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Review Article

Genetic disorders associated with neonatal jaundice

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Abstract. Neonatal jaundice is very common in newborn infants. Although it is often a natural and transitional condition, some infants develop severe hyperbilirubinemia, in which unconjugated bilirubin in the serum may cross the blood-brain-barrier and cause bilirubin encephalopathy (acute bilirubin intoxication) or kernicterus (chronic bilirubin intoxication). To avoid these hazardous conditions, it is important to identify the infants at risk for developing severe hyperbilirubinemia. There are many genetic diseases that can cause or aggravate neonatal jaundice. Thus, the knowledge of the genetic diseases associated with neonatal jaundice may be essential for identification of the infants at highest risk. Here, we review neonatal jaundice and describe some genetic disorders associated with neonatal jaundice, such as bilirubin metabolism disorders, hemolytic disorders, bilirubin transport disorders, and others. It is desirable that rapid and accurate screening systems of genetic disorders should be developed for the proper management of neonatal hyperbilirubinemia.

Key words: Neonatal jaundice, genetic factors, UGT1A1 gene, hemolytic disorders, transport molecules

1. Introduction

Neonatal jaundice is caused by an increased production of bilirubin from senescent fetal red blood cells and/or limited bilirubin elimination in the newborn infant. Although neonatal jaundice is a natural and transitional phenomenon, some newborn infants develop severe hyperbilirubinemia. In these cases, unconjugated bilirubin in the serum may cross the blood-brain-barrier and cause bilirubin encephalopathy (acute bilirubin intoxication in the brain) or kernicterus (chronic bilirubin intoxication in the brain). Here, "kernicterus" is used to indicate the chronic symptoms of bilirubin intoxication in the brain, although kernicterus has also been used as a histopathological term, meaning yellow discoloration of the nuclei. Bilirubin encephalopathy results in acute manifestations of bilirubin toxicity in the first weeks after birth such as lethargy, poor feeding, hypertonia, irritability and seizure. Kernicterus results in chronic and permanent clinical sequelae of bilirubin toxicity such as choreoathetoid cerebral palsy, central neural hearing loss, palsy of the vertical gaze and tooth enamel hypoplasia (1).

Hyperbilirubinemia in the newborn infant can only be managed in the neonatal ward. It is of concern that early discharged infants may develop extremely high bilirubin levels at home. However, when the infants at risk are identified in time, they can remain in the neonatal ward and brain damage due to hyperbilirubinemia can be prevented. Therefore, it is a prerequisite to identify the infants at risk for developing severe hyperbilirubinemia (2).

Some genetic diseases are associated with pathological conditions that may cause or aggravate neonatal jaundice. Thus, the knowledge of these diseases may be helpful in identifying the infants at risk. In this paper, we will review some of the genetic disorders that may be a risk factor for neonatal jaundice.

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2. Inborn errors of bilirubin metabolism

2. 1. Uridine diphosphoglucuronate-glucuronosyltransferase 1A1 deficiency

(Overview) Uridine diphosphoglucuronate-glucuronosyltransferase 1A1 (UGT1A1) deficiency is a hereditary abnormality in the activity of the critical enzyme in the bilirubin glucuronidation pathway (3). Bilirubin is derived from the breakdown of hemoglobin due to senescence of red blood cells. After transportation into hepatocytes, bilirubin is conjugated with glucuronic acid in the presence of UGT1A1. The conjugated bilirubin is hydrophilic, which makes it easier to be excreted into the bile (4).

There are two UGT1A1 deficiency syndromes, Gilbert's syndrome (GS) and Crigler-Najjar syndrome (CN). GS (mild phenotype) and CN Type 2 (CN2; intermediate phenotype) result from a partial deficiency of UGT1A1, while CN Type 1 (CN1; severe phenotype) results from a complete deficiency of UGT1A1. Among UGT1A1 deficiencies, GS is very common, affecting about 6% of the population (5). In contrast, CN is very rare, with a frequency of 0.6 per million (6).

CN1 patients develop severe hyperbilirubinemia in the first 2 to 3 days after birth, and often require exchange transfusions. Brain damage can occur at any time in CN1 patients, even in adulthood (6). CN2 and GS patients usually show less severe hyperbilirubinemia, although some infants show severe jaundice in neonatal period and will require some treatments such as phenobarbital administration or phototherapy (5,7).

(Genetics) The *UGT1A1* gene belongs to the *UGT1A* gene complex on chromosome 2 (8). Three major polymorphic mutations, variant TATA box, c.211G>A and c.-3279T>G, have been found in different populations with different prevalence (9). Variant TATA box with an additional TA insertion, A(TA)7TAA, located in the proximal promoter region of *UGT1A1*, was first found in patients with CN2 and GS (8). Subsequently, the variant TATA box was also found in CN1 (7). The A(TA)7TAA mutation does indeed reduce the UGT1A1 transcriptional activity (10). Bancroft et al. showed that the A(TA)7TAA mutation accelerates development of neonatal jaundice (11). In the Caucasian population, the frequency of homozygosity for A(TA)7TAA in infants with neonatal jaundice was significantly higher than in normal infants (12). However, the A(TA)7TAA mutation may be not sufficient for the development of complete GS: GS patients with A(TA)7TAA may carry other additional mutations in *UGT1A1*. Some studies have reported that most GS patients with homozygosity of A(TA)7TAA were also homozygous for another mutation, c.-3279T>G (13-15).

The c.211G>A mutation is the most common mutation in the East Asian population (16). This mutation replaces a glycine at codon 71 with arginine (G71R), leading to a decrease in UGT1A1 enzyme activity. The c.211G>A mutation was first found in a Japanese male with CN2 (17). In the Japanese population, the allele frequency of c.211G>A in infants with neonatal jaundice was significantly higher than in control infants (18).

These days, there have been many studies on the *UGT1A1* mutation, focusing on mutations upstream of the promoter region. The c.-3279T>G mutation is located in the distal upstream region of *UGT1A1* (19). As mentioned above, it has been reported that most GS patients with homozygous A(TA)7TAA were also homozygous for c.-3279T>G (13-15). This finding suggests a synergistic effect of A(TA)7TAA and c.-3279T>G on transcription activity.

With regard to the prevalence of the *UGT1A1* polymorphic mutations in Southeast Asian countries, we performed a population study in Malays: neither A (TA)7TAA nor c.211G>A were common in Malays (20,21). Tables 1 and 2 show the genotype distributions and allele frequencies of A(TA)7TAA and c.211G>A in Malays, Japanese and Caucasians. However, we found that the frequency of c.-3279T>G was significantly higher in infants with neonatal jaundice than in control infants (in submission). This finding suggests that c.-3279T>G (and some other mutations) is a risk factor for GS or neonatal jaundice in Malays.

3. Hereditary hemolytic disorders

3. 1. Red blood cells enzyme disease: Glucose-6-phosphate dehydrogenase deficiency

(Overview) In red blood cells, glucose-6-phosphate dehydrogenase (G6PD) catalyzes NADP to its reduced form, NADPH, in the pentose phosphate pathway (22). Limited production of NADPH increases the vulnerability of red blood cells to oxidative stress, which may shorten their life span (23).

The main symptom of G6PD deficiency is hemolytic anemia, which usually occurs after

Table 1. Genotype distributions and allele frequencies of TATA box in *UGT1A1*

	Genotype distribution			Allele frequency	Reference
	TA6/TA6	TA6/TA7	TA7/TA7		
Malays*					
Jaundice (n=55)	41	10	4	0.16	21
Non-jaundice (n=50)	43	6	1	0.08	
Japanese*					
Jaundice (n=25)	23	2	0	0.04	18
Non-jaundice (n=50)	37	11	2	0.15	
Caucasian*					
Jaundice (n=82)	20	40	22	0.51	12
Non-jaundice (n=82)	31	41	10	0.37	
			(p=0.03)	(p=0.01)	

* The subjects were infants with and without neonatal jaundice.

Table 2. Genotype distributions and allele frequencies of c.211G>A in *UGT1A1*

	Genotype distribution			Allele frequency	Reference
	G/G	G/A	A/A		
Malays*					
Jaundice (n=55)	52	3	0	0.03	21
Non-jaundice (n=50)	47	3	0	0.03	
Japanese*					
Jaundice (n=25)	11	11	3	0.34	18
Non-jaundice (n=50)	35	14	1	0.16	
			(p=0.04)	(p=0.01)	
Caucasian **					
Jaundice (n=53)	53	0	0	0	15
Non-jaundice (n=83)	81	2	0	0.01	

* The subjects were infants with and without neonatal jaundice.
** The subjects were Gilbert's syndrome patients with mean age of 10.9±5.3 years and unaffected subjects with mean age of 11.1 ±8.0 years.

exposure to certain medications (antimalarias, primaquine, sulfonamides, nitrofurantoin and other drugs), foods (especially fava beans) or even infection (hepatitis viruses A and B, cytomegaloviruses, pneumonia and others) (22,24,25). Whatever the cause of the acute hemolysis in G6PD deficiency, it is clinically characterized by fatigue, back pain, anemia and jaundice (22,24). There are approximately 400 million people suffering from G6PD deficiency throughout the world (25). The deficiency occurs with high frequency in Africa, the Mediterranean (including in Italians, Greeks, Arabs and Sephardic Jews), the Middle East and Southeast Asia. The prevalence of G6PD deficiency correlates with the geographic distribution of malaria, suggesting that mutant G6PD may protect against malaria infection (25,26).

A study conducted in the United States estimated that 30% of jaundiced infants who have permanent brain damage are G6PD deficient (27). However, Kaplan et al. suggested that impaired bilirubin conjugation and delayed clearance by the liver have a considerable contribution to neonatal jaundice (28,29). Jalloh et al. showed, based on their clinical data, that hemolysis is not

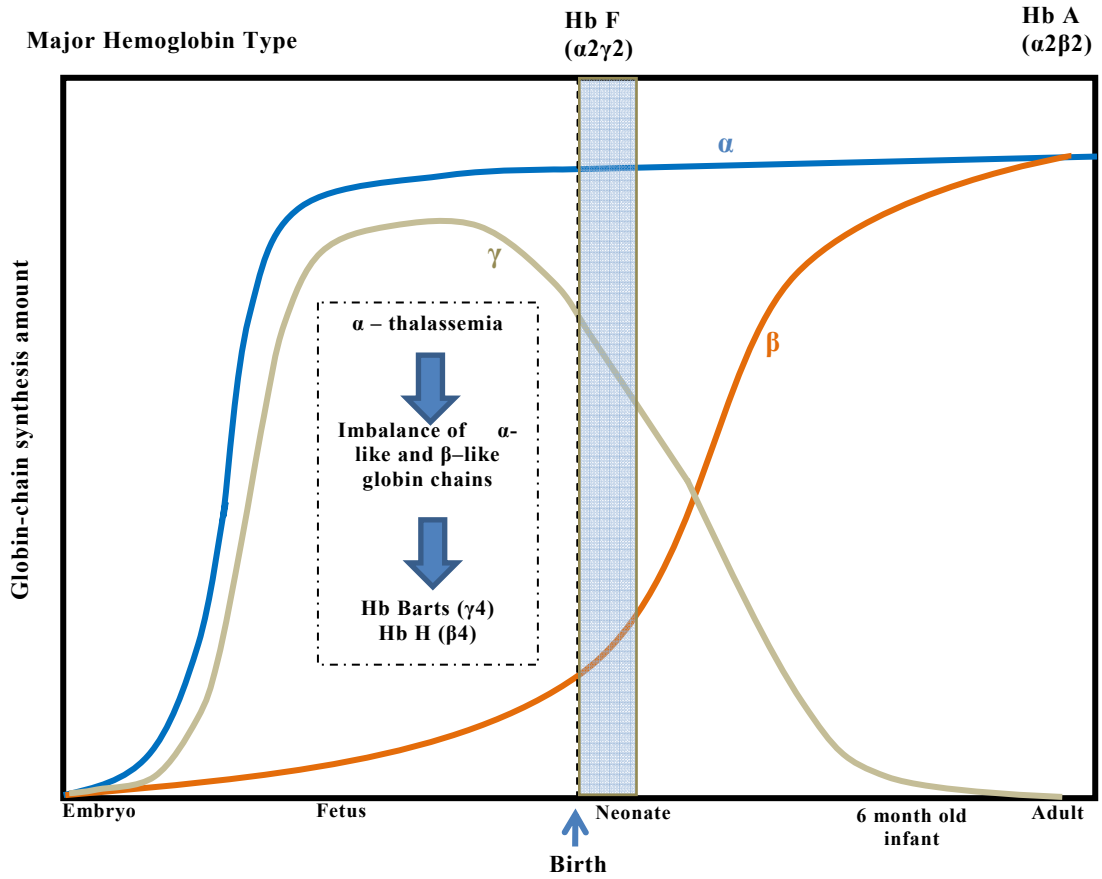

Fig. 1. Haemoglobin switching. During the neonatal period, fetal Hemoglobin (α2γ2) is a major one, then switches into adult hemoglobin (α2β2) at the end of the first year of life. Deletion of three or four α-globin genes leads to formation of Hb H (β4) and Hb Barts (γ4).

a main determinant of neonatal jaundice in G6PD deficient infants (30). Recently, the combined effects of G6PD deficiency and GS on the development of neonatal jaundice have been discussed (31,32).

(Genetics) G6PD deficiency is an X-linked recessive disease (22,25,33). Thus, the disease usually affects males but there are some female patients (33). More than 160 different mutations have been demonstrated so far, most of which are missense mutations (24,25,33). Most polymorphic mutations predominate in specific regions of the world: G6PD A- (376G/202A) is prevalent in Africa and Southern Europe (24,33), G6PD Mediterranean (563T) in Mediterranean countries (24,33), and G6PD Viangchan (871A) in Asian countries (24,25,33). Polymorphic mutations affect amino acid residues throughout the enzyme and decrease the stability of the enzyme in the red blood cells, possibly by perturbing protein folding. However, severe mutations mostly affect amino acid residues at the dimer interface or the residues interacting with a structural NADP molecule that stabilizes the enzyme (33).

3. 2. Hemoglobinopathies: α-Thalassemia

(Overview) Hemoglobinopathies belong to the most common forms of hereditary hemolytic anemia. They are usually autosomal recessive abnormalities, which are characterized by the defective and imbalanced production of globin chains (α- and β-thalassemias), or structurally abnormal hemoglobin variants such as sickle cell disease (34,35).

There are two main thalassemias, α-thalassemia, with impaired α-globin chain production, and β-thalassemia, with impaired β-globin chain production. Developmental differences in globin chain synthesis are responsible for the clinical manifestations of thalassemia in the perinatal period (Figure 1). The main pathological state related to neonatal jaundice is α-thalassemia (36). Most β-globin

chain defects, including β-thalassemia and sickle cell disease, do not present with anemia or hemolysis in the neonatal period, due to the presence of large amounts of fetal hemoglobin (α2γ2) (36).

It recently has been estimated that in excess of 300,000 infants are born with serious inherited hemoglobinopathies each year (37). In sub-Saharan Africa, HbS and α-thalassemia are often observed. In the Mediterranean region and the Middle East, α- and β-thalassemia predominate.

In the eastern parts of the Indian subcontinent, Bangladesh, Myanmar, Thailand, and in other parts of Southeast Asia, Hb E is by far the most common hemoglobin variant, although both α- and β-thalassemia also occur at variable frequencies (38). Heterozygous state of Hb E and β-thalassemia (Hb E β-thalassemia) is the most common severe form thalassemia in many Asian countries (38). Like with G6PD deficiency, the prevalence of these hemoglobinopathies correlates with the geographic distribution of malaria, suggesting that hemoglobinopathies may also protect against malaria infection (26).

(Genetics) The α-like chain genes are encoded in chromosome 16 in the order 5'-ζ2-ψζ1-ψα2-ψα1-α2-α1-θ-3', while the β-like chain genes are encoded in chromosome 11 in the order 5'-ε-^{G}γ-^{A}γ-ψβ-δ-β-3' (39). By 9 weeks of gestation, α-globin is the major α-like chain gene product in humans (36). In contrast, of the β-like chains, β-globin production begins late in the gestation. The switch from fetal hemoglobin (α2γ2) to adult hemoglobin (α2β2) is not completed until the end of the first year of life, and defects in β-globin production may become apparent in late infancy (36).

Generally, α-thalassemia results from the deletion of one or more of the four α-globin genes, and its clinical manifestations are related to the deleted gene number (36,40). A single α-globin gene deletion results in an asymptomatic carrier state. Deletion of two genes results in α-thalassemia trait, which is characterized by microcytosis and mild anemia. Deletion of three genes shows a significant imbalance in α- and β-like chain production and a production of Hb H (β4), resulting in Hb H disease or, rarely, Hb H hydrops fetalis (41). Deletion of all four genes is called "homozygous α-thalassemia" or "α-thalassemia major". Deletion of four genes produces Hb Barts (γ4), leading to Hb Barts hydrops fetalis (41). Patients (fetuses) with Hb H or Hb Barts hydrops fetalis are severely affected, often leading to death in utero (41).

3.3. Red blood cells membrane disease: Southeast Asian Ovalocytosis

(Overview) Hereditary elliptocytosis (HE) is a heterogeneous group of inherited red blood cells membrane disorders that have in common the presence of elongated, oval, or elliptical red blood cells in peripheral blood smears (42). Southeast Asian Ovalocytosis (SAO) is one of the autosomal dominant HEs, that carry a structurally and functionally abnormal band 3 protein, the principal transmembrane protein of red blood cells (43,44). SAO is most prevalent in areas endemic for malaria and confers some protection against malaria on the patients (42). The ovalocytic red blood cells are rigid and may be resistant to invasion by various malarial parasites.

It is thought that SAO is an asymptomatic condition. However, it may contribute to increasing hemolysis and hyperbilirubinemia in the neonatal period (45,46). In 1999, Laosombat et al. reported an SAO infant with neonatal jaundice; the infant showed rapidly rising bilirubin levels and needed not only phototherapy but also exchange blood transfusion (45). Laosombat et al. also reported that half of the newborn infants with SAO in their study had hyperbilirubinemia (46).

(Genetics) The most frequent molecular defect of SAO is a 27 nucleotide deletion in exon 11 of the anion exchanger 1 gene (*AE1*) on chromosome 17 (44,47). This *AE1* gene codes for band 3 protein that is both a component of the red blood cells membrane cytoskeleton and the chloride-bicarbonate anion exchanger in the membrane (47). The band 3 protein is also expressed in the basolateral membrane of renal collecting tubule α-intercalated cells (48). A close relationship between SAO and distal renal tubular acidosis has been reported (48,49).

4. Bilirubin transport system disorders in the hepatic cells

4. 1. Organic anion transporter abnormality

(Overview) Organic anion transporters (OATs) or organic anion transporting polypeptides (OATPs) play an essential role in the elimination of numerous endogenous and exogenous organic anions from the body. The OAT family is expressed in the kidney, liver, brain and placenta (50). Organic anion transporter 2 (OATP2) is involved in the hepatic uptake of a broad array of endogenous compounds, such as taurocholate, leukotriene C4, prostaglandin E2, conjugated

steroid, thyroid hormone and peptide. Recently, OATP2 has also been shown to mediate the cellular uptake of bilirubin and its glucuronide conjugates (51).

(Genetics) The *OATP2* gene is located in chromosome 12. Huang et al. reported that neonates who carried a polymorphic mutation G>A at nucleotide 388 in the *OATP2* gene were at high risk of developing severe hyperbilirubinemia (52). According to their data, the prevalence of the variant *OATP2* gene was significantly higher in infants with neonatal hyperbilirubinemia than in control infants in the Taiwanese population. This polymorphic mutation may increase unconjugated hyperbilirubinemia levels by impairing hepatic bilirubin uptake. Huang et al. also showed that the odds ratio of hyperbilirubinemia in the neonates who carry three risk factors, breast feeding, c.211G>A in *UGT1A1* and c.388G>A in *OATP2*, is 88.00 (95% CI 12.50-642.50, $p<0.001$). However, Prachukthum et al. reported that there was no association between the variant *OATP2* gene and neonatal hyperbilirubinemia in the Thai population: the prevalence of the variant *OATP2* gene in infants with hyperbilirubinemia was not higher than in control infants (53).

4. 2. Glutathione S-transferase abnormality

(Overview) Glutathione S-transferases (GST) are a family of detoxifying isoenzymes that catalyze the conjugation of glutathione to hydrophobic substrates with an electrophilic functional group (54). In addition to this enzymatic function, GST also binds to a variety of endogenous and xenobiotic compounds with high affinity (55).

(Genetics of α-class GST) Unconjugated bilirubin is efficiently bound by ligandin, which is a dimer of α-class GST isoforms, GSTA1 and GSTA2 (56). The *GSTA1* and *GSTA2* genes are located in chromosome 6. Akizawa et al. demonstrated that artificial GSTA2 protein directly binds to UGT1A1 through the region inside the endoplasmic reticulum (ER). They suggested that bilirubin/ligandin complex enters ER and then bilirubin is delivered from ligandin to UGT1A1 for glucuronidation (57).

(Genetics of μ-class GST) Recently, GSTM1, a member of μ-class GST isoforms, has been discussed in relation to the development of neonatal jaundice. The *GSTM1* gene is located in chromosome 1. Muslu et al. reported that total bilirubin levels in neonates with the *GSTM1* null genotype were significantly higher than in neonates with the *GSTM1* wild genotype in the Turkey population (58). They suggested that the *GSTM1* gene polymorphism might affect ligandin function in hepatocytes and lead to hyperbilirubinemia in neonates (58). However, according to their data, the prevalence of the *GSTM1* null genotype in infants with hyperbilirubinemia was not higher than in control infants. Prachukthum et al. also reported that the prevalence of the *GSTM1* null genotype in infants with neonatal hyperbilirubinemia was not higher than in control infants (53).

5. Miscellaneous genetic risk factors

(Hemorrhagic disorders) Intracranial hemorrhage, cephalhematomas, pulmonary hemorrhage, adrenal hemorrhage, or any occult bleeding lead to elevated serum bilirubin levels from breakdown of the extravascular red blood cells (59,60). Some of the hemorrhagic disorders are caused by underlying genetic disorders such as hemophilia A, hemophilia B and other coagulation factor deficiencies (60,61).

(Intestinal disorders) Intestinal disorders may lead to hyperbilirubinemia in neonates (62). Intestinal disorders predominantly contribute to hyperbilirubinemia through increased enterohepatic circulation of bilirubin caused by intestinal obstruction.

There are many diseases that may cause intestinal obstruction, such as meconium ileus, intestinal atresia, intestinal stenosis, or Hirschsprung disease. Meconium ileus is caused by cystic fibrosis due to the *CFTR* mutation, intestinal atresia by chromosomal abnormalities such as trisomy 21 syndrome, and Hirschsprung disease by mutations in genes related to the development and migration of neural cells, such as *RET, GDNF, EDN,* etc.

(Infection or immunodeficiency) Infection may also lead to hyperbilirubinemia because of increased hemolysis, liver dysfunction, decreased albumin-bilirubin binding, etc. (63). It should also be noted that some neonates may develop severe or prolonged neonatal jaundice as one of the symptoms of a severe combined immunodeficiency (64).

6. Conclusion

There are many genetic disorders that are associated with hyperbilirubinemia. In effect, one could say that all genetic disorders lead to hyperbilirubinemia, as all roads lead to Rome. Even in acquired diseases linked with hyperbilirubinemia, such as cephalhematomas or meconium ileus, there may be a genetic

abnormality as an underlying cause of the disease.

The high incidence of neonatal jaundice in Asian populations compared with Caucasian populations is very likely to have a genetic cause. For many populations, especially in South and Southeast Asia, a lot of further research is needed to elucidate the genetic disorders underlying neonatal jaundice.

Rapid and accurate screening systems for these genetic disorders should be established for the proper management of neonatal hyperbilirubinemia so that brain damage can be prevented.

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