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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Jie-Feng Huang, PhD, Associate Chief Physician, Associate Professor, Department of Orthopaedics and Traumatology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, Zhejiang Province, China. 40983285@qq.com

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Clinical features and genetic variations of severe neonatal hyperbilirubinemia: Five case reports

Fen Lin, Jian-Xin Xu, Yong-Hao Wu, Yu-Bin Ma, Li-Ye Yang

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Fen Lin, Jian-Xin Xu, Yong-Hao Wu, Precision Medical Center, Chaozhou Central Hospital Affiliated to Southern Medical University, Chaozhou 521021, Guangdong Province, China

Fen Lin, Department of Biochemistry, Shantou University Medical College, Shantou 515000, Guangdong Province, China

Yu-Bin Ma, Department of Pediatrics, Chaozhou Central Hospital Affiliated to Southern Medical University, Chaozhou 521000, Guangdong Province, China

Li-Ye Yang, Precision Medical Lab Center, People's Hospital of Yangjiang Affiliated to Guangdong Medical University, Yangjiang 529500, Guangdong Province, China

Corresponding author: Li-Ye Yang, MD, Professor, Precision Medical Lab Center, People's Hospital of Yangjiang Affiliated to Guangdong Medical University, No. 42 Dongshan Road, Jiangcheng District, Yangjiang 529500, Guangdong Province, China. yangleeyee@sina.com

Abstract

BACKGROUND

Neonatal hyperbilirubinemia is a common problem faced by pediatricians. The role of genetic factors in neonatal jaundice has been gradually recognized. This study aims to identify genetic variants that influence the bilirubin level in five patients using next-generation sequencing (NGS).

CASE SUMMARY

Five neonates with severe hyperbilirubinemia were retrospectively studied. They exhibited bilirubin encephalopathy, hypothyroidism, ABO blood type incompatibility hemolysis, glucose-6-phosphate dehydrogenase (*G6PD*) deficiency and premature birth, respectively. A customized 22-gene panel was designed, and NGS was carried out for these neonates. Eight variations (*G6PD* c.G1388A, *HBA2* c.C369G, *ABCC2* c.C3825G, *UGT1A1* c.G211A, *SPTB* c.A1729G, *EPB41* c.G520A, c.1213-4T>G and c.A1474G) were identified in these five neonates. Genetic mutations of these genes are associated with *G6PD* deficiency, thalassemia, Dubin-Johnson syndrome, Gilbert syndrome, hereditary spherocytosis, and hereditary elliptocytosis. One of the neonates was found to have compound variants of the *EPB41* splice site c.1213-4T>G and c.G520A (p.E174K), but no elliptocyte was seen on his blood smear of 4 years old.

CONCLUSION

Pathological factors of severe neonatal hyperbilirubinemia are complicated.

Genetic variants may play an important role in an increased risk of neonatal hyperbilirubinemia, and severe jaundice in neonates may be related to a cumulative effect of genetic variants.

Key Words: Neonatal hyperbilirubinemia; Gene variation; Next generation sequencing; Clinical feature; Case report

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Core Tip: This study has emphasized that for severe hyperbilirubinemia neonates, apart from the predominant glucose-6-phosphate dehydrogenase deficiency and ABO hemolysis, other underlying genetic factors such as thalassemia or red blood cell membrane disorders should be considered, and genetic detection may be taken into consideration for early diagnosis of severe hyperbilirubinemia in neonates.

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INTRODUCTION

Hyperbilirubinemia is one of the most prevalent clinical symptoms in neonates. The main feature of neonatal hyperbilirubinemia is increased bilirubin production, which leads to abnormal bilirubin deposition in the mucosa, skin and organs. Severe hyperbilirubinemia may cause bilirubin encephalopathy and kernicterus and can result in hearing loss, cerebral palsy and disorders of mental development[1]. The importance of genetic contributions in neonatal jaundice has been recognized in recent years[2-5]. We previously demonstrated that the genetic polymorphisms of uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*), solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), *SLCO1B3* and glucose-6-phosphate dehydrogenase (*G6PD*) contributed to an increased risk of neonatal hyperbilirubinemia, which reflected the complexity of pathological jaundice[6,7].

Next-generation sequencing (NGS) is an effective tool for genomic screening and is widely used for the molecular diagnosis of pediatric diseases. Here, we present five neonates with severe hyperbilirubinemia and use NGS technology to explore the genetic variants.

CASE PRESENTATION

Chief complaints

Case 1: A 5-d-old male neonate was referred to our hospital with chief complaints of vomiting and jaundiced skin for 4 d.

Case 2: A 6-d-old male neonate was referred to our hospital with chief complaint of jaundiced skin for 3 d.

Case 3: A 4-d-old male neonate with chief complaint of jaundiced skin for 1 d.

Case 4: A 28-d old female neonate was admitted to our hospital with chief complaints of yellow skin and weight stagnation for 25 d.

Case 5: A 7-d-old male neonate was admitted to our hospital with chief complaint of yellow skin for 5 d.

History of present illness

Case 1: The neonate was delivered vaginally with a birth weight of 3.15 kg and received formula feeding. His mother was para 2 and gravida 2. He appeared icteric and vomited milk on day 2 after birth. The yellowing of his skin increased gradually. He was admitted on day 5.

Case 2: The patient was a cesarean born neonate with a birth weight of 3.10 kg. He was breastfed. He had a mother of gravida 2 and para 2. He was found with jaundiced skin for 3 d.

Case 3: The neonate was cesarean born to a mother of gravida 1, para 1, and the blood type of his

mother was O. His birth weight was 3.30 kg. He was found with yellow skin for 1 d.

Case 4: The neonate was born to a mother of gravida 1 and para 1 by cesarean section, she was breastfed, and did not receive neonatal screening, she showed yellow skin at 4 days of birth, her yellow skin continued to her admission in our hospital (age: 28 d), her body weight did not increase after her birth (birth weight 3.25 kg).

Case 5: The neonate was delivered vaginally because of premature rupture of the membrane, his birth weight was 2.65 kg. His mother was gravida 1 and para 1, he was admitted to our hospital due to yellow skin for 5 d.

History of past illness

The neonates had no other previous medical history.

Personal and family history

The neonates had no significant family history.

Physical examination

Case 1: The neonate was found with severe yellow skin and mucous, and abdominal distention were observed during physical examination.

Case 2: Severe yellow skin and mucous were observed during physical examination. His muscle tension and limb activities appeared normal, and he did not show fever or convulsion.

Case 3: Mild yellow skin and yellow sclera.

Case 4: Severe yellow skin and sclera.

Case 5: Severe yellow skin and mild yellow mucous were observed during physical examination.

Laboratory examinations

Case 1: A blood test was performed. His hemoglobin (Hb) was 147 g/L, and his total bilirubin (TBIL) increased significantly (719.50 $\mu\text{mol/L}$, normal upper limit: 20.1 $\mu\text{mol/L}$), and his *G6PD* activity was 0.4 (normal range: 1.1-2.5) (Table 1).

Case 2: The TBIL level was 360 $\mu\text{mol/L}$ on admission. Phototherapy was carried out three times, and the TBIL level decreased to 260 $\mu\text{mol/L}$ on day 9 after birth. He was released and resumed breastfeeding. However, his skin yellowing gradually increased postdischarge, so he was readmitted on day 12 of life for treatment. He had a TBIL level of 527.87 $\mu\text{mol/L}$, and a complete blood count revealed a Hb level of 105 g/L. Moreover, the *G6PD* activity was 0.5.

Case 3: His blood test showed Hb levels of 143 g/L, and he was blood group B and Rh D-positive. Free antibody tests and antibody release tests were positive. He was diagnosed with ABO incompatibility with a TBIL level of 429.6 $\mu\text{mol/L}$ on day 4 after birth, and he had a heterozygous *EPB41* c.A1474G (p.T492A) mutation (Table 2).

Case 4: Serological examination showed increased TBIL (538.7 $\mu\text{mol/L}$) and thyrotropin levels (150 mIU/L, reference 0.35-5.5) with low free triiodothyronine (0.1 pmol/L, reference 3.5-6.5) and free thyroxine (0.60 pmol/L, reference 11.5-22.7) levels. Two heterozygous mutations, *SPTB* c.A1729G (p.I577V) and *ABCC2* c.3825C>G (p.Tyr1275X), were confirmed in this neonate.

Case 5: The TBIL level was 538.7 $\mu\text{mol/L}$ on day 7 after birth.

Imaging examinations

Case 1: A barium meal examination showed congenital hypertrophic pyloric stenosis (CHPS).

Case 2: Head magnetic resonance imaging showed signal changes on T1WI and T2WI.

FINAL DIAGNOSIS

Case 1: The neonate was diagnosed with neonatal hyperbilirubinemia and CHPS.

Case 2: He was diagnosed as *G6PD* deficiency, neonatal hyperbilirubinemia, moderate anemia and bilirubin encephalopathy.

Case 3: The neonate was diagnosed as ABO blood type incompatibility hemolytic disease of newborn.

Table 1 Clinical and laboratory characteristics of five neonates with severe hyperbilirubinemia

Case ID	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Male	Male	Male	Female	Male
Admission time (d)	5	12	4	28	7
Gestational age (wk)	39 + 5	39	40 + 3	40	35 + 4
Birth weight (kg)	3.15	3.1	3.3	3.25	2.65
Mode of delivery	Vaginal	Cesarean	Cesarean	Cesarean	Vaginal
Feeding patterns	Formula	Breast	Breast	Formula	Breast
Postnatal growth retardation	+	-	-	+	-
Skin and mucous membrane yellowing	+	+	+	+	+
Time of jaundice occur after birth (d)	2	3	3	4	2
Maximum TBIL levels ($\mu\text{mol/L}$) ^a	719.5	527.87	429.6	538.7	584.4
Age at maximum TBIL (d)	5	12	4	28	7
Phototherapy	+	+	+	+	+
RBC transfusion	-	+	-	-	-
IVIg ^b or albumin therapy	+	+	+	-	-
Clinical diagnosis	<i>G6PD</i> deficiency; Congenital hypertrophic pyloric stenosis; Neonatal hyperbilirubinemia	<i>G6PD</i> deficiency; Anemia; Bilirubin encephalopathy	ABO blood type incompatibility hemolytic disease	Congenital hypothyroidism; Neonatal hyperbilirubinemia	Premature delivery; Neonatal hyperbilirubinemia

^aNormal upper limit: 20.1 $\mu\text{mol/L}$.

^bIntravenous immunoglobulin.

+: Present; -: Absent; TBIL: Total bilirubin; RBC: Red blood cell; IVIG: Intravenous immunoglobulin; *G6PD*: Glucose-6-phosphate dehydrogenase.

Case 4: The neonate was diagnosed as hypothyroidism and hyperbilirubinemia.

Case 5: The neonate was diagnosed as neonatal hyperbilirubinemia. This neonate was heterozygous for the *UGT1A1* c.G211A (p.G71R) mutation.

TREATMENT

Case 1: He received phototherapy for three days (the indication of phototherapy according to the expert consensus for diagnosis and treatment of neonatal hyperbilirubinemia in *Chinese Journal of Pediatrics* 2014)[8]. Subsequently, he was transferred to the Women and Children's Hospital of Guangdong Province and underwent a surgical operation for CHPS. Two weeks later, he recovered and was discharged. Genetic analysis revealed that he carried the *G6PD* c.G1388A mutation, and he was also a compound heterozygote for the c.1213-4T>G and c.G520A (p.E174K) mutations of the *EPB41* gene (Table 2).

Case 2: He received phototherapy, alkalization of urine, and vitamin K1 supplementation and was subjected to red blood cell (RBC) transfusion (Hb dropping to 95 g/L). The *G6PD* c.G1388A and *HBA2* c.C369G (Hb Westmead) mutations were identified in this neonate (Table 2).

Case 3: The neonate received routine phototherapy.

Case 4: Levothyroxine therapy was initiated (48 μg daily) to adjust the inadequate secretion of thyroxine.

Table 2 Causative mutations and potentially pathogenic variants identified in five neonates

Case numbers	Gene name	rs number	cDNA/protein change	Mutationtaster prediction	PolyPhen2	SIFT	Genotype	Associated disorder
Patient 1	<i>EPB41</i>	rs201231112	c.G520A/p.E174K	Disease-causing	Probably damaging	Tolerated	Hetero	Elliptocytosis
	<i>EPB41</i>	rs188648724	c.1213-4T>G	Disease-causing			Hetero	Elliptocytosis
	<i>G6PD</i>	rs72554664	c.G1388A/p.R463H	Disease-causing	Damaging	Deleterious	Hemiz	<i>G6PD</i> deficiency
Patient 2	<i>G6PD</i>	rs72554664	c.G1388A/p.R463H	Disease-causing	Damaging	Deleterious	Hemiz	<i>G6PD</i> deficiency
	<i>HBA2</i>	rs41479347	c.C369G/p.H123Q	Disease-causing	Probably damaging	Deleterious	Hetero	Thalassemia
Patient 3	<i>EPB41</i>	rs778090351	c.A1474G/p.T492A	Disease-causing	Damaging	Deleterious	Hetero	Elliptocytosis
Patient 4	<i>SPTB</i>	rs144668591	c.A1729G/p.I577V	Disease-causing	Probably damaging	Deleterious	Hetero	Elliptocytosis
	<i>ABCC2</i>	rs554976086	c.C3825G/p.Tyr1275X	Disease-causing	Probably damaging	Deleterious	Hetero	Dubin-Johnson syndrome
Patient 5	<i>UGT1A1</i>	rs4148323	c.G211A/p.G71R	Polymorphism	Probably damaging	Deleterious	Hetero	Gilbert's syndrome

Hetero: Heterozygous; Hemiz: Hemizygote; *EPB41*: Protein 4.1; *G6PD*: Glucose-6-phosphate dehydrogenase; *HBA2*: Hemoglobin alpha 2; *SPTB*: Spectrin beta; *ABCC2*: Adenosine triphosphate-binding cassette subfamily C member 2; *UGT1A1*: Uridine diphosphate glucuronosyltransferase 1A1.

Case 5: The neonate received routine phototherapy.

OUTCOME AND FOLLOW-UP

The five children were followed up, and their intelligence and development were normal.

DISCUSSION

Pathologic jaundice refers to an abnormal increase in serum bilirubin levels, and a pathological investigation to determine hyperbilirubinemia is important in clinical practice to prevent the adverse reactions of severe jaundice. Routine laboratory test results may fail to explain jaundice severity, and we hypothesized that genetic factors might contribute to the development of severe hyperbilirubinemia. In the present study, we analyzed five neonates who had severe hyperbilirubinemia due to *G6PD* deficiency, ABO blood type incompatibility hemolysis, premature delivery and hypothyroidism, which were the most common etiological factors of pathological jaundice in the neonatal period. We also confirmed nine gene variants through NGS.

Based on our results, all five neonates carried at least one genetic variant, and the associated disorders included *G6PD* deficiency, α -thalassemia, hereditary elliptocytosis, hereditary spherocytosis, Dubin-Johnson syndromes and Gilbert's syndrome[9-12]. A previous study reported a case of neonate that had both *G6PD* deficiency and a heterozygous variant of the *UGT1A1* promoter (TA)₆/(TA)₇ who developed severe hyperbilirubinemia and bilirubin encephalopathy[13]. Butorac Ahel *et al*[14] reported a case of infant with unusually severe hyperbilirubinemia due to the coexistence of hereditary spherocytosis and homozygosity for *UGT1A1* (TA)₇. Our report of 5 patients also confirmed that genetic variations of susceptible genes (Figure 1) contributed to the development of neonatal hyperbilirubinemia and severe jaundice in neonates might be related to a cumulative effect of genetic variants.

Notably, to our knowledge, hereditary elliptocytosis (HE) is a congenital red cell membrane disorder characterized by elliptically shaped cells, and the *EPB41* genetic variant is one of the most identified defects. Case 1 was found to have variants for both the *EPB41* splice site c.1213-4T>G and c.G520A (p.E174K). In silico predictions concluded that the above two variants were likely to be damaging or possibly damaging. Generally, HE patients with a single heterozygous mutation are often considered to be asymptomatic, but homozygous mutations or compound heterozygous mutations exhibit moderate to severe hemolysis[15]. However, no splenomegaly, reticulocyte level abnormality or hemolytic anemia was observed in this patient after follow-up for 4 years (data not shown). We propose that the two genetic variations may aggravate the jaundice levels in this case. A previous study noted that spherical-shaped red cells were rarely observed in neonates, which was likely due to the immature RBC

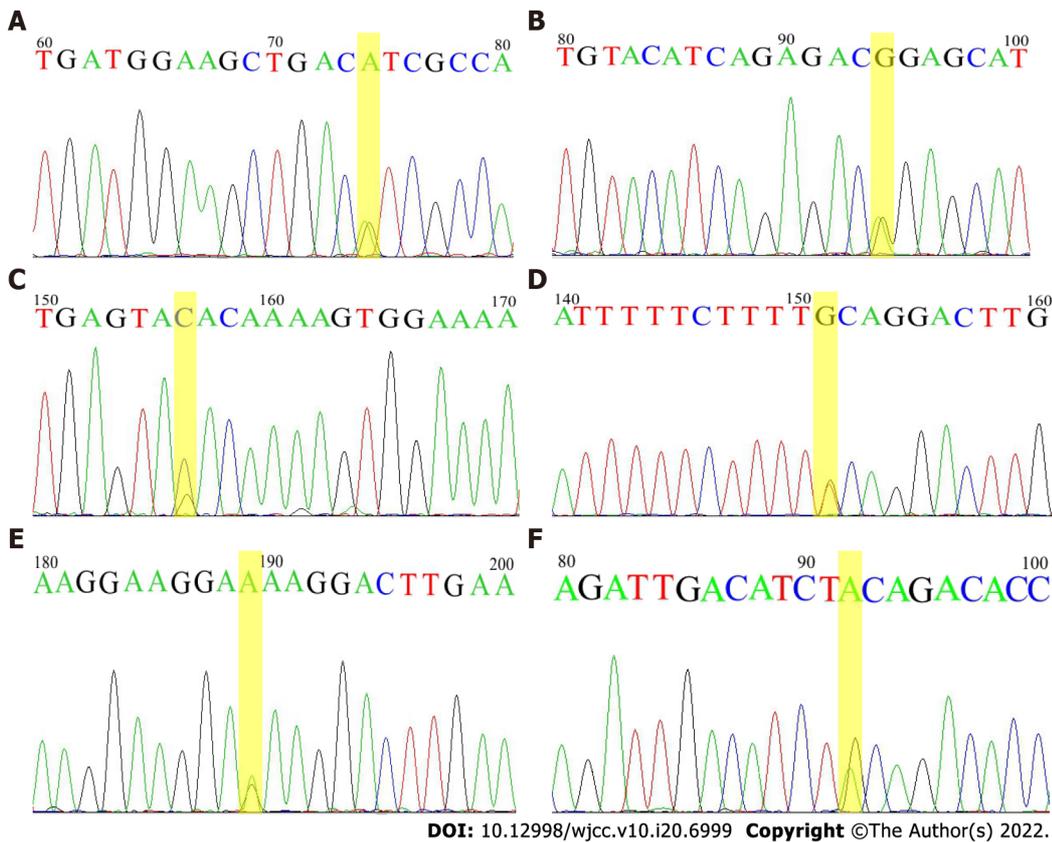


Figure 1 Polymerase chain reaction-Sanger sequencing results. The mutation sites are indicated by yellow bands. A: *SPTB*-rs144668591/c.1729A>G heterozygote; B: *UGT1A1*-rs4148323/c.211G>A heterozygote; C: *ABCC2*-rs554976086/c.3825C>G heterozygote; D: *EPB41*-rs188648724/c.1213-4T>G heterozygote; E: *EPB41*-rs201231112/c.520G>A heterozygote; F: *EPB41*-rs778090351/c.1474A>G heterozygote.

membranes of neonates[16]. This neonate did not receive a blood smear when he was in the hospital. He received a routine examination at 4 years old, and no elliptocyte was seen on his blood smear. The absence of elliptical-shaped erythrocyte in this patient reflects the high heterogeneity of hereditary elliptocytosis. Moreover, although case 4 was clinically diagnosed with hypothyroidism, no genetic variation associated with hypothyroidism was found (data not shown).

CONCLUSION

In conclusion, our study emphasized that for neonates with severe hyperbilirubinemia, apart from the predominant *G6PD* deficiency and ABO blood type incompatibility hemolysis, other underlying genetic factors, such as thalassemia or RBC membrane disorders, should be considered. Furthermore, genetic detection should be considered for the early diagnosis of severe hyperbilirubinemia in neonates.

FOOTNOTES

Author contributions: Yang LY conceived the study and revised the manuscript; Lin F performed all experiments and wrote the manuscript; Xu JX collected the blood samples and biochemical analyses of the patients; Wu YH collected the clinical data, and Ma YB performed the treatments; All authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Fen Lin 0000-0001-9614-7776; Jian-Xin Xu 0000-0002-3431-6834; Yong-Hao Wu 0000-0002-6795-1201; Yu-Bin Ma 0000-0003-4225-4829; Li-Ye Yang 0000-0001-9603-187X.

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