Acute Bilirubin Encephalopathy in Healthy Term Neonates Requiring Exchange Transfusion

Seyedeh Fatemeh Khatami*[1], Pouya Parvaresh[2]

**1-Department of Pediatrics, Division of neonatology, Neonatal Research Center, Ghaem Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

2- Department of Internal Medicine, Faculty of Medical Sciences Szeged, Medical University of Szeged, Hungary

Abstract

Introduction

There is a growing concern about an increasing bilirubin-induced neurological dysfunction (BIND) in healthy term neonates with no evidence of hemolytic disease or other risk factors. This study was done to determine the incidence of BIND in otherwise healthy, breast-fed newborn term infants without hemolysis who underwent exchange transfusion.

Materials and Methods

This study was conducted in jaundiced newborn infants <7 days of age, from April 2005 to April 2007. The infants were selected if they underwent double volume exchange transfusion (ET) in the first week of life. Babies with any condition affecting neurodevelopment were excluded. Data obtained by clinical findings, and predetermined laboratory tests, and questionnaires. Infants with suspected bilirubin associated brain damage were reviewed according to findings.

Results

During the 2- year period, 140 term newborn infants underwent ET; 7 of these patients were excluded; 133 patients were followed and 69 patients were selected without BIND, and 64 were assigned to the group with BIND. This study showed that 48% of jaundiced newborn infants who underwent exchange transfusion, manifested bilirubin induced neurological dysfunction. Unsuccessful breast feeding was found to be a statistically significant risk factor for BIND(p:0.001), sex, route of delivery, family history of jaundice, mean maternal age, number of gravity, parity, abortion, and babies mean admission age ,mean age at jaundice presentation, amount of weight loss, mean total serum bilirubin level were not found to significantly influence BIND.

Conclusion

Of the healthy term neonates who developed jaundice within the first week of life, 48% without hemolysis who underwent exchange transfusion demonstrated BIND. It is still not clear whether acute bilirubin encephalopathy affects neurodevelopmental outcome or not. Unsuccessful breast feeding was found to be a statistically significant risk factor.

Key words

Newborn, Bilirubin, Encephalopathy, Neurologic Dysfunction, Exchange Transfusion

Introduction

The first description of kernicterus of the brain in newborns with jaundice was provided by Hervieux in 1847.[1,2] The relation between the clinical encephalopathy associated with elevated total serum bilirubin (TSB) concentration and the gross pathologic changes seen as yellow staining of specific areas of the central nervous system was observed and described as early as 1875.[3] The terms bilirubin encephalopathy and kernicterus represent clinical and pathologic abnormalities respectively resulting from bilirubin toxicity in the central nervous system; to avoid confusion and encourage greater consistency in the literature, the American academy of pediatrics (APP) recommended that the term acute bilirubin encephalopathy be used

Correspondence: Seyedeh Fatemeh Khatami Ghaem Hospital, Mashhad, Iran,
E-mail: f_khatami@yahoo.com, Cellphone: 09151152758

to describe the acute manifestations of bilirubin toxicity seen in the first week after birth and the term kernicterus be reserved for chronic and permanent clinical sequel of bilirubin toxicity.[4] Recently Johnson and associates suggested the use of the term bilirubin-induced neurologic dysfunction (BIND) to describe the changes associated with acute bilirubin encephalopathy, they also proposed a scoring system to quantify the severity of clinical manifestation[4]. The exact incidence of kernicterus is unknown, it is rare and preventable [5], Current incidence of kernicterus reported as 1/100000 [6,2] Between 1992 and 2002, BIND was reported in 125 healthy term and near term neonates.[7]

There is a concern of increasing BIND in healthy term neonates with no evidence of hemolytic disease or other risk factors in Iran. Because of the lack of universal registry, missed diagnosis and under reporting, the accurate incidence of BIND is unknown. The objective of this study was to determine the incidence of BIND in otherwise healthy term gestation breast-fed newborn infants without hemolysis who underwent exchange transfusion, to provide a framework for prevention of BIND and evaluate strategies, change in policy and management of hyperbilirubinemia in newborn infants.

Method

This prospective, cross-sectional study was conducted on otherwise healthy term gestation, breast-fed newborn infants without hemolysis who underwent exchange transfusion (ET) for treatment of hyperbilirubinemia in the first week of life, admitted to the neonatal division of our center. Jaundiced infants were enrolled from April 2005 to April 2007, after obtaining informed parental consent and ethics committee approval; babies with any condition affecting the neurodevelopment, prematurity, convulsions, asphyxia and hemolytic diseases were excluded from the study. Data was obtained by clinical findings, and predetermined laboratory tests, and questionnaire. Infants with suspected bilirubin–associated brain damage were reviewed according to findings in Table 1.[4]

Infants were assigned to two groups: the patients with BIND, and the patients without BIND. Major clinical features of acute bilirubin encephalopathy divided in three fairly distinct clinical phases: Early phase, intermediate phase and advanced phase. No long-term neurodevelopment outcome was examined in this study. Investigations including: maximum total and direct serum bilirubin level, baby's and mother's blood group, RH, direct/ indirect Coombs' test, complete blood count, peripheral blood smear, reticulocyte count, serum albumin, blood glucose, calcium, sodium and potassium, erythrocyte glucose - 6 - phosphate dehydrogenase (G6PD) level, culture of blood, urine and cerebrospinal fluid according to the patient's condition were done. We recorded demographic findings, gestational age (wk), family history of jaundice in sibling, chronologic age (day), age at presentation jaundice (day), weight (g), and route of delivery (cesarean/vaginal), number of maternal: parity, abortion and gravity, maternal age and type of feeding (exclusive breast milk /mixed). Cry pattern was documented clinically. Pathologic weight loss defined when more than10% of birth weight had been lost, calculated as birth weight – readmission weight×100/birth weight. Severe hyperbilirubinemia was considered≥25 mg/dl.

The double volume exchange was performed according to the standard published guidelines, via umbilical vein catheter [7, 8]. All infants received phototherapy. Data analysis was performed using SPSS version 13 software. Statistical analysis included chi-square test, Mann - Whitney test and T-Test. Statistical significance was set at $p < 0.05$.

Table 1. Major clinical features of acute bilirubin encephalopathy

- ●Initial phase
  - ▪Slight stupor ("lethargic", "sleepy")
  - ▪Slight hypotonia, paucity of movement
  - ▪ Poor sucking, slightly high - pitched cry
- ●Intermediate phase
  - ▪ Moderate stupor - Irritable
  - ▪ Tone variable - usually increased, some with retrocollis - opisthotonos
  - ▪ Minimal feeding, high pitched cry
- ●Advanced phase
  - ▪ Deep stupor to coma
  - ▪ Tone usually increased, some with retrocollis - opisthotonos
  - ▪ No feeding, shrill cry, seizures

Results

During the 2 year period,140 term/near term newborn infants underwent ET; 7 of these patients were excluded because of incomplete data; 133 neonates were followed, 69 patients were selected

in the group without BIND, 64 were assigned to the group with BIND.
The maximum total serum bilirubin was 44 mg/dl, the mean TSB level was not significantly higher in the group with BIND (p=0.41) than the group without BIND. Severe neonatal hyperbilirubinemia was identified in 77(58%) patients (37 in group without BIND and 40 in group with BIND) ; 22(17%) cases had more than 35 mg/dl, 18 cases in group with BIND, 4 cases in group without BIND, 31 (48%) patients were in initial phase of acute bilirubin encephalopathy and 25 (39 %) were in intermediate phase and 8(12%) cases were in advanced phases(seizures observed in 8 cases not related to ET complications) . Unsuccessful breast feeding was found to be statistically significant risk factor for BIND (p=0.001), sex, route of delivery, family history of jaundice, mean maternal age, number of gravity, parity, abortion and mothers blood group/ Rh, and babies blood group/ Rh, and mean babies admission age, mean age at jaundice presentation, amount of weight loss, mean total serum bilirubin level were not found to significantly influence the BIND. Table 2 shows the baseline characteristic findings.
We were unable to follow patients for long term neurodevelopment outcome; this was a limitation of this study.

Discussion

This study demonstrated that 48% of, breast-fed healthy jaundiced term neonates without hemolysis who underwent exchange transfusion, manifested acute bilirubin encephalopathy; this is more than other studies, although our study was not designed to assess the incidence of long term neurological disease (kernicterus), but cases of kernicterus continue to be reported most recently worldwide, in healthy term and near term infants with no evidence of hemolytic diseases or other risk factors (Maisels and Newman,1995,Brown and Johnson,1996, Bhutani,2004) [9,10]. A report showed that 7.3% of jaundice infants had abnormal neurologic examination at the time of ET [11]. A Canadian study reported 19.8% abnormal neurologic symptoms at the time of presentation. [9]. Although a bilirubin level of more than 428 µmol/l (25 mg/dl) was chosen to define severe hyperbilirubinemia since an infant with this degree of jaundice is thought to be at risk of kernicterus [12], the authors observed that the number of babies with abnormal developmental quotient increased proportionately with increase in the level of peak serum bilirubin (PSB) [13]; it is notable that susceptibility for bilirubin neurotoxicity were increased in our study (48%) but mean total serum bilirubin levels were not found to significantly influence the BIND between two groups (p=0.41), severe hyperbilirubinemia was identified in 58% of our patients and TSB > 35 mg/dl was identified in 17% of patients. Vindro reported TSB concentration to be poor predictors of bilirubin toxicity in the sick or preterm infants; [14] we excluded these babies.
A data base of voluntarily reported cases of kernicterus showed 90 of 116 infants with kernicterus had TSB levels of 30 mg per deciliter and more than 76 had levels of 35 mg per deciliter or more. Recent estimates suggest that about 1 in 700 newborn will have a TSB level of 25 mg/dl or more and about 1 in 10000 a level of 30 mg/dl or more. A striking an sustained increase in breast feeding and a concurrent progressive decline in the length of hospital stay after birth appear to have unmasked a previously underappreciated potential for the development of extreme hyperbilirubinemia in some neonates[12]. Unsuccessful breast feeding was found to be statistically significant risk factor for BIND (p= 0.001) in our study, and was accompanied with hypernatremia in 10% of patients. In the Canadian study 21% had lost more than 10% of birth weight at the time of readmission [9]. In our study, there was no significant difference in weight loss between neonates with and without neurologic symptoms. Sex, route of delivery, family history of jaundice, mean maternal age, number of gravity, parity, abortion, and babies mean admission age, mean age at jaundice presentation, were not found to significantly influence the BIND in our study. Although our study was not designed to assess the long term results of severe hyperbilirubinemia including kernicterus, it is still not clear whether acute bilirubin encephalopathy affects neurodevelopmental outcome or not.[9,10]

Conclusion

Although 48% of healthy term neonates who developed jaundice within first weeks of life without hemolysis who underwent exchange transfusion demonstrated BIND, it is still not clear whether acute bilirubin encephalopathy affects neurodevelopmental outcome or not. Unsuccessful breast feeding was found to be a statistically significant risk factor.

Acknowledgments

We gratefully acknowledge the support of Dr. Dashti and the neonatal division personnel.

Table 2. Characteristic findings in patients with/without bilirubin

	Control group without BIND	Case group with BIND	Total count within group	Statistical Test	P value Statistical
Sex-male female	42 (60.9%) 27 (39.1%)	29 (45.3%) 35 (54.7%)	71 (53.4%) 62 (46.6%)	Chi-square	0.072
Rout of delivery	26 (37.7%) 43 (62.3%)	18 (28.1%) 46 (71.9%)	44(3.10%)89 (66.9%)	Chi-square	0.242
Family history of jaundice	20 (29.4%)	23 (35.9%)	43 (32.6%)	Chi-square	0.424
Mean number of gravity	1.8±1.1	1.8±1.5		Mann-Whitney	0.559
Mean number of parity	1.7±0.84	1.6±1.2		Mann-Whitney	0.968
Mean number of abortions	0.19±0.64	0.06±0.35		Mann-Whitney	0.114
Mean admission age (day)	5.57±2.41	5.80±2.22		Chi-square	0.56
Mean age at jaundice presentation(day)	2.88±1.17	3.05±1.56		t-test	0.492
Exclusive breast feeding	52 (81.3%)	53 (76.8%)	105	Chi-square	0.001
Weight loss	34 (54.0%)	34 (53.1%)		Chi-square	0.924
Mean maternal age (year)	26.77 ± 4.9	25.04 ±4.3		t-test	0.084
Mean total serum bilirubin (mg/d)	25.72 ± 5.59	28.71 ± 10		t-test	0.41

References

1. Hansen TW. Pioneers in the scientific study of neonatal jaundice and kernicterus.
Pediatrics 2000; 106(2) E 15.
2. Juretschke LJ. kernicterus: still a concern. Neonatal net w 2005; 24(2): 7–19.
3. Ashima M, Macmahon JR, and Stevenson DK. Neonatal hyperbilirubinemia, in: Taeusch Hw, Ballard RA, Gleason CA .Avery's diseases of the newborn. 8th ed. Philadelphia: Elsevier Saunders 2005; pp.: 1226–1266.
4. Maisels MJ, Jaundice, in: Macdonald M, Mullet M, Seshia M. Avery's neonatology pathophysiology of management of the newborn.6th ed. Philadelphia: Lippincott – Williams of Wilkins. 2005, pp.: 768–846.
5. Suresh GK, Clark RE. Cost effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics 2004; 114(4): 917-924.
6. American academy of pediatrics subcommittee on hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infants 35 or more week of gestation. Pediatrics. 2004; 114(1): 297-316.
7. Al kalay AL, Simmons CF, Hyperbilirubinemia guidelines in newborn infants.
Pediatrics 2005; 115(3): 8224–8258.
8. Wong RJ, Desandre GH, Sibley E, Stevenson D. Neonatal jaundice and liver disease, in: Martin RJ, Fanaroff A, Walsh M, Neonatal- Perinatal medicine.8th edition. Philadelphia: Elsevier Mosby 2006, pp.: 1419-1461.
9. Sugro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. Canadian Medical Association Journal 2006; 175 (6): 587-591.
10. Watchko J, Kernicterus and molecular mechanisms of bilirubin-induced CNS injury in newborns. Neuro Molecular Medicine 2006; (8), 513-529.
11. Badiee Z, Exchange transfusion in neonatal hyperbilirubinemia: Experience in Isfahan, Iran. Singapor med J. 2007; 48(5): 421-3.
12. Watchko J F, Neonatal hyperbilirubinemia - what are the risks? The New England journal of medicine 2006; 354(18): 1947–1950.
13. Arun Th, Vishnu B, Noyal M J.Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyperbilirubinemia. Indian journal pediatrics 2011, published on line.
14. Bhutani VK, Johnson LH. Urgent clinical need for accurate and precise bilirubin measurements in the United States to prevent kernicterus. Clinical chemistry 2004; 50: 477–480.