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Original Article

Developmental outcome of severe neonatal indirect hyperbilirubinemia

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Abstract

Introduction: Indirect hyperbilirubinemia is one of the most common causes of hospitalization in the neonatal period and its potential association with brain damage is well established. This study was conducted to determine neurodevelopmental outcome of children who had severe indirect hyperbilirubinemia in neonatal period and had received intensive phototherapy with or without double volume exchange transfusion for its management.

Methods: This descriptive analytical study was performed in healthy infants with the history of severe indirect hyperbilirubinemia who needed intensive phototherapy with or without exchange transfusion. We followed up the enrolled infants at their 2-3 years age. Neurodevelopmental assessment was performed by a trained nurse using Ages and Stages Questionnaire.

Results: The mean level of total serum bilirubin (TSB) of the studied children was 26.4±4.1 mg/dL at their neonatal period. The estimated rate of severe hyperbilirubinemia 48.7/100 000 live born infants for the patients with the TSB of 25-30 mg/dL and 11.4 /100 000 for hyperbilirubinemia with TSB levels higher than 30 mg/dL. The most common cause of jaundice in patients with exchange transfusion was ABO incompatibility. At their follow up examination, the classic form of bilirubin induced encephalopathy (Kernicterus) was diagnosed in 3 neonates. Two of them had sensory neural hearing loss, too. Eleven children had low score based on ASQ in at least one area. The score was less than 2 SD in 3 patients.

Conclusion: Severe hyperbilirubinemia and kernicterus is still occurring in term and late preterm infants. Early detection and management of severe hyperbilirubinemia may improve the neurodevelopmental outcome in high risk infants.

Introduction

Indirect hyperbilirubinemia is one of the most common causes of hospitalization in the neonatal period and its potential association with brain damage is well established.[1,2] Bilirubin is a yellow pigment derived from catabolism of heme which in low levels has protective anti-oxidant effect; but its higher blood levels are potentially neurotoxic.[2,3] When the total serum bilirubin (TSB) levels exceed infants' neuroprotective defenses, bilirubin induced neurologic dysfunction (BIND) [4] occurs with neuronal injury in basal ganglia, central and peripheral auditory and visual pathways, hippocampus, diencephalon, subthalamic nuclei, midbrain, cerebellum and cerebellar vermis and brain stem nuclei.[2-5] The classic form of bilirubin induced encephalopathy is called kernicterus that describes the yellow staining of deep nuclei of the brain and its clinical findings such as athetoid cerebral palsy, impaired upward gaze and deafness or isolated conditions, for example auditory neuropathy or dyssynchrony or subtle BIND.[4-6] Syndrome of BIND represents a wide range of manifestations from subtle processing disorders to objective disturbances of visual-motor, auditory, speech, cognition, and language which affect infants with moderate to severe neonatal hyperbilirubinemia.[5] Coexisting factors such as prematurity, hemolysis, perinatal-neonatal complications, hypoalbuminemia, duration of hyperbilirubinemia and its severity, and genetic vulnerability of the infant may determine the clinical presentation of kernicterus.[6-8] Disturbances of sensory and sensorimotor integration, central auditory processing, coordination and muscle tone are also associated with BIND.[2] Bilirubin is an important vasoprotective molecule with anti-oxidant, anti-inflammatory, vasodilatory, anti-mutagenic, immune-modulatory, anti-proliferative, and anti-apoptotic properties. Considering that vascular compromise and oxidative stress may play important role in the development of sudden deafness and protective function of bilirubin, it is possible that inner ear injury resulted from bilateral sensory neural hearing loss can benefit from high normal or mildly elevated bilirubin level.[9] In industrialized countries the rate of bilirubin induced neurotoxicity has decreased significantly after introducing phototherapy and exchange transfusion as methods of neonatal hyperbilirubinemia management. The neurotoxicity may be transient or persistent, depending

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on the presence of associated risk factors, duration and the level of serum bilirubin.[4,10] It is suggested that there might be a relationship between neonatal hyperbilirubinemia and developmental delay, but a few studies have identified their direct association. Hyperbilirubinemia is a frequent cause of neonatal admission in our region and active medical and developmental follow up of affected children is necessary. This study was conducted to determine neurodevelopmental outcome of children who had severe neonatal jaundice and have been treated by intensive phototherapy or double volume exchange transfusion in neonatal period.

Methods

This descriptive analytical study was performed in healthy infants with the history of severe indirect hyperbilirubinemia who needed intensive phototherapy with or without exchange transfusion. All studied patients had a history of admission for neonatal jaundice in Tabriz children hospital which is a referral tertiary university center in North West of Iran, from January 2017 to December 2017. Infants with gestation age less than 35 weeks, birth asphyxia (Apgar score less than 7 at 5 minutes), birth trauma, major congenital anomalies, history of meningitis, intrauterine infection, inborn error of metabolism and hypoglycemia were excluded from this study. We also excluded infants with hyperbilirubinemia who had direct bilirubin more than 50% of TSB. All the enrolled neonates had undergone intensive phototherapy. Double volume exchange transfusion was performed in addition to intensive phototherapy in infants whose TSB exceeded the exchange transfusion thresholds based on AAP guidelines.[11] TSB was measured every 4-12 hours depending on its levels, presence of risk factors and age of infant. Acute bilirubin encephalopathy is characterized by lethargy, opisthotonus, high pitch cry, and seizure due to hyperbilirubinemia.

We followed-up the eligible infants at their 2-3 years age. Neurodevelopmental assessment was performed by a trained nurse using ages and stage questionnaire (ASQ).[12] We used the Persian version of the ASQ questionnaire that has been validated in Iran.[13] This developmental questionnaire assesses development of the child in five divided area including communication, gross motor skills, fine motor skills, problem solving and personal/social skills. ASQ was considered abnormal when patients did pass at least in one of the five areas and defined as non-optimal psychomotor development (the score were less than -2SD). All children who had non optimal neural motor function were examined by an experienced pediatrician.

Statistical analysis

Statistical analyses were performed using the statistical package for social sciences (SPSS) version 17.0. Quantitative data were presented as mean ± standard deviation (SD) and qualitative data as frequency and percent. Independent *t* test was used for testing normally distributed continuous data. Categorical data were compared between groups using chi-square or Fisher exact test. *P* value less than 0.05 indicated statistical significance.

Results

There were 69 740 live births during study period and 181 neonates admitted with neonatal hyperbilirubinemia. The gestation age was less than 35 weeks in 25 neonates. There were sepsis, hypoglycemia and other exclusion criteria in 20 neonates. The TSB was less than 22 mg/dL in 46 admitted neonates. Ninety newborn infants had met inclusion criteria including 24 neonates underwent exchange transfusion and 66 neonates received intensive phototherapy. Admitted infants with severe hyperbilirubinemia were followed for developmental outcome. Developmental and neurologic follow up were conducted in 62 babies at 24 to 36 months, (21 cases with exchange transfusion and 41 neonates with intensive phototherapy).

The mean TSB at admission was 26.4±4.1 mg/dL. It was 25-30 mg/dL in 34 cases (54.8%) and higher than 30 mg/dL in 8 infants (12.9%).

In our study, we estimated 48.7/100 000 live born infants developed hyperbilirubinemia with TSB 25-30 mg/dL and 11.4/100 000 developed hyperbilirubinemia with TSB higher than 30 mg/dL.

The mean gestational age and birth weight of studied patients were 37.72 ± 1.21 weeks and 3076 ± 526 g. The mean age of patients at the time of jaundice onset and the time of admission were 2.72±1.40 and 5.51±2.55 days respectively. There were 38 (61.3%) boys and 24 (38.7%) girls admitted with hyperbilirubinemia. Demographic characteristics of infants in two groups are showed in Table 1.

The mean TSB, albumin levels and bilirubin/albumin ratio in studied patients were 26.44±4.14 mg/dL and 4.08±0.45 g/dL, respectively. The most common cause of jaundice in patients with exchange transfusion was ABO incompatibility, which occurred in 25 neonates (40.3%). The laboratory tests are presented in Table 2.

Acute bilirubin encephalopathy was determined in three neonates at admission and resolved in all of them at discharge. The age at onset of jaundice was first day in all of them. One of them was a term 3500 g boy born from Rh negative mother and admitted at age 5 days with TSB 26.2 mg/dL and underwent exchange transfusion. He developed kernicterus at follow up. The second infant also had Rh incompatibility and admitted with TSB 25.4 mg/dL at ages 4 days that had 1 standard deviation (SD) delay in two areas (gross motor and problem-solving skills). The third case had ABO incompatibility and admitted at 3 days with TSB of 29 mg/dL and had normal development at follow up.

Table 1. Demographic characteristics of patients in phototherapy and exchange transfusion groups

	Phototherapy group n=41	Exchange transfusion group n= 21	*P* value
Gestation age (wk)	37.9±1.3	37.3±0.9	0.11
Birth weight (d)	3120±563	2973±444	0.27
Age at onset of jaundice (d)	3.1±1.3	1.9±1.7	0.001
Age of admission (d)	6.1±2.5	4.3±2.2	0.01
Delivery by C/S, n (%)	24 (58.5)	10 (47.6)	0.41
Male, n (%)	23 (56.1)	15 (71.4)	0.24
History of jaundice in siblings, n (%)	7 (17.1)	7 (33.3)	0.14
Number of siblings			0.38
No	27 (65.8)	12 (57.1)	
1	9 (21.9)	5 (23.8)	
2	5 (12.2)	2 (9.5)	
3	0 (0)	1 (4.8)	
4	0 (0)	1 (4.8)	

C/S, cesarean section.
Note. Values are presented as mean ± standard deviation or number (%). Independent *t* test was used for testing continuous data and categorical data were compared between groups using chi-square test.

Table 2. Laboratory findings in patients of two studied groups

	Phototherapy group n=41	Exchange transfusion group n=21	*P* value
Hemoglobin, g/dL	17.3±2.4	14.1±3.0	<0.001
Hematocrit	48.8±5.9	40.1±8.1	<0.001
Reticulocyte	2.1±1.9	3.3±1.8	0.01
TSB, mg/dL	25.6±3.1	27.9±5.3	0.03
Albumin, g/dL	4.0±1.4	4.1±0.4	0.41
Bil/Alb ratio	6.2±0.8	6.6±1.1	0.11
Etiology			0.35
ABO	15(36.6%)	10 (47.6)	
Rh	1 (2.4)	2 (9.5)	
ABO+Rh	1 (2.4)	1 (4.8)	
G6PD deficiency	2 (4.9)	2 (9.5)	
idiopathic	22 (53.7)	6 (28.6)	
Duration of hospitalization, d	4.0±1.0	5.6±5.2	0.06

Bil/ Alb, bilirubin/albumin ratio; G6PD, glucose 6 phosphate dehydrogenase deficiency; ABO, blood group incompatibility; Rh, Rhesus factor; ABO + Rh= blood group + rhesus factor incompatibility.
Note. Values are presented as mean ±standard deviation or number (%). Independent *t* test was used for testing continuous data and categorical data were compared between groups using chi-square test.

Kernicterus was diagnosed in 3 neonates with bilaterally symmetric hyper intensity in globus pallidus, two of whom had sensory neural hearing loss. An incidence of 4.3/100 000 live birth infants was estimated for kernicterus. The first case of kernicterus was a boy with gestation age 36 weeks +3 days admitted with TSB 29 mg/dL at 3 days. The cause of jaundice was ABO incompatibility and he had exchange transfusion. The second case was a term girl with TSB 32.5 mg/dL at age 5 days without ABO or Rh incompatibility that had exchange transfusion developed kernicterus in follow up examination.

Eleven children (5 boys and 6 girls) had low score based on ASQ in at least one area. The score was less than 2SD in 3 patients (problem solving, fine motor and gross motor). All of these patients had received intensive phototherapy for hyperbilirubinemia. The remaining 8 children had the score less than 1SD in problem solving (4 cases), communication (2 cases), fine motor (1 case) and gross motor (1 case).

All children with abnormal neurodevelopmental outcome had a history of delay in admission and treatment of hyperbilirubinemia.

Discussion

In this study, hyperbilirubinemia with TSB ≥30 mg/dL is determined in 12.9% of patients admitted with neonatal jaundice. Chronic bilirubin induced neurotoxicity occurred in 12.5% of infants with severe hyperbilirubinemia. The incidence of TSB ≥ 30 mg/dL (11.4 per 100 000) and kernicterus (4.3 per 100 000) in our

study was higher than other populations.[14-18]

In a study on 992 378 live born infants in Sweden from 2008 to 2016, Alkén et al reported 67 newborns with serum bilirubin levels of 30 mg/dL or higher, 13 of whom developed kernicterus up to 2 years of age. In their study 50/100 000 infants developed hyperbilirubinemia with TSB 25-29.9 mg/dL and 6.8/100 000 infants developed hyperbilirubinemia with TSB ≥30 mg/dL and 1.3/ 100 000 developed kernicterus.[19]

In another study in Denmark, 42/100 000 infants developed severe hyperbilirubinemia and kernicterus occurred in 1.2/100 000 infants.[20]

The incidence of severe hyperbilirubinemia in Western Europe and the United States ranges from 2 to 12 per 100 000. It is estimated the incidence of chronic bilirubin encephalopathy is in the range of 0.5-1/100 000.[21-24]

The high incidence of severe hyperbilirubinemia (1500-3000 per 100 000 births) has been observed in Asian countries with low to middle incomes.[25] Bhutani et al estimated that the risk of kernicterus is about 1 in 7 infants with TSB more than 30 mg/dL.[8]

In our study, the most common cause of jaundice in patients who had exchange transfusion was ABO incompatibility and it was idiopathic in patients who had managed by intensive phototherapy. ABO isoimmunization is more common in Europe[15] and G6PD deficiency is predominant in the United States and Canada.[21]

In our study, 45% of infants developing severe hyperbilirubinemia had no underlying risk factor. A problem in management of severe hyperbilirubinemia is untimely or delayed phototherapy or exchange transfusion that was noted in all of our patients with bilirubin induced neuro-developmental delay.

Neonatal hyperbilirubinemia is a risk factor for hearing loss. On clinical testing 52% of 25 neonates with TSB ≥20 mg/dL had hearing loss and 80% of neonates with TSB >30 mg/dL had abnormal neurodevelopmental outcome.[20] On the other hand, Newman et al reported no feature of encephalopathy at 18 months and 5 years in patients with TSB≥30 mg/dL.[14] In a retrospective study of 796 newborns with hyperbilirubinemia at birth, 185 newborns (23.24%) were referred for brainstem auditory evoked potentials. Thirty-five newborns (4.39%) were diagnosed with hearing loss: 18 (51.43%) with conductive hearing loss and 17 (48.57%) with sensorineural hearing loss, 3 of which were diagnosed bilateral profound hearing loss. Half of the children had other associated risk factors, the most frequent being exposure to ototoxics.[24]

Suresh et al. reported no cases of hearing loss in patients with prolonged exposure to high levels of bilirubin >20 mg/dL.[27] In our study, sensory neural hearing loss was detected in two patients.

Kernicterus has a wide range of clinical and neurologic expression. It is influenced by factors such as TSB, duration of jaundice and the age of infant. The age of jaundice onset in patients with BIND was first 24 hours of life in our study and the duration of jaundice before initiation of intensive phototherapy or exchange transfusion was longer in patients with neurodevelopmental delay in our study. Future well designed prospective studies are recommended with assessment of important functional domains such as learning, academic achievement, and adaptive and social function.

Conclusion

Severe hyperbilirubinemia and kernicterus is still occurring in term and late preterm infants. Early detection and management of sever hyperbilirubinemia may improve the neurodevelopmental outcome in high-risk infants. Future studies with long term follow up of a large number of cases are needed to clarify the minor neurologic consequences of hyperbilirubinemia. Parental education for early referring of infants with neonatal jaundice and its effect on neonatal jaundice and neurodevelopmental outcome is recommended.

Conflict of Interest

Authors declare no conflict of interest in this study.

Ethical Approval

The study protocol was approved by the Ethical Committee of the Tabriz University of Medical Sciences, Tabriz, Iran (research ethics number: IR.TBZMED.REC.1396.826). Written informed consent was obtained from parents before the participation.

Author's Contribution

GMM and GM contributed to the conception and design of the study and literature review. GM and AM collected all data and contributed to data interpretation. GMM and HS drafted the first manuscript. All authors reviewed and approved the final version of the article.

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Study Highlights

What is current knowledge?

- Exchange transfusion is the most effective intervention for prevention of bilirubin induced neurotoxicity in neonatal period.

What is new here?

- It is essential to educate parents and health care providers to refer neonates with hyperbilirubinemia as soon as possible for its timely management and prevention of its long term neurologic morbidity.

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