RESEARCH ARTICLE

Correlation Between Peak Serum Bilirubin During 1st Week of Life and Future Neurodevelopmental Outcome in Healthy Term Babies

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Abstract

Study was done to look for the future neurodevelopmental outcome of the babies with extremely high serum bilirubin level at 1st week of life. Fifty-one term and near term babies were enrolled with features of acute bilirubin encephalopathy (ABE), with bilirubin level more than20 mg/dL. They were followed up at 3rd and 6th month to observe their neurodevelopment. Neurological outcome was measured with Denver Development Screening Test (DDST-II) and brainstem evoked response audiometry (BERA). The mean peak total serum bilirubin (TSB) was 25.3 ± 2.35(mg/dL). Abnormal developmental was found in 23.5% babies (12 out of 51) and abnormalities were more in the babies whose TSB was beyond 28 mg/dL. Abnormal BERA was found among 13.7% babies. TSB value below 25 mg/dL can be considered as safe cut off value for reversibility of bilirubin induced acute brain damage.

Keywords: Hyperbilirubinemia, Neurodevelopmental, Peak Serum Bilirubin.

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Introduction

Neonatal jaundice is commonly observed in first week of life and it occurs approximately in 60% of term babies and 80% of preterm babies.[1] They are mostly physiological and does not cause brain damage. But sometimes it crosses the critical level, causing bilirubin induced neurological dysfunction (BIND)[2] (Kumar M *et al*., 2015). The development of acute bilirubin encephalopathy (ABE) is currently indicating that if serum unconjugated bilirubin level becomes more than the bilirubin binding capacity of albumin, it will cross blood-brain barrier due to its lipophilic nature.[3-5] The level of serum albumin and bilirubin conjugating capacity are relatively constant. So, the level of unbound (with albumin) bilirubin is directly proportional to the total serum bilirubin (TSB) level.[6] Thus, total serum bilirubin (TSB) levels have been used in the management guidelines of the neonates with hyperbilirubinemia to define critical values for intervention such as phototherapy and exchange blood transfusion (ET).[7] But reversibility of brain damage due to ABE is matter of concern even after successful therapy option like ET. As per American Academy of Paediatrics (AAP) guideline, the preponderance of kernicterus cases occurred in infants with a bilirubin level higher than 20 mg/dL.[9]

This study was done to observe the future neuro-developmental outcome of those babies who had very high level of bilirubin (>20 mg/dL) on 1st week of life with features of acute bilirubin encephalopathy.

Methods

The present study was conducted over a period of 1 year during 2015-2016 at a tertiary teaching hospital of eastern India. Term and near-Term neonates presenting with severe hyperbilirubinemia with signs of bilirubin induced acute brain damage were enrolled in this study. Neonates with co morbidities like perinatal asphyxia, IUGR, sepsis, major congenital anomalies and meningitis were excluded from our study as they may have contributory effect on neurodevelopmental sequelae. This study was approved by the Institutional Ethical Committee of Dr. B.C. Roy Post Graduate Institute of Paediatric Sciences, Kolkata. Baseline characteristics of neonates like weight, sex, gestational age and anthropometry were recorded.

Investigations including total and indirect bilirubin concentration, haemoglobin levels, peripheral smear, blood counts, blood grouping and coomb's test, serum albumin level, TSH, G6PD tests were done for the cases. The highest value of total serum bilirubin was considered as peak serum bilirubin for that case. Sepsis screen and blood culture were done in suspected cases of sepsis. According to AAP

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guidelines, the neonates, who satisfy the necessary criteria, were undergone double volume exchange transfusion to prevent future brain damage. These patients were followed up, at age of 3 month and 6 month respectively, at high risk clinic of our hospital to assess neurological outcome with the help of 1) Denver Developmental Screening test (DDST-II) with four different domains namely gross motor, fine motor/ adaptive, personal social and language. 2) BERA was done at 3 month.

Results

Out of 59 cases, 2 babies died and 6 babies lost follow-up and thus analysis was done on 51 babies. The demographical characteristics were given on Table 1. Mean age of admission was 4.7 days, while median age of exchange transfusion was 5 days. Mean peak TSB was 25.4 mg/dL and mean peak indirect serum bilirubin (ISB) was 23.17 mg/dL (Table 2). 45 babies were in the group of ABE stage-1, 4 babies were in stage-2, 2 babies were in stage-3 (Table 3). Majority of the cases of hyperbilirubinemia was idiopathic. Definite etiological causes found as follows; ABO incompatibilities (14 babies, 27.45%), Rh incompatibility among 3 babies, and G6PD deficient in 3 babies.

Results of gross motor and fine motor milestones were found similar at both 3 month and 6 months of age. Twelve babies showed abnormal result (23.53%) for both the milestones. In language domain of DDST-II, ten babies (19.60%) were in abnormal zone while only eight were abnormal (15.68 %) for social domain. Overall analysis showed that twelve babies were abnormal for DDST milestones at six months.

Among the babies showing abnormal result for gross and fine motor development (12 out of 51 babies) seven were in stage-1 ABE (acute bilirubin encephalopathy), 3 were in stage-2, two babies were in stage-3 of ABE (Fig. 1). The mean peak TSB level among them was 28.1 ± 2.70 (Table 4).

In language domain, 10 babies had shown abnormal findings. Among them, 6 babies were in stage 1, 2 babies were in stage 2 and 2 babies were in stage 3 of ABE (Fig. 2). Mean peak TSB was 28.3 ± 2.58 (Table 5).

8 babies showed personal social developmental delay. Among them, 5 babies were in stage-1, 1 baby was in stage-2, 2 babies were in stage-3 (Fig. 3). Mean peak TSB was 28.1 ± 2.47 (Table 6)

Abnormal BERA was found among seven babies out of 51 samples. (Fig. 4).

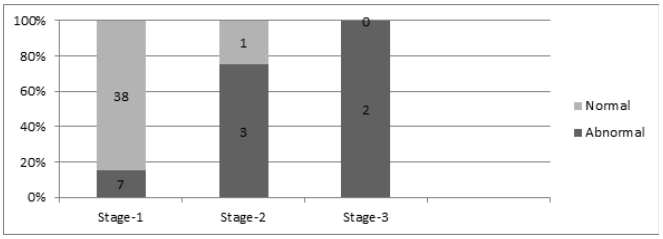

Fig. 1: Association of gross and fine motor developmental milestones with ABE Staging.

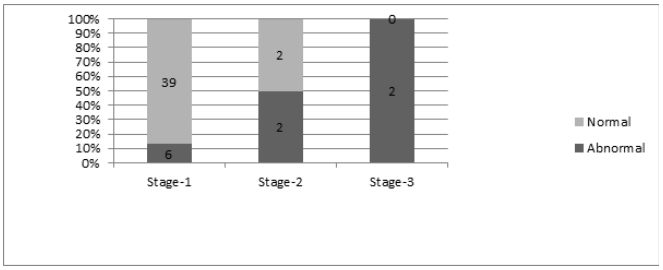

Fig. 2: Association of language developmental milestones with ABE Staging

Table 1: Demographic characteristics of studied Subjects:

S. N.	*Variables*	*n= 51*
1.	Male/ Female	34/17
2.	Gestational ages (weeks)	37.5 ± 0.84
3.	Weight at admission (kg)	2.6 ± 0.37
4.	Age at exchange transfusion (days)	4.8 ± 0.95
5.	Albumin level (mg/dL)	3.8 ± 0.39

Table 2: Peak serum bilirubin levels of studied subjects:

S. N.	*Variables*	*n=51*
1.	Mean peak TSB (total serum bilirubin)	25.4 ± 2.61
2.	Mean peak DSB (Direct)	1.92 ± 0.52
3.	Mean peak ISB (Indirect)	23.17 ± 2.91

Table 3: Distribution of babies with acute bilirubin encephalopathy of different stages [10]

ABE stages	*Frequency (percent)*
1	45 (88.23%)
2	4 (7.84%)
3	2 (3.92%)

Table 4: Correlation of peak TSB with gross motor & fine motor developmental milestones

	Abnormal	*Normal*
Number of Babies	12	39
Peak TSB (mg/dL) Mean ± sd	28.1 ± 2.70	25.3 ± 2.35

p Value <0.01

Table 5: Correlation of language milestones with peak TSB

	Abnormal	*Normal*
Number of baby	10	41
Peak TSB (mg/dL) Mean ± sd	28.3 ± 2.58	25.1 ± 2.35

p-value <0.01

Table 6: Correlation of TSB with personal social developmental milestones

	Abnormal	*Normal*
Number of baby	8	43
Peak TSB (mg/dL) Mean ± sd	28.1 ± 2.47	25.5 ± 2.31

p Value <0.01

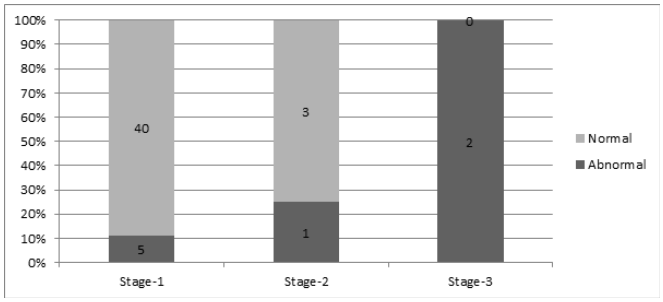

Fig. 3: Association of personal social developmental milestones with ABE Staging

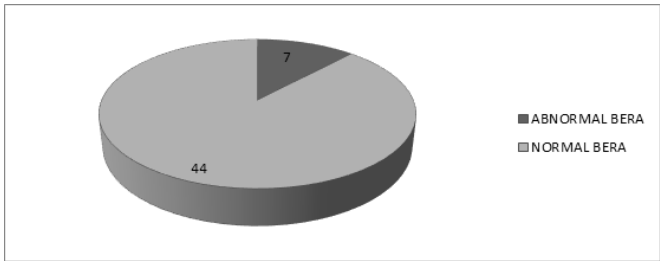

Fig. 4: BERA result of all the babies

Discussion

Our research objective was to determine the future outcome in terms of neurological sequelae with severe hyperbilirubinemia. Similar study by Mukhopadhyay *et al*. (2010) showed 89% poor neurodevelopmental outcome in advanced stages of acute bilirubin encephalopathy even after effective intervention.[9] In another study by Mala Kumar *et al* (2015) found 89% abnormal developmental outcome at 6 months of age.[2] Contrast to Mukhopadhyay *et al*.[9] & Kumar *et al*.[2] in respect of poor long-term outcome, our disability rate was only 23.53%. This variation is probably because; they registered the babies having very high TSB level (mean TSB 36.9 ± 9.2) which caused severe damage**,** missing the scope of beneficial effect by exchange transfusion. Where lies the question of safe cut off value to prevent BIND out of high serum bilirubin level. Thus, previous author (Mukhopadhyay *et al*., 2010) rightly remarked "a safe cut off value of TSB to predict bilirubin encephalopathy remains unknown".[9]

Thus, an effort was taken to prepare an acceptable cut off, where preventive exchange will be beneficial, so that it can be done with top priority using the golden window of opportunity to prevent long term abnormal neurodevelopmental outcome.

To summarise the results of Table no 4 to 6, the mean peak TSB value shows the abnormal development (DDST) tends to correspond with the value of TSB 28 ± 2.5 (mg/dL) and mean peak TSB value with normal outcome tends to correspond with the value of TSB 25 ± 2 (mg/dL).

As per the results, peak TSB of 23–27 mg/dL at 1st week of life having enough chance of reversibility of brain damage while ≥ 28 mg/dL is predictive of long term sequelae in all the domains of developmental milestones.

In the study, we found 7 out of 51 babies (13.72%) showing abnormal BERA (predictor of future sensory neuronal hearing loss). Mukhopadhyay *et al* found 19 out of 22 (76%) babies as abnormal BERA finding, probably because of huge number of late stage with high bilirubin value in their study population.[9]

In their BIND study Jhonson *et al*[11] shows that quick intervention at earliest may prevent the neurological sequale**.** American Academy of Paediatrics (AAP) as well as Agency for Healthcare Research and Quality (AHRQ) review guidelines also recommends that emergent transfusion in acute bilirubin encephalopathy. According to our result, a cut off of 25 mg/dL warrants an urgent intervention to prevent BIND.

At 6th month, majority (75%) of the babies with stage I ABE came out of bilirubin indeed acute brain damage of 1st week of life, while majority (75%) of babies with stage II to III ABE leads to abnormal development.

The limitation of our study is that the babies could have been followed beyond 6 months of age with more accurate long term outcome.

Conclusion

In conclusion, Total Serum Bilirubin (TSB) level below 25 mg/dL can be considered as cut off value for reversibility of acute brain damage and one should not miss the opportunity to intervene. Outcome seems to be poor, if TSB value crosses 28 mg/dL and advanced stage of ABE (stage II & III) appears.

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