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Hyperbilirubinemia in Term Newborns Needing Phototherapy within 48 Hours after Birth in a Japanese Birth Center

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Background: Hyperbilirubinemia in term newborns needing phototherapy within 48 hours after birth, early-onset hyperbilirubinemia, has not been evaluated in recent Japanese healthy birth centers. In this study, we sought to determine the cause of early-onset hyperbilirubinemia in a Japanese healthy birth center and to evaluate the 1992 Kobe University phototherapy treatment criterion requiring total serum bilirubin (TSB) and unbound bilirubin (UB).
Methods: In this retrospective observational study, we collected data on newborns diagnosed with early-onset hyperbilirubinemia between 2009 and 2016 at the Chibune General Hospital. Causes of the disease were investigated, as well as which index (TSB or UB) was used for treatment decisions.
Results: Overall, 76 term newborns were included in the analysis. Twenty-seven newborns (36%) found the cause (ABO blood type incompatibility [n=17, 22%], polycythemia [n=8, 11%], and cephalohematoma [n=2, 3%]). However, 49 newborns (64%) did not find any causes (i.e., idiopathic hyperbilirubinemia). Of these, 27 observed more than 5% weight loss from birth weight. Seventy (92%) newborns had abnormal TSB only, and 5 (7%) had abnormal TSB and UB values. Only 1 (1%) newborn with only abnormal UB values received phototherapy.
Conclusions: Altogether, data from this Japanese healthy birth center suggest that many apparently healthy newborns with or without excessive weight loss develop early-onset hyperbilirubinemia. In the 1992 Kobe University phototherapy treatment criterion, TSB, not UB, was the main index used to make treatment decisions in these patients.

INTRODUCTION

Neonatal physiological jaundice is a process by which a fetus adapts to neonatal life. It is visibly apparent 48 to 72 hours after birth (total serum bilirubin [TSB], 5 to 7 mg/dL), peaks between 4 to 6 days of age (TSB ≤ 12 mg/dL), and naturally disappears between 7 to 14 days of age (1, 2). When jaundice or hyperbilirubinemia occurs earlier, especially within 48 hours of birth (i.e., early-onset hyperbilirubinemia), newborns must receive treatments such as phototherapy (PT) to prevent bilirubin encephalopathy (3). Generally, the causes of early-onset hyperbilirubinemia are sepsis, hemolytic diseases (Rhesus [Rh] D hemolytic disease, ABO blood type incompatibility, or glucose-6-phosphate dehydrogenase [G6PD] deficiency), preterm birth, asphyxia, cephalohematoma, significant bruising of body regions, exclusive breastfeeding, excessive weight loss, and east Asian ethnic background (3). However, the causes of early-onset hyperbilirubinemia in Japanese healthy birth centers may be different from those at other high-risk birth centers.

In addition, although the 1992 Kobe University treatment criterion is generally used for PT treatment decisions (4), to our knowledge, a study evaluating it has not been performed in newborns with early-onset hyperbilirubinemia in Japanese healthy birth centers. We sought to investigate the cause of early-onset hyperbilirubinemia in a healthy birth center at a Japanese general hospital, and evaluate the 1992 Kobe University treatment criterion for treatment decisions in this patient population.

MATERIALS AND METHODS

Study design, setting, and subjects

As part of this retrospective observational study, we collected data on newborns diagnosed with early-onset hyperbilirubinemia between 2009 and 2016 at the Chibune General Hospital. Early-onset hyperbilirubinemia was defined as newborns with hyperbilirubinemia within 48 hours of birth who received PT.

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The Chibune General Hospital is located on the west side of Osaka-city and has a birth center where more than 1,400 newborns are born annually. Of these, more than 1,200 newborns are born to term (i.e., 37-41 weeks of gestation). All term healthy newborns are screened for transcutaneous bilirubin using JM-103 (Konica Minolta, Inc., Tokyo, Japan) (5) based on the criteria shown in Table I. When transcutaneous bilirubin levels are greater than the reference criterion, blood is collected via venipuncture, and TSB and serum unbound bilirubin (UB) levels are measured using a UB-Analyzer (UA-2™, Arrows Co., Ltd, Osaka, Japan) (6). Newborns are diagnosed with hyperbilirubinemia if TSB and/or UB levels are greater than the 1992 Kobe University treatment criterion (Table I), and are indicated to receive PT (4).

As part of a control group, we also enrolled 101 full-term newborns without hyperbilirubinemia, who did not receive PT within 48 hours of birth, born between 2011 and 2012 at the Kobe University Hospital.

This study was approved by the institutional review board of Kobe University Graduate School of Medicine (#1776). We also opened the study's contents to the public in our hospitals. The need for formal informed consent from individual participants was waived.

Table I. Criterion of transcutaneous bilirubin, total serum bilirubin, and unbound bilirubin levels

A. Transcutaneous bilirubin levels warranting a blood test

Birth weight	< 24 hours after birth	24 to 48 hours after birth
≥ 2,500 g	7	9
1,500 to 2,500 g	5	7

B. Total serum bilirubin and unbound bilirubin warranting phototherapy† (4)

Birth weight	Total serum bilirubin		Unbound bilirubin
	< 24 hours after birth	24 to 48 hours after birth	Any time
≥ 2,500 g	10 mg/dL	12 mg/dL	0.6 μg/dL
1,500 to 2,500 g	8 mg/dL	10 mg/dL	

†1992 Kobe University treatment criteria

Definitions of the causes

The causes for hyperbilirubinemia were defined as follows (7, 8): extravascular blood, the presence of blood that remains after a hemorrhagic event (i.e., cephalohematoma, intracranial hemorrhage, and liver or adrenal hemorrhage); RhD hemolytic disease and ABO blood type incompatibilities, hemolytic disease caused by reaction to anti-RhD, or anti-A or anti-B antibodies with antigens on erythrocytes, identified by a direct or indirect antiglobulin (Coombs') reaction, respectively; G6PD deficiency, suspected from family history and confirmed by activity or a genetic test; polycythemia, venous hematocrit > 65% and hemoglobin > 22 g/dL; infection, presence of infectious symptoms, abnormal hematological findings (elevated white blood cell counts [> 20,000/μL] and C-reactive protein level [> 0.5 mg/dL]), and/or positive cultures in any specimens; excessive weight loss, > 5% reduction from birth weight within 48 hours of birth; and idiopathy, no evidence of any causes.

Study methods and statistical analyses

Clinical characteristics and causes of hyperbilirubinemia were evaluated in newborns with early-onset hyperbilirubinemia. We also investigated which index (TSB or UB) was used to make treatment decisions. Data were analyzed using descriptive statistics. Finally, a regression analysis was performed to linearly compare TSB and UB levels using the data from hyperbilirubinemic and non-hyperbilirubinemic newborns; regression equation and correlation coefficient were also calculated. TSB levels corresponding to UB levels of 0.6 μg/dL were analyzed based on the regression equation.

RESULTS

Clinical characteristics

Overall, 76 newborns with early-onset hyperbilirubinemia were included in the analysis. Clinical characteristics are shown in Table II. All patients were of Japanese descent. Feeding was initiated starting 6 hours from birth, and artificial milk with a very small amount of breast milk was given (total amount, 10 ml every 3 hours < 24 hours after birth, and 20 ml every 3 hours 24 to 48 hours after birth).

Thirty-six (47%) newborns were diagnosed with excessive weight loss. None of the patients received infusion or any drugs before the diagnosis, and all received PT.

Table II. Clinical characteristics (n=76)

At birth	Median (range) or number (percent)
Gestational age, weeks	39 (37–41)
Weight, g	3,037 (2,400–3,894)
Length, cm	49.6 (45.0–53.0)
Head circumference	33.0 (29.8–36.0)
Male	39 (51)
Apgar score, 1 min / 5 min	8 (5–9) / 9 (7–10)
O blood type of mother	35 (46)
At the time of diagnosis	
Diagnostic age [number of patients (%)]	
within 24 hours after birth	6 (8)
24 to 48 hours after birth	70 (92)
Weight, g	2,877 (2,236–3,754)
Weight loss from birth weight, %	-5.0 (-7.8–+1.76)
Excessive weight loss	36 (47)
Artificial milk feeding	76 (100)
Infusion	0 (0)
Any drugs	0 (0)
Examination data	
Total serum bilirubin, mg/dL	12.6 (8.2–17.4)
Unbound bilirubin, μg/dL	0.44 (0.14–0.69)
Albumin, g/dL	3.9 (3.3–4.4)
bilirubin/albumin molar ratio	0.30 (0.07–0.53)
Hemoglobin, g/dL	19.2 (10.4–23.2)
Hematocrit, %	55.5 (30.7–68.0)
Treatment	
Phototherapy	76 (100)
Standard (single-surface irradiation using fluorescent tubes)	71 (93)
Intensive (double-surface irradiation using fluorescent tubes)	5 (7)
Duration of phototherapy, days	1 (1–4)
Exchange blood transfusion	0 (0)
Infusion therapy	54 (71)

Causes of hyperbilirubinemia

The causes of hyperbilirubinemia in these patients are shown in Table III. Fourteen patients had two causes for hyperbilirubinemia, but the predominant cause was ABO blood type incompatibility or polycythemia (See the footnote in Table III). Twenty-seven patients (36%) found the cause, such as ABO blood type incompatibility, polycythemia, and cephalohematoma. Forty-nine patients (64%), however, did not find any causes. Of the 49 patients, 27 patients observed excessive weight loss. None of the patients were diagnosed with RhD hemolytic disease, G6PD deficiency, or infection.

Table III. The causes of hyperbilirubinemia (n=76)

	Number (percent)
Hyperbilirubinemia with a known cause	**27 (36)**
ABO blood type incompatibility	17 (22)
Polycythemia	8 (11)
Cephalohematoma	2 (3)
Rhesus D hemolytic disease	0 (0)
Glucose-6-phosphate dehydrogenase deficiency	0 (0)
Extravascular blood except cephalohematoma	0 (0)
Infection	0 (0)
Hyperbilirubinemia with an unknown cause (Idiopathy)	**49 (64)**
Excessive weight loss (+)	27 (36)
Excessive weight loss (−)	22 (29)

* Seven patients with polycythemia showed excessive weight loss, but they are included only in "polycythemia". Other seven patients with ABO blood type incompatibility also showed excessive weight loss, but they are included only in "ABO blood type incompatibility".

Serum bilirubin index

Table IV shows which index was used to make treatment decisions. Of 76 newborns with early-onset hyperbilirubinemia, only 1 received PT solely based on abnormal UB levels.

Table IV. Serum bilirubin index for the diagnosis (n=76)

	Number (percent)
Total serum bilirubin only	70 (92)
Both total serum bilirubin and unbound bilirubin	5 (7)
Unbound bilirubin only	1 (1)

Linear regression analysis between TSB and UB

Median (range) levels of TSB, UB, albumin, and bilirubin/albumin molar ratio in newborns without hyperbilirubinemia (n=101) was 6.8 (1.8–11.0), 0.25 (0.05–0.55), 3.5 (2.3–5.2), and 0.24 (0.07–0.40), respectively. The regression equation was y = 0.033x + 0.02 and the correlation coefficient was 0.71. Based on this regression equation, the TSB level corresponded to the UB level of 0.6 µg/dL was 17.6 mg/dL.

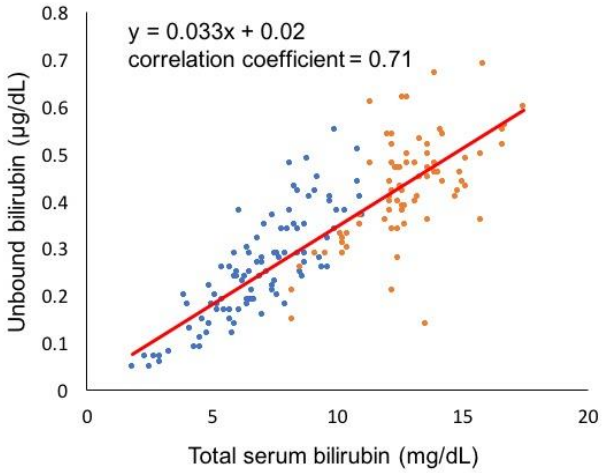

Figure 1. Linear regression analysis between total serum bilirubin and unbound bilirubin. Solid blue points: newborns without hyperbilirubinemia (n=101); solid orange points: newborns with hyperbilirubinemia (n=76); red line: regression equation.

DISCUSSION

In this clinical observational study, we found that the major causes for early-onset hyperbilirubinemia in term newborns were idiopathy and ABO blood type incompatibility in a Japanese healthy birth center, not infection, Rh hemolytic disease, or G6PD deficiency. Of 76 newborns with early-onset hyperbilirubinemia, TSB levels were used to make PT treatment decisions in more than 90% of patients. Only 1 (1%) newborn received PT solely based on abnormal UB values.

Globally, the major cause for severe hyperbilirubinemia is sepsis, Rh hemolytic disease, or G6PD deficiency (9, 10). A very low incidence of early-onset sepsis has been reported in Japan, approximately 0.1% of newborns with a birth weight > 1,000 g (7). Prevention for RhD hemolytic disease using RhD globulin administration in RhD-negative mothers is widely used in Japan (11). Furthermore, G6PD deficiency is very rare in Japanese descent; the prevalence is estimated to be only 0.08% (12). Therefore, our results showing that none of the incidences of early-onset hyperbilirubinemia were due to these diseases is consistent with current clinical data in Japan.

We identified idiopathy with or without excessive weight loss and ABO blood type incompatibility as major causes for early-onset hyperbilirubinemia in term Japanese newborns. According to current classifications of neonatal hyperbilirubinemia, idiopathy generally includes hyperbilirubinemia associated with 211 G to A (G71R) polymorphism in Exon 1 of the *UDP-glucuronosyltransferase1A1 (UGT1A1)* gene, which is often seen in Japanese people (the allele frequency: 0.15–0.16) (13, 14). *UGT1A1* gene polymorphism examination for neonatal hyperbilirubinemia is not currently available in clinical settings. Early-onset idiopathic hyperbilirubinemia may also involve *UGT1A1* gene polymorphism. Further clinical studies are needed to confirm this observation. ABO blood type incompatibility is accepted as a common cause of early-onset hyperbilirubinemia in many countries (3). Pediatricians and obstetricians in Japanese birth centers should be aware that apparently healthy newborns or newborns with more than 5% weight loss from birth weight within 48 hours after birth may develop early-onset

hyperbilirubinemia. They should also understand the importance of checking the ABO blood type of the mother and newborn.

The 1992 Kobe University treatment criterion is often used in Japan to identify hyperbilirubinemia requiring PT (4). A main characteristic of this criterion is to determine the necessity for treatment using TSB and UB levels, both of which are measured using a UB-analyzer. When TSB or/and UB levels exceed PT criterion value, PT is initiated. UB has been reported to be a better index than TSB to predict patients with bilirubin encephalopathy (4, 15-17), because UB crosses the blood-brain barrier and leads to bilirubin-induced neurotoxicity (18). However, because the mass action relationship between UB, TSB, and albumin levels, the binding constant (K) is shown as follows equation: [UB] = [TSB] / K*([albumin] – [TSB]) (17); at any given TSB level, UB levels usually correspond to comparable TSB level, when albumin and K are constant (19). In this study population, the serum concentration ([albumin]) and bilirubin binding affinity (K) were within normal, because of healthy term newborns basically. UB levels have been described to be linearly correlated with TSB levels when the bilirubin/albumin molar ratio is less than 1 (20). Our results show a significant linear correlation between TSB and UB levels (Figure 1).

In this study, most of the 76 newborns with early-onset hyperbilirubinemia were treated with PT based solely on TSB levels. This may be because the 1992 Kobe University treatment criterion has only one UB reference value (0.6 μg/dL, Table I). In Figure 1, we show that UB levels of 0.6 μg/dL correspond to TSB levels of 17.6 mg/dL. Because TSB reference values within 48 hours after birth are 8 to 12 mg/dL according to the 1992 Kobe University treatment criterion (Table I), it is reasonable to diagnose newborns with early-onset hyperbilirubinemia and initiate PT based solely on TSB level.

Although this clinical study used a retrospective design in a single center with a small patient population, we were able to identify that the major causes of early-onset hyperbilirubinemia requiring PT in term newborns in a Japanese healthy birth center included idiopathy with or without excessive weight loss and ABO blood type incompatibility. TSB, not UB, was the main index used to make treatment decisions in this patient population.

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