alpha-fetoprotein. Elevations of multiple amino acids, such as citrulline, methionine (Met), phenylalanine (Phe), and threonine (Thr), may also occur; early elevation of citrulline is of great significance for diagnosis. In this case, the infant had an early onset and presented with intrahepatic cholestasis, but lacked the other above-mentioned characteristics, so NICCD could

not be diagnosed. Through further inquiry about the medical history, we learned that the infant was exclusively breastfed, and the mother had a history of using the antiallergic drug loratadine. Whether the heterozygous mutation of the SLC25A13 gene and loratadine in this infant are triggering factors or comorbid factors for the onset of PFIC type 3 requires further investigation.

The epidemiological characteristics of PFIC type 3 in China remain unclear. In this case, the infant had an early onset, with jaundice persisting since the neonatal period, and presented with typical manifestations of biliary cholestatic liver disease at the time of consultation. Two heterozygous missense mutations were detected in the ABCB4 gene; Sanger sequencing confirmed that both mutations were inherited from the father, while the mother had the wild-type genotype. Through family history inquiry, it was found that the infant's father and his relatives had no history of pruritus, jaundice, or other liver diseases. A literature search showed that the above two heterozygous mutations were newly identified types that had not been reported previously. Onset in the late neonatal period or early infancy may be one of the characteristics of the pathogenicity of these gene mutations. ABCB4 gene deficiency can manifest in adulthood. Both the infant and his father in this case carried two heterozygous mutations of the ABCB4 gene. Although the father had no history of suspected liver diseases such as pruritus or jaundice, and all laboratory tests were normal, both the father and the son still need regular follow-up.

For PFIC type 3 patients with non-DCM benign substitution mutations, symptoms are usually mild, and they respond well to UDCA [14]. In this case, the infant was treated with integrated Traditional Chinese and Western medicine, including glucuronolactone, UDCA, and the TCM Lidan Mixture. After one course of treatment, the therapeutic effect was significant: laboratory indicators quickly returned to normal, and clinical symptoms were relieved rapidly. In TCM theory, this case belongs to the category of "Fetal Jaundice (Tai Huang)", with the syndrome type of cold-dampness obstruction [15]. The prescription was formulated based on the principles of detoxifying and promoting bile flow, activating blood circulation to remove blood stasis, and protecting the spleen and stomach. The TCM preparation exerts effects through multiple pathways and targets, such as resisting free radical damage, anti-inflammation, and anti-apoptosis, thereby improving cholestasis [16]. Through syndrome differentiation and treatment, TCM corrects the imbalance of Yin and Yang in the body as a whole, and can address various discomforts of the infant, such as pruritus and fussy crying, resulting in a more comprehensive therapeutic effect [17]. The good therapeutic effect of integrated Traditional Chinese and Western medicine was demonstrated in this infant case.

5. Conclusion

This case demonstrates that integrated traditional Chinese and Western medicine can achieve significant therapeutic effects in an infant with biliary cholestatic liver disease caused by novel ABCB4 gene mutations. The combination of UDCA, hepatoprotective agents, and the TCM formula Lidan Mixture effectively resolved cholestasis and clinical symptoms, with no recurrence during follow-up. This approach provides a valuable reference for the early diagnosis and comprehensive management of rare genetic cholestatic diseases in infants.

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Disclosure statement

The authors declare no conflict of interest.

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