Etiological Analyses of Marked Neonatal Hyperbilirubinemia in A Single Institution in Taiwan

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Background: Hyperbilirubinemia is a common disorder during the neonatal period. Severe neonatal hyperbilirubinemia (NH) carries a potential for permanent neurological impairment. The current study analyzed possible etiologies leading to NH.

Methods: A retrospective cohort of neonates with total serum bilirubin (TSB) ≥ 20 mg/dL was surveyed from 1995 to 2007. Subjects with gestational ages < 34 weeks were excluded, leaving a total of 413 enrolled neonates.

Results: The most common etiology in relation to marked NH was breast milk feeding (38.5%), followed by glucose-6-phospahate dehydrogenase (G6PD) deficiency (24.0%), ABO incompatibility (21.8%), extravascular hemorrhage (6.5%), Rh incompatibility (2.9%), bacterial infection (2.2%), hereditary spherocytosis (1.2%), dehydration (1.2%), diabetic mother (1.0%), polycythemia (0.7%), and gastrointestinal obstruction (0.7%). Other rare etiologies included Down syndrome, Chinese herb intake, asphyxia, galactosemia and congenital hypothyroidism. We did not identify any known cause in 63 neonates (15.3%). Neonates with more than one etiology tended to have higher TSB than subjects without a known etiology ($p < 0.05$). Anemia was more common in those with G6PD deficiency, blood group incompatibility, hereditary spherocytosis, and gastrointestinal obstruction. Neonates fed breast milk tended to have prolonged NH.

Conclusion: This study depicts the clinical features of marked NH. Breast milk feeding, G6PD deficiency and ABO incompatibility are common etiologies in Taiwan. Prolonged NH is more common in neonates fed breast milk than those who were given formula.

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Key words: neonatal hyperbilirubinemia, total serum bilirubin, breast milk, G6PD deficiency, blood group incompatibility

Neonatal hyperbilirubinemia (NH) is associated with a variety of conditions. Physiological aspects that contribute to NH include increased bilirubin production, less efficient hepatic conjugation, and enhanced bilirubin absorption by the enterohepatic circulation.[1] In addition to physiologic jaundice, common identified pathologic causes include isoimmune hemolytic disease and glucose-6-

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phospahate dehydrogenase (G6PD) deficiency.[2-4] Etiologies leading to NH carry a geographic difference. For instance, in one study from Singapore, NH was more common in babies of Chinese ethnic origin than those of Indian, Malay and other origins.[5]

Severe NH poses a direct threat of kernicterus, a permanent neurological sequel.[6,7] Early identification of neonates at great risk of NH is of paramount importance in preventing brain damage. Total serum bilirubin (TSB) has been used as a surrogate index to evaluate the risk of adverse outcomes. Although a safe threshold for TSB has not been defined, most physicians have adopted a TSB ≥ 20 mg/dL as indicating vulnerability to neurotoxicity.[8] In this study, the spectrums of neonates with TSB ≥ 20 mg/dL are evaluated. We described the clinical features of marked NH according to etiological factors.

METHODS

Approval to collect data was granted by the Institutional Review Board of Chang Gung Memorial Hospital. Medical charts of newborns admitted to the neonatal intensive care units at Chang Gung Children's Hospital from 1995 to 2007 with TSB ≥ 20 mg/dL were reviewed. Neonates with either a direct bilirubin /TSB > 20% or gestational age < 34 weeks were excluded. The direct bilirubin and TSB values were measured in a clinical laboratory with a Unistat bilirubinometer (Cambridge Instruments, Buffalo, NY, U.S.A.).

Patient data and clinical manifestations were obtained from medical charts. Mortality was defined as death occurring within 7 days after the development of marked hyperbilirubinemia without other known causes of death. Routine laboratory examinations included complete blood count, reticulocyte count blood smear, total and direct bilirubin, G6PD enzymatic activity, blood and urine cultures, blood type, and direct Coombs' test. In addition, data were collected from the national newborn screening for congenital hypothyroidism, galactosemia, G6PD deficiency, phenylketonuria, and homocystinuria. Any possible etiologies causing neonatal hyperbilirubinemia, including G6PD deficiency, diabetic mother, polycythemia, inborn error of metabolism (such as congenital hypothyroidism, galactosemia), hereditary spherocytosis, bacterial infection (such as sepsis, omphalitis, urinary tract infection), dehydration (defined as body weight loss of more than 10% of birth weight), gastrointestinal obstruction (defined as pathological obstruction requiring medical treatment, such as malrotation), exclusive breast feeding, extravascular hemorrhage (such as cephalohematoma, bruising, adrenal hemorrhage), Down syndrome, asphyxia, ABO incompatibility (any blood group A or B neonate of a group O mother), Rh incompatibility (Rh-positive infants born to Rh-negative mothers), were recorded.[1] G6PD deficiency was confirmed with an enzyme activity below 12.5 U/gm Hb. Polycythemia was defined as a hematocrit value > 65% via venous sampling or > 63% via arterial sampling. Infants with spherocytosis on a blood smear were referred to pediatric hematologists for regular follow up. Hereditary spherocytosis was thereafter confirmed using an osmotic fragility assay.

The statistical analyses were conducted using SPSS for Windows, version 12.0 (SPSS Inc., IL, U.S.A.). Categorical variables were analyzed using the chi-square test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney test. Significance was defined as $p < 0.05$.

RESULTS

There were 413 neonates with TSB ≥ 20 mg/dL during the 13-year study period. Extreme hyperbilirubinemia, defined as TSB ≥ 25 mg/dL, was noted in 111 neonates (26.9%), with a TSB of 25-29.9 mg/dL in 81 (19.6%) neonates, 30-34.9 mg/dL (4.1%) in 17, 35-39.9 mg/dL (1.2%) in 5, 40-44.9 mg/dL *(0.8%) in 3, and 45-49.9 mg/dL (1.2%) in 5. A total of 245 neonates were boys (59.3%). In addition, 143 neonates were late preterm (34.6%).

The etiologies in relation to NH are summarized in Table 1. The most common etiology was exclusive breast feeding (38.5%), followed by G6PD deficiency (24.0%), and ABO incompatibility (21.8%). There were 63 neonates without an identified etiology (15.3%). Neonates with Rh incompatibility included 6 mismatches in Rh D, 4 in Rh E and 2 in Rh E,c. Neonates with extravascular hemorrhage included 19 with cephalohematoma (4.6%), 3 with massive bruising (0.7%), 2 with subgaleal hemorrhage (0.5%), 2 with adrenal hemorrhage (0.5%), and 1 with intracranial hemorrhage (0.2%). Bacterial infection was found in 9 neonates, including 3 with sepsis (*E. coli*), 4 with omphalitis (*E. coli*) and 2

Table 1. Etiology of Hyperbilirubinemia in Neonates

Etiology	TSB ≥ 20 mg/dL N = 413 n (%)	TSB ≥ 25 mg/dL N = 111 n (%)	TSB ≥ 30 mg/dL N = 30 n (%)
Exclusive breast feeding	159 (38.5)	38 (34.2)	9 (30.0)
G6PD deficiency	99 (24.0)	41 (36.9)	18 (60.0)
ABO incompatibility	90 (21.8)	26 (23.4)	5 (16.7)
Unknown	63 (15.3)	12 (10.8)	2 (6.7)
Extravascular hemorrhage	27 (6.5)	4 (3.6)	1 (3.3)
Rh incompatibility	12 (2.9)	7 (6.3)	2 (6.7)
Bacterial infection	9 (2.2)	4 (3.6)	2 (6.7)
Hereditary spherocytosis	5 (1.2)	2 (1.8)	0 (0)
Dehydration	5 (1.2)	2 (1.8)	0 (0)
Diabetic mother	4 (1.0)	1 (0.9)	0 (0)
Polycythemia	3 (0.7)	1 (0.9)	0 (0)
Paralytic ileus	2 (0.5)	1 (0.9)	0 (0)
Malrotation	1 (0.2)	1 (0.9)	1 (3.3)
Down syndrome	1 (0.2)	1 (0.9)	0 (0)
Chinese herb intake	1 (0.2)	1 (0.9)	1 (3.3)
Asphyxia	1 (0.2)	1 (0.9)	0 (0)
Galactosemia	1 (0.2)	0 (0)	1 (0.2)
Congenital hypothyroidism	1 (0.2)	1 (0.9)	1 (0.2)

Abbreviations: TSB: total serum bilirubin; G6PD: glucose-6-phospahate dehydrogenase.

with urinary tract infection (*Klebsiella pneumoniae, Enterobacter cloacae*). In addition, 3 neonates had gastrointestinal tract obstruction. One infant had organic obstruction caused by malrotation. This patient had a peak TSB level just after surgical treatment. Two neonates had paralytic ileus with the clinical manifestations of abdominal distension and vomiting.

The most common etiology in neonates with extreme hyperbilirubinemia (defined as TSB ≥ 25 mg/dL) was G6PD deficiency (36.9%), followed by exclusive breast feeding (34.2%), and ABO incompatibility (23.4%). Similarly, the most common etiology in infants with TSB ≥ 30 mg/dL was G6PD deficiency (60.0%), followed by exclusive breast feeding (30.0%), and ABO incompatibility (16.7%).

The correlation of TSB with the number of etiological factors is shown in Table 2. The TSB in neonates with two or more etiologies was significantly higher than those with an unknown etiology.

Table 2. Correlation of Total Serum Bilirubin with the Number of Etiological Factors

Number	n (%)	Total serum bilirubin (mg/dL)	*p* value
0	63 (15.3)	22.7 ± 3.1	reference group
1	288 (69.7)	23.6 ± 4.2	0.090
2	54 (13.1)	24.6 ± 4.7	0.012
> 2	8 (1.9)	30.8 ± 10.4	0.009

We further evaluated the clinical characteristics by etiology. Neonates with more than one etiology were eliminated in an attempt to better understand the profile of each etiology (Table 3). In infants with a hemoglobin level < 14 g/dL, those with Rh incompatibility had the lowest average hemoglobin, followed by those with hereditary spherocytosis, G6PD deficiency, ABO incompatibility and gastrointestinal tract obstruction. In addition, prolonged NH (defined as age at peak TSB > 15 days old) was found only in neonates fed breast milk. Neonates with an average age at peak TSB of less than 3 days old included those with ABO incompatibility, hereditary spherocytosis and Rh incompatibility.

DISCUSSION

Although NH has been thoroughly evaluated, there are few reports on the manifestations within different etiologies.[9] There are often multiple reasons causing NH in a given neonate. Combined etiologies may result in greater severity of NH.[10] We omitted neonates with multiple etiologies to better understand the manifestations of NH caused by a single factor. To our knowledge, the current study is the first to compare the clinical presentations of NH by etiological factor.

Overall, exclusive breast feeding was the most common cause of NH. There are an increasing number of studies showing that breast feeding is the most important factor leading to NH.[11-14] We found that NH caused by breast feeding increased significantly after the governmental initiative to encourage breast feeding which began in 2001 (1995-2001: 2002-2007 = 25%: 50%). A similar report from Huang *et al.* also showed an increase of NH after global promotion of this policy.[15] In particular, our study demonstrated all neonates with prolonged NH, defined as

Table 3. Laboratory and Patient Information for 288 Neonates with a Single Etiological Factor.

Etiology	TSB (mg/dL) mean ± SD (range)	Hemoglobin (g/dL) mean ± SD (range)	Age at peak TSB (d) mean ± SD (range)
Exclusive breast feeding (n = 118)	22.8 ± 2.8 (20.0–32.5)	14.9 ± 2.1 (9.3–19.4)	9.73 ± 5.60 (3–30)
G6PD deficiency (n = 61)	25.6 ± 6.6 (20.1–47.2)	13.1 ± 2.7 (7.5–19.6)	6.92 ± 3.16 (3–15)
ABO incompatibility (n = 63)	23.3 ± 3.2 (20.0–38.6)	13.4 ± 2.3 (8.7–18.0)	3.70 ± 2.08 (1–8)
Extravascular hemorrhage (n = 14)	21.1 ± 1.2 (20.0–24.0)	14.1 ± 2.3 (10.1–17.0)	4.57 ± 1.60 (3–8)
Rh incompatibility (n = 10)	26.1 ± 3.0 (22.0–30.7)	11.3 ± 2.2 (8.7–15.4)	2.60 ± 1.43 (1–5)
Bacterial infection (n = 4)	23.6 ± 2.8 (20.7–27.2)	16.6 ± 1.5 (14.7–18.0)	3.50 ± 0.58 (3–4)
Hereditary spherocytosis (n = 3)	23.8 ± 3.3 (21.6–27.6)	12.4 ± 0.3 (12.1–12.7)	1.67 ± 0.58 (1–2)
Dehydration (n = 5)	23.3 ± 3.1 (20.5–27.9)	16.2 ± 2.2 (13.7–19.2)	8.40 ± 4.45 (6–15)
Diabetic mother (n = 3)	21.1 ± 1.1 (20.1–22.2)	15.6 ± 0.2 (15.4–15.8)	3.67 ± 0.58 (3–4)
Polycythemia (n = 2)	23.1 ± 0.1 (23.0–23.2)	20.1 ± 2.1 (18.6–21.5)	5.00 ± 2.83 (3–7)
Gastrointestinal tract obstruction (n = 2)	29.6 ± 11.5 (21.5–37.7)	13.4 ± 0.8 (12.8–13.9)	5.50 ± 0.71 (5–6)
Down syndrome (n = 1)	26.0	15.8	9
Galactosemia (n = 1)	20.9	17.6	3
Chinese herb intake (n = 1)	33.8	17.2	5

Abbreviations: TSB: total serum bilirubin; G6PD: glucose-6-phospahate dehydrogenase.

NH noted at age > 15 days, were fed breast milk. Although breast feeding has been encouraged because it has many advantages, its impact on NH still raises concerns. However, the risk of long-term neurological complications (kernicterus) with this etiology is very low.[2] NH resolves spontaneously within a few months in breast-fed infants. Therefore, NH caused by breast feeding has been treated with a gentle approach. Our previous report also showed that breast milk feeding carries no significant risk for kernicterus.[16] Bilirubin has been proposed as an effective antioxidant, and modest elevations of bilirubin may be beneficial in compromised neonates.[17] Further studies are needed to investigate the pathophysiological mechanism of breast milk feeding leading to NH.

ABO incompatibility and G6PD deficiency were also common causes of NH in this study, and other studies.[2-4,9,18] Anemia is more common in these two groups, indicating that hemolysis plays an important role in the development of NH.[3,4,19]

Previous investigations have documented an association between NH and bacterial infection, especially sepsis and urinary tract infection.[20-24] How bacterial infection causes NH is not clear. An induction of heme oxygenase-1, the rate-limiting enzyme in bilirubin production, has been proposed as the mechanism.[17,25] In our study, 3 neonates with sepsis were all infected by *E. coli,* which is the most common gram-negative pathogen during the newborn period.[20,21] Furthermore, our study demonstrated that urinary tract infection was an infrequent cause of NH. The pathogens in the urinary tract infections were gram-negative bacilli. There has been a debate on routine urine cultures for well infants with NH.[26] In this study, neonates with urinary tract infection developed clinical manifestations other than NH. Our study also found *E. coli* was the most common pathogen in infants with omphalitis. Taken together, the data suggest that neonates infected by gram-negative bacilli are more susceptible to NH.

In our study, the incidence of hereditary spherocytosis was 1.2%, which was much higher than in the overall population. Similar findings were observed by Saada *et al.*[27] There is difficulty in the diagnosis of hereditary spherocytosis at birth, leading to an underestimation of its correlation with NH.[28,29] Infants with hereditary spherocytosis often develop early NH, similar to those with blood group incompatibility. Although hemolysis is the contributor to NH, only a few cases developed extreme NH requiring exchange transfusion.[30,31]

Infants of diabetic mothers have an increased risk of NH. Neonates born to diabetic mothers who

have macrosomia tend to have bruising at birth, and resorption of subcutaneous blood can contribute to NH.[32] In addition, some rare etiologies leading to NH were identified in this study. We found two neonates with inborn error of metabolism disorders. Galactosemia has been documented as an uncommon presentation of early-onset NH.[33] Furthermore, neonates with Down syndrome or congenital hypothyroidism may develop NH beyond the age of physiological jaundice.[34,35] Our study also found gastrointestinal tract obstruction was a contributor to NH. It's well known that a lower gastrointestinal tract obstruction increases the absorption of bilirubin.[1] In our study, one neonate received a proprietary preparation of Chinese herbs. There has been little monitoring of Chinese medicine in neonates.[36] Therefore, parents should be discouraged from treating their neonates with herbal medicine.

There were some limitations to this study. First, the pattern of etiological factors may have great geographic variations. Therefore, our findings may not apply in other countries. Second, the cause of NH could not be determined in a substantial number of neonates in this study. Some potential factors leading to NH were not examined, such as Gilbert syndrome.[37] In most of these neonates, peak TSB levels were reached on the third to sixth day after birth with normal limits of hematologic parameters. Thus, they may display a severe form of physiologic jaundice. Third, some etiologies were present in only few subjects and, as a result, interpretation of data from these patients should be done cautiously.

In conclusion, our study disclosed the clinical features of marked NH within different etiologies. Breast milk feeding, G6PD deficiency and ABO incompatibility are common etiologies of NH in Taiwan. Prolonged NH is more common in neonates fed breast milk. In particular, we reported the manifestations of NH caused by uncommon etiologies. Clinicians may distinguish the etiological factor according to the clinical presentation of NH.

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嚴重新生兒高膽紅素血症之病因性分析～某單一醫療機構之研究

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背 景： 高膽紅素是新生兒時期常見的疾病。膽紅素過高可能造成永久性的神經傷害，本回溯性研究即探討新生兒嚴重黃疸之病因性分析。

方 法： 研究對象爲 1995 年至 2007 年膽紅素超過 20 mg/dL 之新生兒，排除出生週數 < 34 週之早產兒，共收案 413 位新生兒。

結 果： 造成新生兒高膽紅素血症最常見之原因爲純母乳哺餵 (38.5%)，其次爲蠶豆症 (24.0%)、ABO 血型不相容 (21.8%)、血管外出血 (6.5%)、Rh 血型不相容 (2.9%)、細菌感染 (2.2%)、遺傳性非球性紅細胞貧血 (1.2%)、脫水 (1.2%)、母親糖尿病之嬰兒 (1.0%)、紅血球增多症 (0.7%)、腸道阻塞 (0.7%)。其他少見之病因包括唐氏症、服用中藥、窒息、半乳糖血症及先天甲狀腺機能不足。本研究共有 63 位新生兒找不到明確的病因 (15.3%)。具有一項以上病因的新生兒其血清總膽紅素較沒有病因的新生兒爲高 ($p < 0.05$)。蠶豆症、血型不相容 (21.8%)、遺傳性非球性紅細胞貧血、腸道阻塞較會有貧血之現象。延遲性新生兒高膽紅素血症較會出現在純母乳哺餵之嬰兒。

結 論： 本研究提供了嚴重新生兒高膽紅素血症的臨床表現，尤其是少見病因的探討。本研究進一步探討各個病因在臨床上的差異性，發現純母乳哺餵之嬰兒較容易出現延遲性之新生兒高膽紅素血症。

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關鍵詞： 高膽紅素血症，血清總膽紅素，母乳，蠶豆症，血型不相容

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