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Original Article

Risk factors for acute bilirubin encephalopathy in full-term infants - a multicenter study

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Abstract: Objective: The purpose of this study was to evaluate the neurotoxicity risk factors in predicting acute bilirubin encephalopathy (ABE) at admission in infants with severe hyperbilirubinemia. Methods: We analyzed the general clinical data and risk factors as determinants of ABE in a total of 329 full-term newborns treated with total serum bilirubin (TSB) at a level of 20 mg/dL (342 μmol/L) to 7 neonatal intensive care units in Hebei Province, China over the past 18 months. Results: Admission of TSB level ranged from 20 to 56.2 mg/dL. There were 13 newborns (4.0%) of subtle ABE at admission and 22 newborns (6.7%) of moderate or severe ABE at admission. Twelve infants (3.6%) had evidence of bilirubin encephalopathy (BE) at the time of follow-up. Sepsis (OR: 17.05) greatly increased the risk for ABE, and TSB and bilirubin to albumin ratio (B/A) level were risk factors of adverse outcome in logistic regression (OR: 1.009, 1.308, respectively). Conclusions: TSB, B/A and sepsis are risk factors for ABE.

Keywords: Risk factors, acute bilirubin encephalopathy, severe hyperbilirubinemia

Introduction

Bilirubin is a beneficial antioxidant at low levels [1], but extremely high total serum bilirubin (TSB) levels can lead to kernicterus or chronic bilirubin encephalopathy [2]. Although the American Academy of Pediatrics formulated guidelines for the treatment of neonatal jaundice in 2004 [3], and China implemented protocols for screening and management of severe hyperbilirubinemia in 2014, acute bilirubin encephalopathy (ABE) is still common in China. Kernicterus has been considered as one of the few preventable causes of cerebral palsy. Early detection of high risk factors (RF) can prevent and reduce the incidence of ABE and bilirubin encephalopathy (BE). The purpose of this study was to identify RFs for ABE in full-term neonates with severe jaundice.

Methods

We conducted a retrospective analysis in the full-term neonates with severe jaundice admitted to 7 neonatal intensive care units in Hebei Province, China from June 2015 to December 2016. Inclusion criteria included infants with estimated gestational age at 37 or more weeks or admission weight of ≥ 2500 g, TSB level of ≥ 20 mg/dL. General clinical data and RFs of ABE of all patients were recorded. Patients with asphyxia, digestive tract deformity and TORCH infection were excluded from the study. This study has been approved by the ethic committee of our hospital. All parents of the infants signed the informed consent. The bilirubin-induced neurologic dysfunction protocol (BIND score) was used to evaluate the clinical signs and neurologic characteristic of ABE after

Table 1. The bilirubin-induced neurologic dysfunction protocol (BIND score)

Mental state (0-3)	0= Normal
	1= Drowsiness, poor appetite
	2= Lethargy, Refused to drink milk, irritation
	3= Semiconscious, apnea, convulsions
Muscle tone (0-3)	0= Normal
	1= Muscle tone is lightly reduced
	2= Moderate reduction or increase in muscle tone, bicycle-like posture, slight opisthotonus
	3= Severe muscle tension decreased or increased muscle tension, severe opisthotonis
Cry (0-3)	0= Normal
	1= Crying high-profile
	2= Frequent or sudden screams
	3= No consolation after stimulation

Mental state, muscle tone, and cry were evaluated; 1-3 are classified as mild ABE, 4-6 as moderate ABE and 7-9 as severe ABE.

Table 2. Subject characteristics

Characteristics	n	%
Gender		
Male	199	60.5
Female	130	39.5
Mode of delivery		
Vaginal	200	60.8
Cesarean	129	39.2
Feeding pattern		
Breast feeding	129	39.2
Formula	99	30.1
Mixed feeding	101	30.7
Admission age		
0.1-7	231	70.2
7-14	67	20.4
14-28	31	9.4
TSB		
20-24.9	223	67.8
25-29.9	73	22.2
> 30	33	10.0

admission [4]. Mental status, muscle tone, and cry were evaluated; a score of 0 to 3 was assigned to each category, yielding a total score ranging from 0 to 9. Scores of 1-3 indicate subtle, normally reversible, toxic effects of bilirubin. Scores of 4-6 reflects moderate but potentially reversible ABE, whereas scores of 7-9 indicates that severe ABE may result in long-term disability from kernicterus [5]. The recommendations of the AAP for the management of severe neonatal were performed to manage the patients. Children discharged from hospital were followed up to investigate whether there were neurological sequelae. In order to investigate the effects of TSB, and neurotoxicity risk variables on adverse effects/outcomes (ABE, BE), multiple logistic regression was performed (**Table 1**).

Results

The proportion of boys was significantly higher than that of girls

The proportion of boys (60.5%) was significantly higher than that of girls (39.5%, $P < 0.001$). The age of admission ranged from 0.1 to 28 days, and 231 (70.2%) were early newborns. There were 223 neonates with TSB levels ranging between 20 and 24.9 mg/dL (mean: 22.2 mg/dL), 73 neonates with TSB levels ranging between 25 and 29.9 mg/dL (mean: 27.1 mg/dL), and 33 neonates with TSB levels between 30 and 56.2 mg/dL (mean: 36.8 mg/dL) (**Table 2**).

Hemolytic disease and sepsis accounted for the larger proportion

Hemolytic disease and sepsis accounted for the larger proportion of 20.7% and 24.0%, respectively. Inadequate intake accounted for 12.5%, and 114 (34.7%) infants had unexplained jaundice. All infants were treated with phototherapy, and 46 infants (14%) received exchange transfusions. At the time of admission, there were 22 infants (6.7%) of moderate or severe ABE (BIND scores 4-9), 13 infants (4.0%) of subtle evidence of neurotoxicity

Table 3. Suspected causes of hyperbilirubinemia

Suspected cause	n	%
hemolytic disease	68	20.7
Rh incompatibility	62	18.9
ABO incompatibility	6	1.8
Sepsis	79	24.0
Inadequate intake	41	12.5
Perinatol factors	25	7.6
Unidentified	114	34.7

Perinatol factors: Cranial hematoma, Polycythemia.

Table 4. Effect of risk factors and TSB on neurotoxicity

Risk factor	n	No ABE/BE	ABE only	BE
No risk factors, TSB < 30 mg/dL	89	64	0	0
No risk factors, TSB ≥ 30 mg/dL	78	42	3	2
No risk factors, total	167	106	3	2
ABO/Rh, TSB < 30 mg/dL	42	20	1	0
ABO/Rh ,TSB ≥ 30 mg/dL	26	16	3	1
ABO/Rh, total	68	34	4	1
Sepsis, TSB < 30 mg/dL	35	2	2	13
Sepsis, TSB ≥ 30 mg/dL	44	9	4	17
Sepsis, total	79	11	6	30

Table 5. BIND score as a predictor of BE

BIND	n	BE	TSB median (range)
0 (normal)	294	3	24.0±3.9 (20.1-46.7)
0-3 (subtle)	13	1	25.3±4.1 (20.0-32.9)
4-6 (moderate ABE)	12	3	25.7±6.4 (20.5-38.6)
7-9 (severe ABE)	10	5	38.0±10.0 (26.8-56.2)
Total	329	12	24.5±4.9 (20.0-56.2)

(BIND scores 1-3), and 294 infants (89.4%) of no evidence of ABE (**Table 3**). 12 (3.6%) infants had evidence of BE at 12 months after discharge.

Six of 11 infants (55%) with evidence of sepsis developed signs of BE, and 4 of these 6 infants had a TSB level of < 30 mg/dL (**Table 4**). Sixteen of 28 infants with Rh (or Rh/ABO) incompatibility (57%) developed BE, and 6 of these infants had a TSB level of < 30 mg/dL; 13 of 16 died. In contrast, only 1 of 26 infants with ABO/RH hemolytic disease as the only RF and TSB level of > 30 mg/dL developed BE.

A total of 294 infants (89.3%) had no evidence of ABE, with a TSB level of 24.0±3.9 (20.1-46.7) mg/dL, and 3 (1.0%) infants developed BE at time of follow-up. There were 13 infants of subtle evidence of neurotoxicity (BIND 1-3), and 1 (7.7%) infant developed BE. There were 22 infants (6.7%) of moderate or severe ABE (BIND scores 4-9), and 8 infants (36.4%) of evidence of BE (**Table 5**).

Age of admission, formula and mixed feeding (compared to breastfeeding) decreased the risk, but did not achieve statistical significance

We performed single factor logistic regression analysis to evaluate the effects of TSB and other RFs on ABE (**Table 4**). Age of admission, formula and mixed feeding (compared to breastfeeding) decreased the risk, but did not achieve statistical significance. All other factors evaluated increased the odds of an adverse outcome. The presence of sepsis greatly increased the risk for ABE (12.542 times), and TSB and B/A levels were RFs of adverse outcome in logistic regression (OR: 1.009, 1.308, respectively) (**Table 6**).

Discussion

In spite of the implementation of treatment protocols and procedures for neonatal jaundice, severe hyperbilirubinemia and negative neurological outcomes remain an ongoing problem in China [6]. Infants delivered vaginally are often discharged from the hospital before age of 48 hours or even 24 hours, but bilirubin levels usually peak on the fourth or fifth day after birth [7], so appropriate outpatient follow-up is extremely important [8]. Late presentation and ineffective phototherapy lead to excessive rates of severe hyperbilirubinemia and exchange transfusions that are avoidable.

In this study, TSB, B/A and sepsis are RFs for ABE. Studies by Newman et al. [9] and Gamaleldin et al. [10] indicated that healthy full-term infants have a greater tolerance for se-

Table 6. Odds of having ABE at admission

Variable	B	SE	Wals	OR	95% CI	*P*
Gender(1= male; 2= female)	0.086	0.368	0.054	1.090	0.529-2.243	0.816
Age at admission (d)	-0.016	0.038	0.171	0.985	0.915-1.060	0.680
TSB	0.008	0.002	22.019	1.009	1.005-1.012	< 0.001
B/A	0.268	0.063	18.376	1.308	1.157-1.478	< 0.001
Risk factors						
Hemolytic disease	1.276	0.725	3.098	3.581	0.865-14.818	0.078
Sepsis	2.529	0.640	15.628	12.542	3.579-43.948	< 0.001
Inadequate intake	1.072	0.838	1.637	2.921	0.565-15.091	0.201
Perinatol factors	1.169	0.941	1.542	3.217	0.509-20.353	0.214
Unidentified			21.110			< 0.001
Feeding pattern						
Breastfeeding			2.210			0.331
Formula	-0.004	0.395	0.000	0.996	0.459-2.161	0.992
Mixed feeding	-0.823	0.578	2.024	0.439	0.141-1.364	0.155
Sepsis	2.836	0.771	13.524	17.05	3.761-77.301	< 0.001
TSB	0.160	0.040	16.304	1.173	1.086-1.267	< 0.001
B/A	0.228	0.066	11.969	1.256	1.104-1.430	0.001

vere hyperbilirubinemia. Gamaleldin et al. [10] reported that the response to TSB in the pathogenesis of ABE depends largely on other biological factors. In the case of hemolysis, infection, hypoxia, acidosis and other pathological conditions, the free bilirubin not bound to albumin is increased, then passes through the blood-brain barrier, causing cerebral neurotoxicity and acute hearing damage [11].

ABE is characterized by lethargy, hypotonia and poor sucking in the early stage, with no specificity. Positive intervention measures can reverse brain damage, but wrong or negative treatments may cause hypertonia, hypotonia, opisthotonus, high pitched cry, and seizures, which may cause irreversible brain damage. The long-term sequelae of bilirubin toxicity are characterized by a combination of abnormal motor control, movements and muscle tone, disturbed auditory processing, impairment of upward vertical gaze, and dysplasia of the enamel of deciduous teeth [12]. Just as Apgar score is used to assess the severity of asphyxia, pretreatment BIND score can be used to assess the severity of ABE, which is a very good predictor of outcome [13]. Johnson et al. [14] and Mukhopadhyay et al. [15] found that when the BIND score is > 7, even with active intervention, the likelihood of poor prognosis remains high. This study found that the higher BIND score indicated the higher incidence of poor prognosis. We have shown that, 1 (7.7%) infant of BIND (0-3) developed BE, 3 infants (25.0%) of BIND (4-6) and 5 infants (50.0%) of BIND (7-9) had evidence of BE. Therefore, identification of ABE is a particularly important clinical work.

During the follow-up, three infants without signs of ABE developed BE were observed. The neurotoxicity caused by bilirubin depends on the complex interaction between the level and duration of central nervous system [16]. Meanwhile, photoisomers, which was produced during phototherapy, may affect bilirubin-albumin binding, and the formation rate of photoisomers and the concentration accumulated in the circulation might have the risk of kernicterus [17].

The current study showed a high mean peak of TSB level (24.5±4.9) mg/dL: range (20.0-56.2) mg/dL. Bilirubin encephalopathy increased with the increase of TSB [18, 19]. TSB ≥ 300 μmol/L is associated with increased risk of complex minor neurological dysfunction [20], but TSB alone is of limited value in predicting neurologic negative outcomes in infants with hyperbilirubinemia [7, 21, 22]. ABE and excessive TSB levels at least 30 mg/dL are predictive of repeat exchange transfusion [23]. UCB free is able to cross the blood-brain barrier, and has a better correlation with bilirubin neu-

rotoxicity than the TSB [24, 25]. But it cannot be routinely measured in clinical practice [26].

The current study showed that 79 (24%) of the severe jaundice were associated with sepsis. Multiple logistic regression suggested that infection was a RF for ABE (OR = 17.050). Maisels et al. reported that sepsis can result in acute, severe hyperbilirubinemia [8]. Severe infection can increase the permeability of blood-brain barrier, leading to a large amount of plasma bilirubin to enter into brain tissue, accumulation and deposit in nerve cells resulting in brain damage, meanwhile infection can also reduce the binding of bilirubin and albumin, so as to increase the risk of bilirubin neurotoxicity.

The current study stated B/A was a RF for ABE (OR = 1.256). Albumin has a powerful attractive effect on tissue bilirubin [27]. Arnolda et al. [13] found that the B/A ratio seemed to be a more useful indicator than UCB free levels to predict ABE. Even though it had already been incorporated indirectly into exchange transfusion criteria, bilirubin-albumin binding was also influenced by endogenous and exogenous substances, such as drugs, which can interfere with bilirubin albumin binding. Hulzebos et al. [28] and Iskander et al. [29] found that B/A offered no additional advantage over TSB alone, and it was not a good predictor of ABE. The relationship between ABE and B/A still needs further exploration.

ABE and BE should be an event that never happens and can be completely avoided. For infants with severe jaundice associated neurotoxicity RFs, we should be especially alert to the occurrence of ABE.

Disclosure of conflict of interest

None.

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