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Original Article

Neonatal Hyperbilirubinemia and Neurodevelopmental Delay Assessment at Six Months of Age

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ABSTRACT

Background: Being toxic to the developing central nervous system, hyperbilirubinemia may cause neurological damage or developmental delay. This study aimed to assess the relationship between hyperbilirubinemia and developmental delay at six months of age in infants with neonatal severe hyperbilirubinemia.

Methods: A prospective cohort study was conducted on infants with a gestational age of >35 weeks and hyperbilirubinemia from 2014 to 2020. The neurodevelopmental assessment was performed using the Denver Developmental Screening Test II (DAS II). The collected data were statistically analyzed by SPSS software (version 26).

Results: Among the three main causes of hyperbilirubinemia, 9.6% of the neonates had blood group incompatibility; ABO, Rh, and ABO +Rh were observed in 7.5%, 1.6%, and 1.1% of the neonates, respectively, and 1.1% of the infants were diagnosed with glucose-6-phosphate dehydrogenase deficiency. The correlation between hyperbilirubinemia and developmental delay in all four domains according to the DAS II test was statistically significant (P<0.001). Moreover, the severity of hyperbilirubinemia was proved to have a positive correlation with the severity of the developmental delay. Furthermore, this study found a significant correlation (P<0.001) between the causes of icterus and the probability of neurodevelopmental delay at six months of age (Correlation Coefficient=0.470, sig=0.000).

Conclusion: There is a strong correlation between hyperbilirubinemia and developmental delay at six months of age in infants with neonatal hyperbilirubinemia. The severity of hyperbilirubinemia is significantly associated with the cause of jaundice. It is also demonstrated that the severity of hyperbilirubinemia has a positive correlation with the severity of the developmental delay.

Keywords: Developmental delay, Hyperbilirubinemia, Neonatal, Neurodevelopment, Neurology

Introduction

Hyperbilirubinemia is a common finding in infants during the first week of their life and is chemically defined as total serum bilirubin (TSB) greater than 2.0 mg/dl (1). It is mostly a normal and temporary phenomenon that indicates the physiologic process of adaptation of neonates to life outside the uterus. Excessive amounts of bilirubin may be toxic for the developing central nervous system and neurological deficiencies are likely to happen (2,3); moreover, hyperbilirubinemia is an important cause of brain damage among infants. Bilirubin can permeate through the brain-blood-barrier, with its subsequent accumulation leading to axonal injury. Among the complications of hyperbilirubinemia are lethargy, auditory response reduction, acute bilirubin encephalopathy, and kernicterus which are chronic and permanent sequelae of hyperbilirubinemia occurring in 30% of neonates with TSB of 25-30 mg/dl or higher (4).

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Kernicterus is caused by excessive bilirubin deposits in the brainstem and basal ganglia and is associated with choreoathetosis, paresis of upward gaze, sensorineural deafness, and occasionally developmental delays (5). Abnormalities in Brainstem-Evoked Response Audiometry (BERA) and neurobehavioral measures are also suggested to be associated with hyperbilirubinemia (6). Since an early diagnosis of developmental delay in neonates with bilirubin encephalopathy can refine the prognosis, monitoring developmental delay and other neurological complications in these infants is crucial. Moreover, the severity of the neurotoxicity of bilirubin can vary among different ethnicities. Although the reasons remain unclear, different etiologies in these ethnic groups might help to vindicate this assumption. For instance, glucose-6-phosphate dehydrogenase (G6PD) deficiency is common in Orientals, whereas rhesus incompatibility is rare (7). This study aimed to assess the relationship between neonatal peak TSB and neurodevelopmental outcomes in six-month-old infants with neonatal hyperbilirubinemia in the northeast of Iran.

Methods

This prospective cohort study was conducted in the Department of Pediatrics, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, from 2014 to 2020. A predesigned questionnaire was used to record the patients' data. Validation of the contents of the questionnaire was accomplished by five experts from the faculty of Medicine. This study included all infants with hyperbilirubinemia admitted to Ghaem Hospital at a gestational age of >35 weeks during the study period. On the other hand, infants with congenital anomalies, meningitis, sepsis, intracerebral hemorrhage, asphyxia, hypoglycemia, cholestasis, epilepsy, malnutrition, hypothyroidism, and Down syndrome were excluded from the study. These conditions may affect the development of the infant; therefore, they were considered interfering factors and were removed from the research procedure. In all cases, hyperbilirubinemia was managed by phototherapy and exchange transfusion according to the guidelines published by the American Academy of Pediatrics subcommittee on hyperbilirubinemia (8). The age of the patients at referral, the causes of their jaundice, complications, and their gender were recorded. A complete examination was performed on the patients. All required tests were conducted to determine the cause of jaundice, including platelet direct and indirect bilirubin using the diazo method, hematocrit, Coombs test, neonatal and maternal blood groups, G6PD, and urine culture.

The conditions attributed to neonatal jaundice in this study include: 1) unknown cause, 2) ABO incompatibility, 3) Rh incompatibility, and 4) G6PD deficiency (G6PDD). The diagnostic criteria of Rh incompatibility include negative maternal Rh with positive neonatal Rh and positive Coombs test of the baby. The diagnosis of ABO incompatibility is achieved once it is determined that the maternal blood group is O, and the neonatal blood group is A or B and at least two of the following conditions exist: 1) first-day jaundice, 2) positive direct Coombs test, 3) presence of micro spherocytosis in peripheral blood smear, and 4) positive indirect Coombs test. The evaluation of the G6PD activity rate was performed by a semi-quantitative and dye fluorescence method. An activity rate of less than 30 was considered G6PDD (7).

After discharge, our study group was followed up and examined at six months of age, and their neurodevelopment was assessed by the Denver Developmental Screening Test II (DAS II). DAS II is a method used to assess the development of children from birth to the age of six and is divided into four domains: gross motor, fine motor, language, and social. Having a problem in each of these domains is considered a developmental delay. The results were categorized as normal, developmental delay in one domain, and developmental delay in more than one domain (global developmental delay).

The data analysis was performed using the Chi-square test for determining the association between the cause of icterus and neurodevelopment; along with an independent sample t-test for detecting the association between each of the four domains of neurodevelopment according to DAS II and bilirubin levels. Kendall's tau B was used to find the correlation between the cause of jaundice and the severity of prognosis at six months. All data were statistically analyzed by SPSS software (version 26). A P-value of <0.05 with a 95% confidence interval (CI) was considered significant.

Ethical approval

The study protocol was approved by the Ethics Committee and Research Department of Mashhad University of Medical Sciences, and informed consent was obtained from the parents (code: IR.MUMS.MEDICAL.REC.1397.538).

Results

Of the total 221 infants who participated in the

Table 1. Comparison of mean bilirubin levels in different causes of icterus

Variable	Causes of hyperbilirubinemia				Sig
	Unknown (Median±IQR)	G6PDD (Median±IQR)	ABO incompatibility (Median±IQR)	Rh incompatibility (Median±IQR)	
Bilirubin level(mg/dl)	17.7±10.2	28.5±3.77	27±8.88	30±7.3	0.001*

*between unknown and others cause

study, 19 neonates were excluded due to direct hyperbilirubinemia (n=3), hypothyroidism (n=4), an infection (n=5), Down syndrome (n=2), a history of developmental delay in their family (n=2), and the familial history of seizure (n=3). Moreover, 19 other infants were removed from the study due to no follow-up at six months. In total, a population of 183 cases were evaluated and followed up during the study. The majority of these infants (n=183) were male (58.4%), the mean referral age was 7.21±3.76 days, and the mean level of bilirubin was 20.32±5.72.

Of all the evaluated cases, 82.3% had no determinable cause of hyperbilirubinemia. Our study shows that the severity of hyper-bilirubinemia is correlated with the cause of jaundice. A comparison of bilirubin levels in different causes of jaundice is illustrated in Table 1. It demonstrates that RH incompatibility is accompanied by a higher bilirubin level, compared to other causes. Additionally, 9.6% of the neonates had blood group incompatibility. ABO, Rh, and ABO +Rh were observed in 7.5%, 1.6%, and 1.1% of them, respectively, and 1.1% were diagnosed with G6PDD. The results of the neurodevelopmental assessment indicate that 155 (85.16%) infants had normal development, while 20 (10.98%) cases showed a developmental delay in one domain, and 7 (3.84%) neonates had a neurodevelopmental delay in more than one domain. The severity of hyperbilirubinemia has a positive correlation with the severity of developmental delay (Table 2). Moreover, a significant correlation was found (P<0.001) between the causes of icterus and the probability of neurodevelopmental delay at six months of age (Correlation Coefficient=0.470, sig=0.000). The number of cases with normal/abnormal development in each of these four domains is illustrated in Figure 1.

Table 2. Comparison of mean and standard deviation of bilirubin levels in infants with normal development and developmental delay in 6 months

Variable	Prognosis at six months of age			Sig
	Normal outcome (Median±IQR)	Developmental delay in one domain (Median±IQR)	Developmental delay in more than one domain (Median±IQR)	
Bilirubin level(mg/dl)	18.2±6.8	28.65±2.9	34.1±6.6	0.001*

*between unknown and others cause

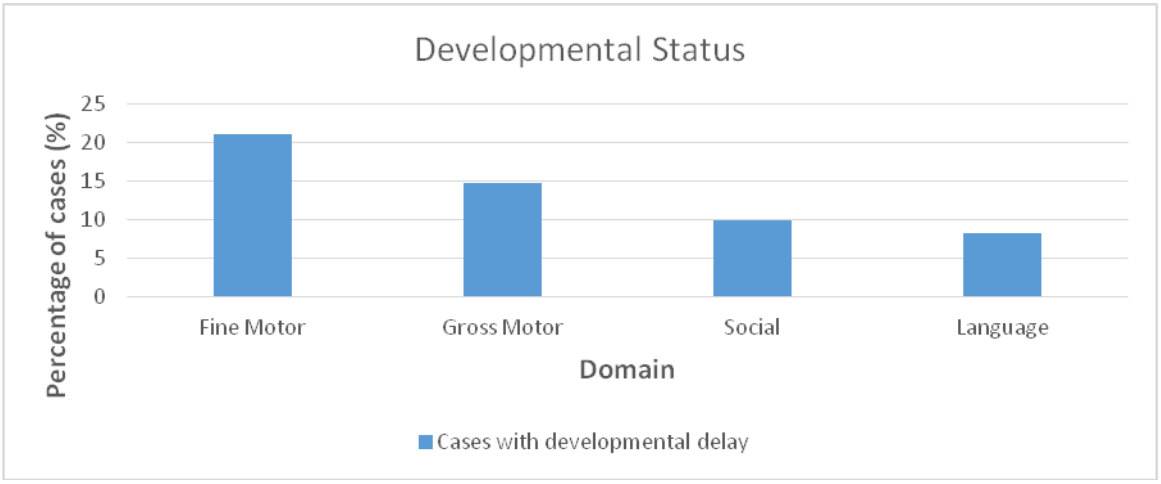

Figure 1. Comparison between the percentage of developmental delay in children with hyperbilirubinemia at six months of age in each of the four studied domains

Discussion

The passage of unconjugated bilirubin through the blood-brain barrier and its conjugation to the brain phospholipid membrane may cause

neuronal injury, especially when its amount exceeds the albumin-binding capacity. The most prominent concern about hyperbilirubinemia is its potential neurotoxic effects on the developing nervous system of neonates; however, there is also the possibility of general cellular injury. The deposition of unconjugated bilirubin in the basal ganglia and vestibule-cochlear nucleus results in a condition known as kernicterus and sensor neural hearing loss, making it a leading cause of preventable brain damage. The studies concerning the effects of hyperbilirubinemia on infants' neurodevelopment have shown many controversies; therefore, further evaluations seem necessary. This study attempted to focus on neurodevelopmental assessment rather than BERA and with a greater number of cases, careful examination, and follow-up of the participants. For evaluation, DAS II was performed on four main domains (e.g., gross motor, fine motor, language, and social).

The present study showed a significant association between the severity of hyper-bilirubinemia and developmental delay. In a study conducted by Oh et al., it was reported that the prevalence of neurodevelopmental defects is higher in patients with hyperbilirubinemia (9) whereas, Wradharma et al. declared that their study had not found a significant association between hyperbilirubinemia and developmental delay in any domain. Instead, they suggested that gestational age significantly influences the likelihood of developmental delay (10).

Our study also showed that high bilirubin levels have a significant association with language delay. Even though this result differs from some earlier studies (11,12), it is consistent with those of Özgürhan et al., Jangaard et al., and Chen et al. (13-15). Additionally, social delay was also found to have a significant association with higher levels of bilirubin. This finding significantly differs from previous results reported in the literature by Ozguran et al. (15); however, it approves the results published by some earlier studies by Chen et al. and Jangaard et al. (13,14).

Our results claiming that hyperbilirubinemia is associated with a greater risk of gross and fine motor delays were similar to some of the previous studies (12,13). However, this association was not found for gross motor in a study performed by Özgürhan et al. (15). In contrast with some previous studies (12,15), fine motor delay had a higher prevalence than language delay; this might be the result of our study population's age (6 months) which is not completely reliable for language assessment. Moreover, according to our results, the severity of hyperbilirubinemia is correlated with the cause of jaundice, demonstrating that jaundice due to the Rh incompatibility had the highest severity, followed by G6PDD, ABO incompatibility, and ABO incompatibility accompanied by Rh incompatibility, which is consistent with a former study by Boskabadi et al. (16).

Our most important finding is the effect of hyperbilirubinemia on infants' prognosis at six months of age, indicating that almost 10% of the newborns with hyperbilirubinemia had developmental problems, while 3% had obvious developmental defects. Our study shows that the developmental prognosis worsens as the severity of hyperbilirubinemia increases, and there is a strong correlation between the severity of hyperbilirubinemia and poor prognosis of cases at six months of age (Kendall's tau-B test=0.476, $P<0.001$) to the extent that in mean bilirubin levels of more than 26 mg/dl, we observe mild developmental delay, and in the cases with mean bilirubin of more than 30 mg/dl, moderate to severe developmental delay is observed. Among the newborns with developmental delay as a result of hyperbilirubinemia, the most prevalent affected domain was fine motor (21%), followed by gross motor (15%), language, and social delays.

The strength of our study was its prospective cohort design. Moreover, this is the first study conducted in the east of Iran, concerning the effect of hyperbilirubinemia on developmental delay. The limitation of this study was the short duration of the follow-up period. Longer developmental follow-ups is recommended in future studies.

Conclusion

According to the results of this study, the severity of hyperbilirubinemia is associated with the cause of jaundice, and the highest levels of jaundice were due to RH incompatibility, G6PDD, ABO incompatibility, and unknown causes in descending order. Furthermore, hyperbilirubinemia has been effective in the prognosis of infants at six months of age. As the severity of hyperbilirubinemia increases, the developmental prognosis worsens. There is a strongly significant correlation between the severity of hyperbilirubinemia and poor prognosis in infants at six months of age. Among the cases with developmental delay due to hyperbilirubinemia, the most commonly affected domains were fine motor, gross motor, language, and social in descending order. Close follow-up should be considered in infants with a history of

neonatal hyperbilirubinemia in spite of having been managed by an appropriate approach.

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Conflicts of interest

The authors of this manuscript declare no conflict of interest in its writing and publication.

References

1. Boskabadi H, Maamouri G, Bagheri S. Significant Neonatal Weight Loss Related to Idiopathic Neonatal Hyperbilirubinemia. Int J Pediatr. 2014; 2(4.1):225–31.
2. Yilmaz Y, Karadeniz L, Yildiz F, Degirmenci SY, Say A. Neurological prognosis in term newborns with neonatal indirect hyperbilirubinemia. Indian Pediatr. 2001;38(2):165–8.
3. Soorani-Lunsing I, Woltil HA, Hadders-Algra M. Are moderate degrees of hyperbilirubinemia in healthy term neonates really safe for the brain? Pediatr Res. 2001;50(6):701–5.
4. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017;78(12):699–704.
5. Boskabadi H, Ashrafzadeh F, Azarkish F, Khakshour A. Complications of Neonatal Jaundice and the Predisposing Factors in Newborns Complications of neonatal jaundice and the predisposing factors in newborns. J Babol Univ Med Sci. 2015;17(9):7–13.
6. Agrawal A, Pandya S, Shrivastava J. Neurodevelopmental outcome at 6 months of age in full-term healthy newborns with neonatal hyperbilirubinemia. J Clin Neonatol. 20201; 9(2):138-42.
7. Boskabadi H, Masoud O, Shahin M. Prevalence and Clinical Manifestation of Glucose-6-Phosphate Dehydrogenase Deficiency in Newborns with Hyperbilirubinemia in Mashhad, Iran. Maced J Med Sci. 2010;3(4):383-7.
8. Boskabadi H, Akhondian J, Afarideh M, Maamouri G, Bagheri S, Parizadeh SM, et al. Long-term neurodevelopmental outcome of neonates with hypernatremic dehydration. Breastfeeding Med. 2017;12(3):163-8.
9. Oh W, Tyson JE, Fanaroff AA, Vohr BR, Perritt R, Stoll BJ, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics. 2003; 112(4):773–9.
10. Wiradharma W, Windiani IG, Haksari E. Developmental delay in 3-month-old low birth weight infants with hyperbilirubinemia. Paediatr Indones. 201331;53(4):228-31.
11. Amin SB, Prinzing D, Myers G. Hyperbilirubinemia and language delay in premature infants. Pediatrics. 2009;123(1):327-31.
12. Arimbawa IM, Soetjiningsih S, Kari IK. Adverse effects of hyperbilirubinemia on the development of healthy term infants. Paediatr Indones. 2006; 46(2):51-6.
13. Tsao P-C, Yeh H-L, Shiau Y-S, Chang Y-C, Chiang S-H, Soong W-J, et al. Long-term neurodevelopmental outcomes of significant neonatal jaundice in Taiwan from 2000–2003: a nationwide, population-based cohort study. Sci Rep. 2020;10(1):11374.
14. Jangaard KA, Fell DB, Dodds L, Allen AC. Outcomes in a population of healthy term and near-term infants with serum bilirubin levels of >or=325 micromol/L (>or=19 mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000. Pediatrics. 2008;122(1):119–24.
15. Özgürhan G, Comert S. Neurodevelopmental Evaluation of Term Newborns with Significant Hyperbilirubinemia. Istanbul Med J. 2020;21(5):370–4.
16. Boskabadi H, Zakerihamidi M, Moradi A, Bakhshaee M. Risk Factors for Sensorineural Hearing Loss in Neonatal Hyperbilirubinemia. Iran J Otorhinolaryngol. 2018;30(99):195–202.