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*Observational Study*

**Etiology analysis for term newborns with severe hyperbilirubinemia in eastern Guangdong of China**

Etiology analysis for severe hyperbilirubinemia

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**Abstract**

**BACKGROUND**

Neonatal hyperbilirubinemia is one of the common diseases of newborns that typically presents with yellow staining of skin, resulting in sequelae such as hearing loss, motor and intellectual development disorders, and even death. The pathogenic factors of neonatal hyperbilirubinemia are complex. Different cases of hyperbilirubinemia may have a single or mixed etiology.

**AIM**

To explore the etiological characteristics of severe hyperbilirubinemia in term newborns of eastern Guangdong of China.

**METHODS**

Term newborns with severe hyperbilirubinemia in one hospital from January 2012 to December 2021 were retrospectively analyzed. The etiology was determined according to the laboratory results and clinical manifestations.

## RESULTS

Among 1602 term newborns with hyperbilirubinemia in eastern Guangdong of China, 32.20% (580/1602) was severe hyperbilirubinemia. Among the causes of severe hyperbilirubinemia, neonatal hemolysis accounted for 15.17%, breast milk jaundice accounted for 12.09%, infection accounted for 10.17%, glucose-6-phosphate dehydrogenase (G6PD) deficiency accounted for 9.14%, and the coexistence of multiple etiologies accounted for 6.55%, unknown etiology accounted for 41.72%. ABO hemolysis and G6PD deficiency were the most common causes in the 20 cases with bilirubin encephalopathy. 94 severe hyperbilirubinemia newborns were tested for UGT1A1\*6 variant (rs4148323, c.211G>A, p.Arg71Gly), 9 cases were 211 G to A homozygous variant, 37 cases were 211 G to A heterozygous variant, and 48 cases were wild genotypes.

## CONCLUSION

The main cause for severe hyperbilirubinemia and bilirubin encephalopathy in eastern Guangdong of China were the hemolytic disease of the newborns, G6PD deficiency and infection. *UGT1A1* gene variant was also a high-risk factor for neonatal hyperbilirubinemia. Targeted prevention and treatment according to the etiology may reduce the occurrence of bilirubin encephalopathy and kernicterus.

**Key Words:** Severe hyperbilirubinemia; Term newborns; Etiology; Uridine diphosphate glucuronosyltransferase 1A1; Glucose-6-phosphate dehydrogenase deficiency

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**Core Tip:** The main cause for severe hyperbilirubinemia and bilirubin encephalopathy in eastern Guangdong of China were the hemolytic disease of the newborns, glucose-6-phosphate dehydrogenase deficiency and infection. Uridine diphosphate

glucuronosyltransferase 1A1 gene variant was also a high-risk factor for neonatal hyperbilirubinemia.

## INTRODUCTION

Neonatal hyperbilirubinemia is one of the common diseases of newborns, which is mainly caused by the imbalance between the production and elimination of bilirubin in the body<sup>[1]</sup>. It can be manifested as yellow staining of skin mucosa and sclera and usually resolves within 1 wk after birth, and most of neonates with jaundice have a good prognosis. However, if the total bilirubin level exceeds a certain threshold, it can lead to bilirubin encephalopathy, resulting in sequelae such as hearing loss, motor and intellectual development disorders, and even death, which will bring a heavy burden to the society and family.

The pathogenic factors of neonatal hyperbilirubinemia are complex. Different cases of hyperbilirubinemia may have a single or mixed etiology. The etiological composition and related genetic variants of hyperbilirubinemia in different regions may be different, resulting in different degrees of hyperbilirubinemia in clinic. The American Academy of Pediatrics published the percentile curve of hourly total serum bilirubin (TSB) of newborns in venous blood, which defined bilirubin more than 95% percentile as hyperbilirubinemia and should be intervened<sup>[2]</sup>. According to the level of bilirubin and clinical symptoms, hyperbilirubinemia can be divided into significant hyperbilirubinemia (TSB < 342  $\mu\text{mol/L}$ ), severe hyperbilirubinemia (TSB  $\geq$  342  $\mu\text{mol/L}$ ), extreme hyperbilirubinemia (TSB  $\geq$  428  $\mu\text{mol/L}$ ), hazardous or critical hyperbilirubinemia (TSB  $\geq$  513  $\mu\text{mol/L}$ ), acute bilirubin encephalopathy, and kernicterus<sup>[3,4]</sup>.

Glucose 6-phosphate dehydrogenase (G6PD) deficiency is one of the commonest human enzymopathies, with an estimated global prevalence of 4.9% that affects more than 500 million individuals worldwide<sup>[5]</sup>. The prevalence of G6PD deficiency in Chaozhou was 3.36%<sup>[6]</sup>. To date, 12 mutations have been reported in Chaozhou population, Canton (c.1376 G>T) and Kaiping (c.1388 G>A) were the most common variants<sup>[6]</sup>. Uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) is a rate-limiting enzyme in the process of bilirubin metabolism<sup>[7]</sup>. It catalyzes the glucuronic acid binding reaction and converts unconjugated bilirubin into conjugated bilirubin<sup>[8]</sup>.

UGT1A1 (*UGT1A1*\*6, c.211G>A, p.Arg71Gly, rs4148323), <sup>5</sup> one of the most common *UGT1A1* gene polymorphisms in the coding regions, was reported to be a risk factor for neonatal hyperbilirubinemia<sup>[9]</sup>.

Early detection of high-risk factors for severe hyperbilirubinemia and prompt treatment are crucial for the prevention of bilirubin encephalopathy. This study analyzed the clinical data of term newborns with severe hyperbilirubinemia retrospectively, to explore the etiology and clinical characteristics of severe hyperbilirubinemia in term newborns in Chaozhou, eastern Guangdong province, and to provide basis for clinical prevention and early treatment of hyperbilirubinemia.

## **MATERIALS AND METHODS**

### ***Subjects***

All of term newborns with hyperbilirubinemia (gestational age > 37 wk) admitted to neonatal intensive care unit of Chaozhou <sup>12</sup> Central Hospital from January 2012 to December 2021 were selected. The age of admission was 1-28 d. <sup>3</sup> Demographic and clinical data were collected from the medical records of the studied participants. Hyperbilirubinemia was defined for bilirubin more than 95% percentile and TSB ≥ 342 μmol/L was used as the diagnostic standard for severe hyperbilirubinemia<sup>[3,4]</sup>.

<sup>1</sup> This study was initially approved by the Ethics Committee of Chaozhou Central Hospital in 2011 (No. 2011021), and then the second ethical approval was obtained in 2015 (No. 2015001). The data was collected retrospectively, which did not require informed consent form.

### ***Methods***

<sup>10</sup> General information including sex, gestational age, birth weight, admission age and weight, mode of delivery, feeding pattern, and treatment were collected. The major clinical etiologies included hemolytic disease of the newborn (HDN) (ABO hemolysis and Rh hemolysis), G6PD deficiency (G6PD enzyme activity ≤ 2500 U/L, Co-Heath Beijing Laboratories Co., Ltd.), infection (sepsis, pneumonia, urinary tract infection),

extravascular hemorrhage (intracranial hematoma, scalp hematoma and other bleeding), polycythemia (venous red blood cells  $> 6 \times 10^{12}/L$ , hemoglobin  $> 220$  g/L, and hematocrit  $> 65\%$ ), congenital hypothyroidism (diagnosed by neonatal screening), insufficient breastfeeding (breastfeeding newborns with 10% birth weight loss after birth), and breast milk jaundice. Breast milk jaundice was diagnosed by exclusion. Therefore, it is not included in the combined factors. Prolonged jaundice was defined as jaundice persisting for more than 2 wk, with bilirubin level  $> 150$   $\mu\text{mol}/L$ . Bilirubin encephalopathy (hyperbilirubinemia and clinical symptoms of nervous system for encephalopathy), and blood exchange indications (blood exchange reference standard recommended by American Academy of Pediatrics in 2004.) were also recorded<sup>[2]</sup>.

The whole blood samples of ethylenediamine tetraacetic acid anticoagulants in newborns with severe hyperbilirubinemia were prospectively collected after clinical diagnosis and stored at  $-40$   $^{\circ}\text{C}$  in a biobank. The whole blood DNA extraction kit (Chaozhou Hybribio Co., Ltd.) was used to extract DNA according to the instructions of the kit, and then the DNA quantity and purity were tested (NanoDrop One, Thermo Fisher Scientific Co., Ltd.). MJ Mini Personal Thermal Cycler (Bio-Rad Company) was used for polymerase chain reaction amplification of *G6PD*, and then, *G6PD* gene variant was detected by reverse dot blot method (Chaozhou Hybribio Co., Ltd.) for 13 common *G6PD* mutation types c.95A>G (*G6PD* Gaohe), c.392G>T (*G6PD* Qing Yan), c.487G>A (*G6PD* Mahidol), c.493A>G (*G6PD* Taipei), c.592G>T (*G6PD* Coimbra), c.871G>A (*G6PD* Viangchan), c.1004C>T (*G6PD* Fushan), c.1024C>T (*G6PD* Chinese-5), c.1360C>T (*G6PD* Union), c.1376G>T (*G6PD* Canton), c.1387C>T (*G6PD* Keelung), c.1388G>A (*G6PD* Kaiping), c.1381G>A (*G6PD* Yunan) and one polymorphism c.1311C>T<sup>[10]</sup>. *UGT1A1* gene was amplified and sequenced (3500Dx, Life Technologies) to detect c.211G>A variant (*UGT1A1*\*6, rs4148323), which was specifically described in our previous study<sup>[10]</sup>.

A total of 94 severe hyperbilirubinemia newborns were tested for *UGT1A1*\*6 variant (rs4148323). The control 65 newborns for *UGT1A1*\*6 test were the term newborns without hyperbilirubinemia, and with a TSB not requiring phototherapy, their clinical characteristics were described previously<sup>[11]</sup>.

### *Statistical analysis*

SPSS 20.0 was used for data analysis. The continuous variables in the data group were expressed as mean  $\pm$  SD. Count data was described by frequency and percentage. The Pearson chi-square test was used, and  $P < 0.05$  was considered as statistically significant.

## **RESULTS**

### *General clinical characteristics*

A total of 1602 newborns with hyperbilirubinemia (915 males and 687 females) were collected in this study, 580 newborns (346 males and 234 females) were severe hyperbilirubinemia (32.20%, 580/1602). In these 580 cases, birth weight was 2050-5500 g, with an average of  $3211.6 \pm 444.53$  g, gestational age was 37-42 wk, with an average of  $39.07 \pm 1.10$  wk; the age of the highest bilirubin value was 1-28 d, with an average of  $8 \pm 5$  d; 315 cases were vaginal delivery, 265 cases were cesarean section; 174 cases were breastfeeding, 165 cases were formula feeding, 195 cases were mixed feeding and 46 cases were unknown. The peak value of TSB was 342.05-817.8  $\mu\text{mol/L}$ , with an average of  $398.07 \pm 55.09$   $\mu\text{mol/L}$ . Among them, 213 cases met the standard of blood exchange, 52 cases were prolonged jaundice (22 cases were breast feeding), and 20 cases were complicated with bilirubin encephalopathy (Table 1).

### *Etiology composition*

Among the cases of severe hyperbilirubinemia with clear etiology, the most common was neonatal hemolysis (15.17%), followed by breast milk jaundice (12.09%), infection (10.17%), G6PD deficiency (9.14%), and combined factors (6.55%), the etiology for the remaining 41.72% (242/580) cases was not clear. Among combined factors, neonatal hemolysis combined with infection (36.84%) was the most common, followed by G6PD deficiency combined with infection (26.32%) and infection combined with vascular



bleeding (13.16%). In all cases of neonatal hemolysis, one case of Rh hemolysis was identified, the other 106 cases were ABO hemolysis (Figure 1).

### ***G6PD genotype and UGT1A1\*6 variant***

Among 580 cases of severe hyperbilirubinemia, 68 cases were G6PD deficient by enzyme activity test, and 43 newborns were tested for 13 common *G6PD* gene mutations in Chinese<sup>[10]</sup>. Gene mutations were found in 40 cases, including 1 case c.95A>G (*G6PD* Gaohe), 1 case c.1024C>T (*G6PD* Chinese-5), 14 cases c.1376G>T (*G6PD* Canton), 23 cases c.1388G>A (*G6PD* Kaiping), and 1 case of composite mutation c.1311C>T combined with c.871G>A (*G6PD* Viangchan). No mutation was detected in the remaining 3 cases.

A total of 94 neonates with severe hyperbilirubinemia were selected to detect *UGT1A1*\*6 variant (*UGT1A1*\*6, c.211G>A, p.Arg71Gly, rs4148323). 48 cases were wild type, 37 cases were heterozygous variants, and 9 cases of homozygous variants were detected, with a gene variant frequency of 48.94 % (46/94). Among that 94 cases, a total of 18 cases of G6PD deficiency combined with *UGT1A1* variants were found, including 2 cases of homozygous variants of *UGT1A1*\*6 with c.1376G>T, 2 cases of homozygous variants of *UGT1A1*\*6 with c.1388G>A, 4 cases of heterozygous variants of *UGT1A1*\*6 with c.1376G>T, 10 cases of heterozygous variants of *UGT1A1*\*6 with c.1388G>A (Table 2). Compared with our previous study on the *UGT1A1* c.211G>A variant in 65 full-term newborns with normal bilirubin (Table 3)<sup>[11]</sup>. The proportion of c.211G>A variant in newborns with severe hyperbilirubinemia was higher than that in term neonates with normal bilirubin ( $P < 0.001$ ). ABO hemolysis occurred in 34 of these 94 cases, and 10 cases (10.64%, 10/94) were ABO hemolysis combined with *UGT1A1*\*6 variant.

### ***Bilirubin encephalopathy***

Among 580 cases of severe hyperbilirubinemia, 20 cases were bilirubin encephalopathy, including 11 cases of male and 9 cases of female, and TSB bilirubin level was 359-817.8  $\mu\text{mol/L}$ , with an average of  $480.21 \pm 64.19 \mu\text{mol/L}$ . The main causes of bilirubin encephalopathy were ABO hemolysis (6 cases), followed by infection (sepsis in 1 case,

pneumonia in 4 cases), G6PD deficiency (4 cases), unknown causes (3 cases), one case was ABO hemolysis combined with infection, and one case was ABO hemolysis combined with G6PD deficiency and infection.

## DISCUSSION

Neonatal hyperbilirubinemia is one of the common diseases in neonatal period. The pathogenesis of severe neonatal hyperbilirubinemia is often multifactorial. In recent years, there have been many studies on the etiology and related risk factors of neonatal hyperbilirubinemia in China and abroad<sup>[12-14]</sup>. However, the etiology of hyperbilirubinemia is easily affected by environment and other relative factors. Therefore, the analysis of the etiology of neonates with severe hyperbilirubinemia in eastern Guangdong is of great significance to reduce the incidence of severe hyperbilirubinemia and its serious complications in this region.

Our study found that 32.20% of the 1602 hospitalized newborns with hyperbilirubinemia were severe hyperbilirubinemia. HDN was the most common cause of severe hyperbilirubinemia in term newborns. ABO blood group incompatibility is one of the most common causes of HDN which often occurs in infants of blood type A or B with mothers of blood type O. The blood type antibody in mother combines with the corresponding antigen on the surface of fetal red blood cells during pregnancy. Macrophages and natural killer cells in newborn destroy sensitized red blood cells, resulting in hemolysis, jaundice and anemia after birth<sup>[15]</sup>.

A total of 68 cases of G6PD deficiency was identified (11.72%, 68/580) in this study, 53 cases were single G6PD deficiency and 15 cases were combined factor with other causes. The incidence of G6PD deficiency was relatively high, which might be related to the geographical location of Chaozhou. The prevalence of G6PD deficiency in Chaozhou was 3.36%<sup>[6]</sup>. The prevalence<sup>1</sup> of G6PD deficiency in severe hyperbilirubinemia group was higher than that of the general population.<sup>4</sup> G6PD deficiency causes increased susceptibility of erythrocytes to H<sub>2</sub>O<sub>2</sub> and other reactive oxygen species that can lead to hemolytic anemia, and in neonatal hyperbilirubinemia cases, it even results in neonatal

kernicterus. G6PD deficiency is an important reason for severe hyperbilirubinemia in term newborns. Of the 68 cases with G6PD deficiency, 11 cases were combined with infection. Infection was the main inducing cause of acute hemolysis in G6PD deficiency<sup>[16]</sup>. We performed gene analysis in 43 cases of G6PD deficiency and found that **c.1388G>A and c.1376G>T were the most common variants in** severe hyperbilirubinemia neonates. The bilirubin level in severe hyperbilirubinemia caused by hemolysis is high, and it occurs early and develops rapidly. In addition, neonatal blood-brain barrier is not fully matured, bilirubin encephalopathy and even death are prone to occur.

Infection was another cause of severe hyperbilirubinemia (10.17%). Hyperbilirubinemia caused by infection may be due to the imperfect immune function of newborns and lack of mature defense ability, and the neonate is easily to be infected by viruses and bacteria. The destruction of the erythrocyte membrane by the pathogen themselves or secreted toxins, results in hemolysis and increased bilirubin production. At the same time, infection can cause liver dysfunction, inhibit the activity of UGT1A1, and reduce the ability of liver to deal with bilirubin. Hyperbilirubinemia may be the only manifestation of infection<sup>[17]</sup>. Because of the low positive rate of blood culture, and late diagnosis for infection, the bilirubin may increase and progress to severe hyperbilirubinemia.

Breast milk jaundice is a clinical diagnosis made after excluding the known causes of hyperbilirubinemia. At present, there is still a lack of reliable laboratory testing methods to get this diagnosis. Breast milk jaundice can be divided into early breastfeeding jaundice and late breast milk jaundice<sup>[18]</sup>. In our study, 9 cases (1.55%) of early breastfeeding jaundice and 70 cases (12.07%) of late breast milk jaundice were identified. Early breast feeding deficiency leads to insufficient calorie intake, reduced intestinal peristalsis, and increased bilirubin enterohepatic circulation, resulting in early hyperbilirubinemia, which is manifested by a weight loss of 10% within one week after birth. Late breast milk jaundice occurs relatively late, and the bilirubin generally peaks on the 7<sup>th</sup> to 14<sup>th</sup> days of life. The jaundice can last for 2-3 wk or even 2-3 mo, which may be caused by many factors<sup>[19]</sup>.

The variant of *UGT1A1* c.211G>A was an important cause of breast milk jaundice in newborns, and the serum bilirubin level of breast milk jaundice newborns with this variant was significantly higher than that of breast milk jaundice newborns without this variant<sup>[20,21]</sup>. This indicated that the presence of *UGT1A1* c.211G>A variant could promote breast milk jaundice. The product encoded by *UGT1A1* gene is bilirubin uridine diphosphate glucuronyltransferase. *UGT1A1* variant make the activity of this enzyme reduced, so that bilirubin cannot combine with glucuronide to form conjugated bilirubin. The unconjugated bilirubin accumulates in the body, and resulting in different degrees of hyperbilirubinemia<sup>[22,23]</sup>.

The *UGT1A1* c.211G>A was a risk factor for neonatal severe hyperbilirubinemia in eastern Guangdong, which might occur with other causes simultaneously. Among the 94 cases with *UGT1A1* variant data, we found that 18 cases were *UGT1A1* gene variant combined with G6PD deficiency, 10 cases were *UGT1A1* gene variant combined with ABO hemolysis. Our previous study found that, in the newborns with hyperbilirubinemia which due to G6PD deficiency, bilirubin level showed an increasing trend with the accumulation of *UGT1A1* c.211G>A variants<sup>[10]</sup>. Yang *et al*<sup>[24]</sup> reported that the risk of neonatal severe hyperbilirubinemia increased significantly when ABO hemolytic neonates were combined with *UGT1A1* gene mutation (especially 211A>G homozygous mutation).

The causes for 41.2% of severe hyperbilirubinemia cases were unknown in our study. Previous studies have shown that mutations of other genes, such as heme oxygenase-1, biliverdin reductase A, and solute carrier organic anion transporter family member 1B1 could also affect the serum bilirubin<sup>[25,26]</sup>. For severe hyperbilirubinemia neonates with unknown etiology, due to limited conditions, we did not perform gene detection for all cases, resulting in some missing causes. For neonates with unknown etiology, except for *UGT1A1* variants, other gene variants might contribute to increased bilirubin. Pathological jaundice, especially severe jaundice, is often the result of multiple influencing factors. Detection of bilirubin-related genes such as *G6PD* and *UGT1A1* in neonates can be used as an auxiliary test for clinicians to assess the risk of neonatal severe

hyperbilirubinemia, which will benefit for early prevention, etiological exploration and genetic counseling.

## **CONCLUSION**

The main causes of severe hyperbilirubinemia in Chaozhou are neonatal hemolysis and infection. Genetic factors such as *UGT1A1* variant and G6PD deficiency, were also the important risk factors for neonatal severe hyperbilirubinemia. It is very important to clarify the etiology and to treat neonatal severe hyperbilirubinemia timely, which can reduce the occurrence of acute bilirubin encephalopathy and kernicterus.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Neonatal hyperbilirubinemia is one of the common diseases of newborns, the pathogenic factors of neonatal hyperbilirubinemia in eastern Guangdong is not clear.

### ***Research motivation***

To understand the etiology for severe neonatal hyperbilirubinemia in Chaozhou.

### ***Research objectives***

To analyze the pathological factors contributing to severe hyperbilirubinemia in neonates.

### ***Research methods***

The clinical data were retrospectively collected and genetic variants of glucose-6-phosphate dehydrogenase (G6PD) and *UGT1A1* were determined by polymerase chain reaction and sequencing.

### ***Research results***

Among the causes of severe hyperbilirubinemia, neonatal hemolysis accounted for 15.17%, breast milk jaundice accounted for 12.09%, infection accounted for 10.17%, G6PD deficiency accounted for 9.14%, and the coexistence of multiple etiologies accounted for 6.55%, unknown etiology accounted for 41.72%. ABO hemolysis and G6PD deficiency were the most common causes in the 20 cases with bilirubin encephalopathy. 94 severe hyperbilirubinemia newborns were tested for UGT1A1\*6 variant (rs4148323, c.211G>A, p.Arg71Gly), 9 cases were 211 G to A homozygous variant, 37 cases were 211 G to A heterozygous variant, and 48 cases were wild genotypes.

### ***Research conclusions***

The main causes for severe hyperbilirubinemia and bilirubin encephalopathy in eastern Guangdong of China were the hemolytic disease of the newborns, G6PD deficiency and infection. *UGT1A1* gene variant was also a high-risk factor for neonatal hyperbilirubinemia.

### ***Research perspectives***

Multiple genetic variants may regulate the bilirubin levels in neonate, these gene analysis may contribute to the prognosis and management for neonatal jaundice.



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