Predictors of abnormal neurodevelopment at 6 months in term babies with early neonatal hyperbilirubinemia - A prospective cohort study from South India

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Vol. 15, No. 2 (2011-07 - 2011-12)

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Abstract

Present study was conducted to identify predictors of abnormal neurodevelopment at 6 months in term babies with early neonatal hyperbilirubinemia. Neonatal intensive care unit with follow up clinic in a tertiary care teaching hospital. All the term neonates having peak serum bilirubin (PSB) values of above 15mg/dl within first week of life were enrolled in the study. A detailed history, investigations and treatment given were recorded. These babies were followed and development quotient was calculated at 6 months using Baroda devel-opment screening test (BDST). Peak serum bilirubin > 25 mg/dl, need for exchange transfu-sion, Rh incompatibility and onset of jaundice within 2 days of birth were found to predict abnormal neurodevelopment at 6 months. Such significant difference were not noted with other factors like sex, head circumference and birth weight. The presence of these risk fac-tors should alert the clinician regarding the potential risk of abnormal development.

Key words: Neonatal jaundice, Hyperbilirubinemia, Neurodevelopment
Accepted March 11 2011

Introduction

Jaundice is a common condition requiring medical atten-tion in newborns. It is still a leading cause of preventable brain damage, physical and mental handicap, and early death among infants. In most infants, unconjugated hy-perbilirubinemia reflects a normal transitional phenome-non. More than one fourth of all term newborns develop clinical jaundice [1]. However, in some infants, serum bilirubin levels raise to high levels causing neuro toxicity and subsequent death or lifelong neurological sequelae in surviving infants [2]. Identifying cerebral impairment due to neonatal jaundice as early as possible is of prime con-cern to the treating physician. The early detection of an abnormality should allow us to provide the infant with early and appropriate therapy. This study was done inor-der to identify predictors of neurodevelopmental outcome in cases of neonatal hyperbilirubinemia.

Material and Methods

The present study was conducted over a two year period from March 2007 to March 2009, at a tertiary care teach-ing hospital located in South India. All the term neonates who developed jaundice with at least one serum bilirubin value of above 15mg/dl within first week of life were en-rolled in the study. Babies with major congenital anoma-lies, prematurity, intrauterine growth retardation, sus-pected or culture positive sepsis, birth asphyxia, convul-sions or any other disease process which could possibly affect the neurodevelopment were excluded from the study. An informed written consent was obtained from all the parents before their babies were included in the study. This study was approved by the Institute Research and Ethics committee. A detailed antenatal history, baseline characteristics and investigation results of included neo-nates were recorded. Standard institutional protocol for treatment of neonatal jaundice was followed. Treatment modalities started and response to treatment were re-corded. After discharge all

cases were followed up till 6 months of age and assessed using Baroda development screening test (BDST) [3]. The developmental age and quotients were calculated for each case according to BDST.

Statistical analysis

Data entry and analysis were done using SPSS for Win-dows Version 16.0 (SPSS Inc, Chicago, IL, USA). We compared their means using unpaired t test, Mann-Whitney test, One-way ANOVA and Kruskal-Wallis test. The factors found to significantly reduce the mean devel-opmental quotient were further tested by logistic regres-sion analysis. P value < 0.05 was considered statistically significant.

Results

Out of the total 66 cases included, 21 cases were lost to follow up and the remaining 45 s which completed the study were taken for analysis. The mean (SD) birth weight of the neonates was 2.90 (± 0.40) kg and the mean (SD) head circumference was 33.96 (± 1.64) cms. The effects of various factors on the development quotient of the babies are summarized in Table 1. Rh incompatibility, peak serum bilirubin > 25 mg/dl, occurrence of jaundice within 2 days and exchange transfusion were found to significantly affect the development quotient of the babies at 6 months of age. Logistic regression analysis too con-firmed the same except for exchange transfusion (Table 2). Head circumference, birth weight and sex were not found to significantly influence the development quotient of the babies at 6 months.

Table 1: Effect of various factors on the development quotient of the babies

Parameter	Frequency	Development quotient Mean ± SD	P value
Sex			0.0804
Male	24	78.38 ± 16.42	
Female	21	86.00 ± 11.26	
Head circumference			0.3507†
≤ 34	24	81.04 ± 13.18	
> 34	21	82.95 ± 16.35	
Birth weight			0.5215
2 – 2.5 Kg	8	79.13 ± 12.80	
2.51 – 3.0 Kg	21	84.62 ± 12.63	
More than 3.0 Kg	16	79.81 ± 17.82	
Diagnosis*			0.0056
ABO incompatibility	28	89.50 (61, 100)	
Rh incompatibility	11	66.00 (45, 100)	
Miscellaneous	6	86.00 (83, 94)	
Peak Serum Bilirubin			0.0046

Mild (15 – 20 mg %)	21	88.95 ± 09.27	
Moderate (21 – 25 mg %)	13	78.31 ± 10.21	
Severe (> 25 mg %)	11	72.82 ± 20.73	
Exchange transfusion			0.0019
Not done	32	87.41 ± 09.23	
Done	13	68.46 ± 16.91	
Day of presentation			0.0001
1 – 2	10	67.10 ± 17.24	
3 – 4	29	84.52 ± 10.26	
5 – 7	6	94.17 ± 09.73	

- Kruskal-Wallis test (Nonparametric ANOVA) was performed instead of one-way ANOVA as there were significant differences among the SDs
† Mann-Whitney test was performed as one column failed the normality test with P < 0.05

Table 2: Logistic regression analysis of the probable predictors of abnormal developmental quotient

Factor	P value	Adjusted Odds ratio	95% Confidence interval	
			Lower	Upper
PSB	0.037	5.038	1.838	30.279
Rh incompatibility	0.025	5.417	1.527	55.675
Exchange transfusion	0.121	2.902	658	16.539
Jaundice within first 2 days of life	0.033	2.219	1.951	5.181

Discussion

Studies have identified that severe jaundice with bilirubin levels of more than 15 mg % can be associated with neurodevelopmental delay [4]. A cut of value of 15 mg/dl was chosen in this study to exclude physiological jaun-dice in term newborns and to include the potentially ‘at risk’ newborns with higher peak serum bilirubin levels.

In our study, peak serum bilirubin was found to signifi-cantly influence the development quotient of the babies with jaundice. The presence of mild hyperbilirubinemia (PSB 15-20 mg/dl) did not significantly reduce the devel-opment quotient. However, moderate hyperbilirubinemia with PSB 21-25 mg/dl and severe jaundice with PSB > 25 mg/dl significantly reduced the development quotient and were associated with a mean development quotient of about 78 and 72 respectively. Therefore, the PSB can be used as a prognostic marker in neonatal jaundice. In a similar study PSBconcentration during the first 2 weeks of life directly correlated with Neurodevelopmental im-pairment [5].

We also observed that the babies for whom exchange transfusion was done showed a significant reduction in development quotient with a mean value of 68. However, logistic regression analysis did not show exchange trans-fusion as an independent predictor of abnormal develop-mental quotient. Exchange transfusion is normally per-formed only for the babies with high levels of bilirubin [6]. Therefore, the reduction in development quotient of the babies in whom exchange transfusion was done could be indirectly due to the high level of bilirubin, rather than the direct effect of exchange transfusion. Rh incompatibility was significantly associated with a reduction in development quotient of the babies. Neonatal jaundice is usually caused by retention of unconjugated bilirubin during the normal, transient postnatal imbalance between unconjugated bilirubin production and elimina-tion [7]. In babies with Rh incompatibility, the excessive hemolysis results in enormous production of unconju-gated bilirubin which can not be effectively conjugated in the liver. This excess bilirubin, which remains unbound to albumin, is later taken up by the lipid cells in the brain with serious consequences [7]. Severity of neonatal jaun-dice and neurotoxicity is comparatively higher in Rh in-compatibility than ABO incompatibility [8]. The babies who presented with jaundice within 2 days showed a sig-nificant reduction in the development quotient compared to those who presented later, suggesting that the progno-sis of babies with early occurrence of jaundice is rela-tively poor.

Conclusion

Peak serum bilirubin > 25 mg/dl, need for exchange trans-fusion, Rh incompatibility and onset of jaundice within 2 days of birth are independent predictors of abnormal neu-rodevelopment at 6 months. These factors can be used as prognostic markers in predicting the neurological out-come of babies with neonatal jaundice.

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