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Paediatrics Section

A Study of Neurodevelopmental Outcome in Hyperbilirubinaemic Neonates Admitted in NICU

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ABSTRACT

Introduction: Hyperbilirubinaemia may be toxic to the developing central nervous system and may cause neurological impairment. The developing brain of premature babies is extremely vulnerable to injury. With increased level of bilirubin, the risk for neurodevelopmental deficit increases with decreasing gestational age and birth weight resulting in relatively high risk of cerebral palsy, developmental delay, hearing and vision impairment and subnormal academic achievement.

Aim: This study was conducted to identify factors and pattern of abnormal neurodevelopment at three and 12 months in babies having birth weight >1.5 Kg and gestational age >34 weeks with neonatal hyperbilirubinaemia.

Materials and Methods: This prospective study was conducted at Sardar Patel Medical College, Bikaner (Rajasthan), India, from 2014 to 2015. Hyperbilirubinaemia in newborns were examined at three month and 12 month age and their neurodevelopmental assessment done by DASI method. All the collected data was tabulated and stastically analysed by using SPSS software.

Results: Out of 96, 67 (69.79%) of hyperbilirubinaemic neonates were males and 29 (30.21%) were females. The prevalence of neurodevelopmental abnormalities (DQ≤70) was 10.42% at three months where as it was 6.25% at 12 months follow-up. Early onset of jaundice (≤1 day), serum bilirubin level >25 mg/dL, duration of hospital stay >3 days and requirement of exchange transfusion was significantly associated with adverse neurodevelopmental outcomes (DQ≤70) at three and 12 months of age.

Conclusion: This study found a high prevalence of adverse neurodevelopmental outcome in neonates with hyperbilirubinaemia. Early detection of neurodevelopmental abnormalities and initiation of early intervention measures to reduce the prevalence of neurodevelopmental abnormalities in hyperbilirubinaemic neonates.

Keywords: Central nervous system, Jaundice, Kernicterus

INTRODUCTION

Jaundice is the commonest abnormal physical finding during first week of life. Neonatal hyperbilirubinaemia is a common problem. Approximately 60% of term and 80% of preterm infants develop jaundice in the first week of life [1]. When total serum bilirubin exceeds 25 mg/dL, infants are at risk for neurological damage. Unconjugated bilirubin is able to cross the blood-brain barrier and can accumulate in the brain leading to a number of possible adverse neurodevelopmental outcomes. Lethargy is common among infants with high total serum bilirubin levels, and as levels increase, auditory responses can diminish, and most severely, acute bilirubin encephalopathy or kernicterus can develop. Kernicterus is a form of chronic brain damage specifically caused by hyperbilirubinaemia, where the brainstem and basal ganglia are stained by bilirubin, accompanied by neurological deficits such as athetoid cerebral palsy, auditory dysfunction or intellectual deficits [2]. Careful assessments of the risk factors involve a systematic approach to the detection and follow-up of jaundice with the appropriate investigations and treatment so as to avoid complications [3].

In order to prevent immediate and late neurological sequelae early detection of hyperbilirubinaemia and neurodevelopmental impairment is essential. It is important to initiate the early intervention measures for better developmental outcome. It is by no means a predictor of future intelligent quotient and any deviation from the normal is brought to the notice of the parents, only in reassuring ways [4].The relation between developmental deficits and hyperbilirubinaemia can be much more complicated. But the risk of developmental disabilities is more in neonates exposed to hyperbilirubinaemia.The preliminary analysis and statistics from many children, developmental centers and out-patient departments in hospitals have showed that babies with

neonatal hyperbilirubinaemia have higher incidence of delayed developmental milestones and other associated problems, and many of these are reversible by early intervention.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Paediatrics of Sardar Patel Medical College, Bikaner (Rajasthan) India, between 2014 to 2015 over the period of one year. The Institutional Committee was approved for this study. Total 115 newborns who where admitted in NICU (65 inborn + 50 out born) with jaundice were enrolled.

Neonates admitted to the Paediatric Hospital with jaundice, requiring phototherapy/exchange transfusion as per standard treatment guidelines, gestational age >34 weeks; birth weight >1.5 Kg were included in the study.

Babies with congenital anomalies, gestational age <34 weeks, sick neonates having sepsis, neonatal seizures, birth asphyxia, hypothyroidism were excluded from the study.

Data about birth history, gestational age, antenatal history, maternal history, total bilirubin level day of onset, blood grouping, sepsis screening, risk factors, treatment given, and condition at discharge were collected in a predesigned praforma. At time of enrollment informed consent from parents was taken and guardians were counseled about treatment of hyperbilirubinaemia, milestones of infant, feeding practices and risk of hyperbilirubinaemia.

In 115 cases, 17 cases were excluded because they did not turn up for the second follow-up also, two cases were excluded due to CNS causes. In all 96 newborns were examined at three month and 12 month age and their neurodevelopmental assessment done by Developmental Activities Screening Inventory (DASI) method. Neurodevelopmental assessment was done and a composite DQ (motor and mental DQ) was calculated by DASII method. Both mental development index and psychomotor development index was calculated by DASII. The age placement of the item at the total score rank of the scale was noted as the child's developmental age. This converted the child's total scores to his Motor Age (MoA) and Mental Age (MeA). The developmental ages were used to calculate his motor and mental development quotients respectively by comparing them with his chronological age and multiplying it by 100. All the collected data was tabulated.

STATISTICAL ANALYSIS

Statistical analysis was done by using SPSS software (SPSS version 15.0, Windows, Linux on Z systems, IBM Corporation, United States) methods.

RESULTS

Total 96 hyperbilirubinaemic neonates were enrolled in our study. Of these, 67 (69.79%) of hyperbilirubinaemic neonates were males and 29 (30.21%) were females 27.08% were preterm (gestational age <37 week) and 72.92% were term babies (≥37 week). About 50% neonates were having ≥2.5 Kg birth weight. Peak serum bilirubin in 91.66% neonates was <25 mg/dL while 8.34% had levels ≥25 mg/dL. 51.04% hyperbilirubinaemic neonates had haemolytic and 48.96% had others etiology of jaundice. Majority (86.46%) of neonates were discharged within three days, only 13.54% stay for more than three days. About 71.17% hyperbilirubinaemic neonates were treated by phototherapy but 20.83% required exchange transfusion. The prevalence of neurodevelopmental abnormalities (DQ≤70) was 10.42% at three months whereas, it was 6.25% at 12 months follow-up. 8.33% had motor and 10.42% had mental abnormalities at three months meaning thereby that in majority of patients motor abnormalities coexisted with mental abnormalities. Similar pattern was observed at 12 months where motor and mental abnormalities coexisted in all cases (6.25%). No statistically significant association was observed between these factors and mean DQ. The association of peak serum bilirubin level ≥25 mg/dL with prevalence of neurodevelopmental abnormalities was found statistically significant ($p<0.05$).

Nearly, 37%, and 25% cases with peak serum bilirubin level ≥25 mg/dL had abnormal DQ (≤70) at three and 12 months respectively as compared to 7.9% and 4.54% in those who had peak serum bilirubin <25 mg/dL. The association of peak serum bilirubin ≥25 mg/dl and mean DQ was also significant at three and 12 months follow up. Early onset of jaundice (≤1 day) was significantly associated with adverse neurodevelopmental outcomes (DQ≤70) at three and 12 months of age on follow-up. Highly significant association of mean DQ was observed with day of onset of jaundice. Highly significant association of duration of hospital stay was observed with abnormal DQ (≤70) at three months follow-up. About 38.46% babies with abnormal DQ (≤70) had >3 days hospital stay while only 6.02% cases with duration of stay ≤3 days had abnormal DQ (≤70) ($p=0.002$). However, this association was not found significant at 12 months follow-up. Statistically significant association of mean DQ at three and 12 months of age was observed with haemolytic etiology of hyperbilirubinaemia. The prevalence of neurodevelopmental abnormalities was significantly greater in cases that had undergone exchange transfusion in comparison to neonates receiving only phototherapy. Mean DQ was significantly lower in neonates who required exchange transfusion.The association of these parameters (early onset of jaundice, serum bilirubin level >25 mg/dL and duration of hospital stay) with mean DQ was confirmed by logistic regression analysis.

DISCUSSION

Neonatal hyperbilirubinaemia is a common problem requiring medical attention in newborn and a leading cause of preventable brain damage, physical and mental disabilities

and early deaths among infants. The cause and effect relationship between neurodevelopment and risk factors of hyperbilirubinaemia is more complex and we cannot simply presume that neonatal hyperbilirubinaemia and presence of various risk factors will always lead to adverse neurodevelopmental outcome. Yet, because the neonatal hyperbilirubinaemia is a known, treatable risk factor so early detection and regular follow-up for developmental abnormalities in these patients is important to initiate early intervention measures for better developmental outcome.

A total of 96 neonates with hyperbilirubinaemia, admitted to NICU and fulfilling the inclusion/exclusion criteria were included in the study and developmental evaluation was done at three and 12 months by Developmental Assessment scales for Indian Infants (DASII) method. This is a revision of 1970 Baroda Norms from birth to 30 months based on BSID RF 61, with indigenous material. Out of 96 hyperbilirubinaemic neonates enrolled in the study, 69.79% were males while 30.21% were females. About 27.08% were preterm (gestational age <37 weeks) while the rest 72.92% were term (gestational age >37 weeks) deliveries. Birth weight of these hyperbilirubinaemic neonates were between 1.50 to 1.99 Kg for 27.08%, 2.00 to 2.49 Kg for 22.92% and >2.5 Kg for 50%. Peak serum bilirubin level of 91.66% neonates was below 25 mg/dL while 8.34% cases were having peak level equal to or higher than 25 mg/dL [Table/Fig-1].

In our study, 9.38% cases had onset of jaundice within 24 hours of birth while in 90.62% cases, time of onset of jaundice was more than 24 hours of birth. Total 86.46% hyperbilirubinaemic neonates stayed in hospital for ≤3 days while in 13.54% hyperbilirubinaemic neonates, duration of stay was more than three days. Etiology for hyperbilirubinaemia was haemolytic in 51.04% cases (ABO, Rh, ABO+Rh, DCT positive) and non-haemolytic in the rest 48.96%. 79.17% hyperbilirubinaemic neonates received phototherapy while 20.83% cases required exchange transfusion.

Peak Serum Bilirubin (mg/dL)	Mean IQ		
	3 Months	6 Months	12 Months
<25 (n=88)	89.50+10.12	92.42+9.17	95.17+9.05
≥25 (n=8)	81.30+13.47	86.22+12.10	88.26+13.00
p-value	0.035	0.078	0.049

[Table/Fig-1]: Mean IQ at 3,6,12 months in relation to peak serum bilirubin level.

Neuro-developmental outcome	3 Months		6 Months		12 Months	
	Cases	%	Cases	%	Cases	%
Normal (DQ>70)	86	89.58	90	93.75	90	93.75
Abnormal (DQ≤70)	10	10.42	6	6.25	6	6.25
Total	96	100	96	100	96	100

[Table/Fig-2]: Neurodevelopmental outcome at 3, 6 and 12 months.

In our study, the prevalence of abnormal neurodevelopmental outcome (DQ≤70) according to DASII method was 10.42% at three months which decreased to 6.25% on follow-up at 12 months suggesting that some component of neurodevelopmental abnormalities due to hyperbilirubinaemia could be transient or reversible [Table/Fig-2]. Similar decrease in prevalence has been reported by Wong V et al., (10.42% in haemolytic group and 2% in non haemolytic group were neurodevelopmentally abnormal at initial evaluation and returned to normal on follow-up at three years) [4]. Yilmaz Y et al., in 2001 reported neurodevelopmental abnormalities in 11.5% cases in their study using DDST [5]. This prevalence is quite similar to the prevalence of neurodevelopmental abnormalities in our study (10.42%). The difference in the prevalence can be due to the difference in the used tools for developmental assessment, different ages for follow-up and different socio-demographic factors and variables associated with hyperbilirubinaemia. Hyman CB et al., reported that the prevalence of neurodevelopmental abnormalities was higher in hyperbilirubinaemic neonates with >20 mg/dL bilirubin levels [6]. In this study evaluation was done at four years of age. Prevalence of adverse neurodevelopment outcome (6.25%) at one year in our study was quite similar to that reported by Grunebaum E et al.,[7]. Wolf MJ et al., reported that 23% cases were neurodevelopmentaly abnormal in their study by using BSID (Bayley,s Scales for Infant Development) at one year of age and 12% were with abnormal motor outcome [8]. Newman TB et al., in 2006 found in their study that 17% cases of hyperbilirubinaemia had abnormal neurological findings [9].

Soorani-Lunsing I et al., found abnormal neurological condition in 55% cases at three months of age according to assessed by observations of general movement, and 50% at one year of age according to Touwen's assessment [10]. On further evaluation these values decreased at six and 12 months as abnormal motor and abnormal mental outcome was 6.25% at six and 12 months [Table/Fig-3]. Rosta J et al., found 5% cases having lower IQ at eight years, in their study [11]. We analysed

Follow-up	Total no. of Cases Evaluated for Neuro-developmental Abnormalities	Motor Abnor-mality		Mental Abnor-mality		DQ (≤70)	
		No.	%	No	%	No.	%
3 months	96	8	8.33	10	10.42	10	10.42
6 months	96	6	6.25	6	6.25	6	6.25
12 months	96	6	6.25	6	6.25	6	6.25

[Table/Fig-3]: Revalence and pattern of neurodevelopmental abnormalities at 3, 6 and 12 months of age in cases with hyperbilirubinaemia.

the relation of various demographic factors and risk factors of hyperbilirubinaemia on neurodevelopmental outcome.

Mean DQ in male neonates was also not statistically different to the mean DQ observed in female neonates. Out of 70 hyperbilirubinaemic neonates with gestational age ≥37 weeks, 8 (11.42%) and 2 (7.14%) were abnormal (DQ≤70) at three and 12 month. Out of 26 cases with gestational age ≥37 weeks, 2 (7.69%) and 1 (3.84%) were neurodevelopmentally abnormal at three and 12 month of age. The difference in prevalence in relation to gestational age not found significant. In contrast to these, other studies like Scheidt PC et al.,reported significant relationship of gestational age and neurodevelopmental abnormalities which were more in babies with low gestational age [12]. Wolf MJ et al., reported that neurodevelopmental abnormalities were more in those hyperbilirubinaemic neonates who were having lower gestational age [8]. Prevalence of abnormal neurodevelopmental outcome in neonates having peak serum bilirubin (PSB) >25 mg/dL was 37.5% and 25% in follow-ups at three months and 12 months. The prevalence was observed to be lower in those having PSB <25 mg/dL which was 7.95% at three months, and 4.54% at 12 months. The difference in both groups was significant at three months (p=0.008) as well as 12 months (p=0.022). A similar study has supported this conclusion [13].

The significant association between time of onset of jaundice and neurodevelopmental outcome has also been reported by Arun Babu T et al., [14]. A study by Oh W et al., found PSB concentration during the first two weeks of life directly correlated with neurodevelopmental impairment [15]. In our study early onset of jaundice significantly associated with abnormal neurodevelopment. A longer duration of hospital stay was found to be positively associated with neurological abnormalities. We compared the mean DQ at all follow-ups between the two groups and observed a significant association between mean DQ and duration of hospital stay at three months (p=0.004) but not at 12 months (p=0.073). Nilsen ST et al., also supported this that longer duration of hospital stay is associated with lower IQ [16].

We noticed a significantly higher prevalence of neurodevelopmental abnormalities in those who required exchange transfusion as compared to those who received phototherapy. Amongst those cases who required exchange transfusion, 45% and 25% were found to have abnormal neurodevelopmental outcome (DQ≤70) on evaluation at three and 12 months whereas, only 1.31% of those who received phototherapy were found to have abnormal neurodevelopmental outcome (DQ≤70) at three month and 12 months. Difference in prevalence of abnormal neurodevelopmental outcome in both groups was statistically significant on evaluation at three months (p=0.0001) and 12 months (p=0.001). Mean DQ was significantly lesser in those cases who required exchange transfusion on evaluation at three months (p=0.0001), six months and 12 months (p=0.0001) as compared to those cases who received phototherapy. The hyperbilirubinaemic neonates who were having haemolytic etiology, the prevalence of abnormal neurodevelopmental outcome (DQ≤70) was higher (16.33% at three month, 10.20% at 12 months) as compared to those neonates who were having non haemolytic etiology (4.26% at three month, 2.13% at 12 months) in our study. Mean DQ was found significantly higher in non haemolytic group than haemolytic group on evaluation at three and 12 months (p=0.0001).

LIMITATION

In our study sample size was small, need large small size to reduce observer bias. In this study we were unable to make etiological diagnosis in few hyperbilirubinaemic neonates, due to lack of investigations like G6PD, pyruvate kinase enzyme assay and Coomb's test.

CONCLUSION

This study shows a high prevalence of adverse neuro-developmental outcome in neonates with hyperbilirubinaemia. The prevalence of neurodevelopmental abnormalities was lesser at 12 months evaluation in comparison to prevalence at three months, signifying that neurodevelopmental abnormalities due to hyperbilirubinaemia are partially reversible. This finding underscores the importance of early detection of neurodevelopmental abnormalities and initiation of early intervention measures to reduce the prevalence of neurodevelopmental abnormalities in hyperbilirubinaemic neonates.

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