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AUDITORY BRAINSTEM RESPONSE ALTERATIONS IN NEONATAL HYPERBILIRUBINEMIA: AN EARLY MARKER OF NEUROTOXICITY.

Paediatrics

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ABSTRACT

INTRODUCTION- Bilirubin toxicity remains one of the major challenges in neonatal care in spite of advancement in jaundice treatment. Neonatal jaundice is one of the causes of early sensorineural hearing loss (SNHL) in developing countries, and increased blood indirect bilirubin can cross the blood-brain barrier and deposit in the auditory ventricular nucleus cells. Screening for hearing impairment in neonatal period pivotal for timely detection and appropriate treatment. The auditory brainstem response (ABR) is another test used to detect hearing loss and neural type in particular, and has the efficiency and sensitivity required for infants with hyperbilirubinemia. **METHOD-** It was an institution based descriptive observational study was conducted with prospective study design. The study was conducted at Sick newborn care unit (SNCU) in Bankura Sammilani Medical College and hospital with a timeframe of about one year. The statistical analysis was carried out using standard statistical software (SPSS 25 version). **RESULT-**Our study result showed preterm birth, low birth weight, ABO/Rh incompatibility, G6PD deficiency, exchange transfusion, and higher bilirubin levels were significantly associated with abnormal ABR, whereas age, sex, neonatal sepsis, and duration of phototherapy were not. **CONCLUSION**-Using of Otoacoustic Emission (OAE) test alone in screening programs for high-risk neonates, before discharge from the hospital, is inadequate. BERA wave changes have been associated with hyperbilirubinemia in newborn, BERA monitoring of jaundiced infants may be an important clinical tool for detecting early reversible bilirubin injury and decreases neonatal mortality and morbidity.

KEYWORDS

Auditory Brainstem Response (abr), Hyperbilirubinemia, Otoacoustic Emission (oae), Sensorineural Hearing Loss (snhl).

INTROUCTION-

Neonatal hyperbilirubinemia is one of the most common clinical conditions encountered in the early neonatal period [1,2]. While most cases are benign and self-limiting, excessive unconjugated bilirubin can cross the immature blood–brain barrier and exert neurotoxic effects on the central nervous system. The auditory pathway, particularly the brainstem nuclei, is highly sensitive to bilirubin toxicity, often being affected even before the appearance of overt clinical signs of encephalopathy[3,4,5]. It has been reported that bilirubin levels higher than 20 mg/dl in the newborn period are associated with hearing loss in children under 2.5 years old [6]. Screening for hearing impairment in neonatal period is pivotal for timely detection and appropriate treatment.

The otoacoustic emission (OAE) test is one of the routines after-birth screening procedures for risk-factor-free infants [5,6]. The auditory brainstem response (ABR) is another test used to detect hearing loss and neural type in particular[4], and has the efficiency and sensitivity required for infants with hyperbilirubinemia [7,8]. Subclinical alterations in ABR waveforms—such as prolonged latencies and interpeak intervals—have been reported in neonates with hyperbilirubinemia, suggesting early involvement of neural pathways [7,8].

Early identification of bilirubin-induced neurotoxicity is crucial, as timely intervention can prevent irreversible neurological damage, including kernicterus and long-term auditory deficits. In this context, ABR may serve as a valuable early marker for detecting subtle neurophysiological changes before clinical manifestations become apparent.

This study aims to evaluate ABR alterations in neonates with hyperbilirubinemia and to assess its role as an early indicator of bilirubin-induced neurotoxicity.

METHODS-

STUDY DESIGN AND PERIOD

This is an observational study with prospective study design, was conducted on 108 neonates with hyperbilirubinemia in the SNCU of the Department of Paediatrics, Bankura Sammilani Medical College, from November 2022 through to December 2023.

STUDY METHOD-

The study population were all the admitted neonates with hyperbilirubinemia in SNCU and follow up infants in ENT OPD for BERA screening, satisfying all inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

All the neonates having jaundice with serum bilirubin level>15mg/dl admitted in SNCU.

Exclusion criteria:

1. Babies whose parents are not giving consent for this study.
2. Babies who did not survive the maximal screening period of ABR.
3. Babies with severe congenital anomalies.

Execution of study:

Before starting examination of infants informed consent in written format were taken from their parents after properly explaining the study procedure.

Complete physical examination of infants as well as medical history, age, gender, birth weight, gestational age, and Apgar score were recorded, together with the mother's age and blood type. In addition, the infant's bilirubin, hematocrit, direct Coombs levels, reticulocytes count, glucose-6-phosphate dehydrogenase (G6PD) enzyme levels, and both the mother's and infant's blood type and complete blood cell count were determined.

Hearing assessment: The hearing status of the neonates was investigated using the ABR method after discharge, at 3 months of age. ABR is a non-invasive method for early detection of impaired hearing pathways. ABR test impairment is usually transient in most patients and improves with rapid and effective treatment.

Statistical analysis:

Data was analyze using chi square and p value of less than 0.05 was considered statistically significant.

RESULT –

The present study was conducted to assess the auditory brainstem response in neonatal hyperbilirubinemia among 108 neonates admitted with hyperbilirubinemia in SNCU and during follow up of the infants in ENT OPD for BERA screening during the study period at a tertiary level healthcare facility of West Bengal.

The findings of the study are discussed with tables and its interpretation below.

Table 1: Distribution of study subjects according to Auditory brainstem response (ABR) (n=108)

Auditory brainstem response (ABR)	Number	Percentage (%)
At 3 months		
Normal	100	92.6
Abnormal	8	7.4
At 6 months		
Normal	100	92.6
Abnormal	8	7.4

Table 1 showed that 7.4% of the neonates were having abnormal Auditory brainstem response (ABR) at 3 months and at 6 months the incidence of abnormal Auditory brainstem response was same (7.4%). Only neonatal hyperbilirubinemia does not always cause ear damage and cause abnormal ABR but also many biochemical, physiological and effective and timely treatment of neonatal hyperbilirubinemia also determines and aggravate the amount of damage.

Table 2 showed there was no statistically significant association between age at assessment (1–5 days vs 6–10 days) and ABR outcome (χ^2 = 0.21, p = 0.65). The odds of abnormal ABR among infants assessed at 1–5 days compared to 6–10 days was not significant (OR = 0.61; 95% CI: 0.07–5.14).

Sex was also not significantly associated with ABR abnormality, although a higher proportion of abnormal results was noted among males compared to females (11.9% vs 2.0%; χ^2 = 3.76, p = 0.052). The odds of abnormal ABR were higher in males compared to females, but this did not show statistical significance (OR = 6.46; 95% CI: 0.76–54.7).

Table 2: Distribution and association of ABR at 3 months by background variables (n=108).

Background variables	ABR at 3 months		Total n (row %)	p value
	Normal	Abnormal		
Age (days)				
1-5	81 (92)	7 (8)	88 (100)	0.649(>0.05)
6-10	19 (95)	1 (5)	20 (100)	
Sex				
Female	48 (98)	1 (2)	49 (100)	0.052(>0.05)
Male	52 (88.1)	7 (11.9)	59 (100)	
Gestational age				
Term	70 (97.2)	2 (2.8)	72 (100)	0.009(<0.05)
Pre-term	30 (83.3)	6 (16.7)	36 (100)	
Birth weight				
Normal	70 (98.6)	1 (1.4)	71 (100)	0.001(<0.05)
Low	30 (81.1)	7 (11.9)	37 (100)	

In contrast, gestational age showed a statistically significant association with ABR outcome. Preterm infants had a significantly higher proportion of abnormal ABR compared to term infants (16.7% vs 2.8%; χ^2 = 6.24, p = 0.012). The odds of abnormal ABR in preterm infants were significantly higher than in term infants (OR = 7.00; 95% CI: 1.33–36.7).

Birth weight was also significantly associated with ABR results, with low-birth-weight infants demonstrating a markedly higher frequency of abnormal ABR compared to those with normal birth weight (11.9% vs 1.4%; χ^2 = 10.07, p = 0.0015). Low birth weight infants had significantly increased odds of abnormal ABR (OR = 16.33; 95% CI: 1.93–137.9).

Table 3 showed Neonatal sepsis was not significantly associated with abnormal ABR (14.3% vs 6.9%; χ^2 = 0.52, p = 0.47), with an odds ratio of 2.24 (95% CI: 0.24–20.8).

In contrast, ABO incompatibility showed a strong association with abnormal ABR, with all affected infants demonstrating abnormal outcomes (100% vs 5.7%; χ^2 = 10.5, p = 0.001). The odds of abnormal ABR were markedly increased (OR = 83.7; 95% CI: 3.0–2300).

Similarly, Rh incompatibility was significantly associated with abnormal ABR (χ^2 = 10.5, p = 0.001), with a comparable increase in risk (OR = 83.7; 95% CI: 3.0–2300).

Table 3: Distribution and association of ABR at 3 months by clinical profile (n=108)

Clinical profile	ABR at 3 months		Total n (row %)	p value
	Normal	Abnormal		
Neonatal sepsis				
No	94 (93.1)	7 (6.9)	101 (100)	0.472(>0.05)
Yes	6 (85.7)	1 (14.3)	7 (100)	
ABO incompatibility				
No	100 (94.3)	6 (5.7)	106 (100)	
Yes	-	2 (100)	2 (100)	
Rh incompatibility				0.001(<0.05)
No	100 (94.3)	6 (5.7)	106 (100)	
Yes	-	2 (100)	2 (100)	
G6PD deficiency				0.006(<0.05)
No	100 (97.2)	7 (2.8)	107 (100)	
Yes	-	1 (100)	1 (100)	
Exchange				0.001(<0.05)
No	99 (96.1)	4 (3.9)	103 (100)	
Yes	1 (20)	4 (80)	5 (100)	

G6PD deficiency also demonstrated a significant association, with all affected infants showing abnormal ABR (χ^2 = 7.6, p = 0.006). The odds ratio was 39.3 (95% CI: 1.5–>1000), indicating a markedly increased risk.

Exchange transfusion showed the strongest association with abnormal ABR (80% vs 3.9%; χ^2 = 24.1, p < 0.001), with infants requiring exchange transfusion having substantially higher odds of abnormal ABR (OR = 99; 95% CI: 8.5–1150).

Table 4 showed the independent samples t-test demonstrated a statistically significant association between serum bilirubin levels and abnormal ABR outcomes at 3 months (p = 0.001), indicating that higher peak bilirubin is a strong predictor of auditory pathway dysfunction. However, duration of phototherapy was not significantly associated with ABR abnormalities (p = 0.981), suggesting that treatment duration alone does not reflect neurodevelopmental risk.

Table 4: Distribution and association of ABR at 3 months by bilirubin level and duration of phototherapy (n=108).

Clinical profile	ABR at 3 months		p value
	Normal Mean (SD)	Abnormal Mean (SD)	
Bilirubin level	17.20 (1.16)	23.87 (3.22)	0.001(<0.05)
Duration of phototherapy	2.11 (0.58)	2.50 (1.69)	0.981(>0.05)

Table 5: Distribution and association of ABR at 3 months by OAE (n=108)

Clinical profile	ABR at 3 months		Total n (row %)	p value
	Normal	Abnormal		
OAE				0.001
Fail	-	5 (6.9)	5 (100)	
Pass	100 (97.1)	3 (2.9)	103 (100)	

Table 5 showed the distribution and association between OAE results and ABR findings at 3 months among neonates. All neonates who failed OAE screening (100%) were found to have abnormal ABR. In contrast, among those who passed OAE, only 2.9% exhibited abnormal ABR findings, while 97.1% had normal ABR. Statistical analysis using the chi-square test revealed a highly significant association between OAE and ABR outcomes (χ^2 = 65.56, p < 0.001). This indicates that failure on OAE screening is strongly predictive of abnormal ABR at 3 months.

DISCUSSION:

The present study examined auditory brainstem response (ABR) outcomes among neonates with hyperbilirubinemia and investigated various perinatal and biochemical factors influencing auditory dysfunction. At 3 and 6 months of age, 7.4% of neonates demonstrated abnormal ABR findings, indicating that a subset of infants exposed to hyperbilirubinemia may experience persistent auditory pathway

abnormalities despite treatment. This finding supports previous research suggesting that bilirubin-induced neurotoxicity may selectively affect the auditory pathway and result in long-term auditory dysfunction even in the absence of overt kernicterus.

Although neonatal hyperbilirubinemia is a known risk factor for auditory neuropathy, the current results emphasize that bilirubin alone does not fully determine auditory outcome. The extent of ABR abnormality appears to depend on a combination of biochemical factors, physiological vulnerability, and the timeliness and effectiveness of treatment.

Age at assessment (1–5 days vs. 6–10 days) did not significantly influence ABR outcomes, suggesting that the critical period for bilirubin neurotoxicity may not be limited to the first week of life, provided that appropriate management is instituted. Similarly, no statistically significant difference was observed between sexes, although males had a numerically higher incidence of abnormal ABR, aligning with reports that male neonates may have slightly greater susceptibility to neonatal complications due to differences in hormonal and developmental factors.

In contrast, gestational age and birth weight were significantly associated with ABR abnormalities. Preterm and low-birth-weight infants demonstrated higher rates of auditory dysfunction than their term and normal-weight counterparts. This observation is consistent with earlier studies showing that immature neural development, poor bilirubin conjugation, and compromised antioxidant defences increase the vulnerability of preterm infants to bilirubin-induced neuronal injury.

Several etiological factors related to haemolysis—including ABO incompatibility, Rh incompatibility, and G6PD deficiency—showed strong associations with abnormal ABR. In all these conditions, the incidence of auditory dysfunction was markedly elevated, with odds ratios indicating significantly increased risk. These findings suggest that haemolytic disorders contribute substantially to bilirubin neurotoxicity, likely due to rapid bilirubin production and sudden increases in unbound bilirubin fractions capable of crossing the blood-brain barrier.

Among treatment-related factors, exchange transfusion was found to be a major predictor of abnormal ABR. Infants who required exchange transfusion demonstrated the highest risk for auditory abnormalities, implying that these cases often represent severe hyperbilirubinemia with greater potential for neural injury. Conversely, the duration of phototherapy showed no significant association with ABR outcome, indicating that treatment duration alone may not reflect disease severity or predict long-term auditory sequelae.

Biochemical correlation revealed that higher peak total serum bilirubin was significantly associated with abnormal ABR, reinforcing the role of elevated bilirubin as a direct neurotoxic agent affecting the auditory brainstem pathways. This aligns with existing evidence suggesting that bilirubin-induced neurotoxicity preferentially affects auditory nuclei before other brain regions.

A strong relationship was also noted between the Otoacoustic Emission (OAE) and ABR findings. All neonates who failed OAE screening demonstrated abnormal ABR, while those who passed OAE had predominantly normal ABR outcomes. This robust concordance ($\chi^2 = 65.56$, $p < 0.001$) indicates that OAE screening can serve as an effective early diagnostic tool for identifying infants at risk of auditory pathway dysfunction following hyperbilirubinemia.

CONCLUSION:

This study highlights that auditory dysfunction, as detected by ABR, persists in a notable proportion of neonates with hyperbilirubinemia despite clinical recovery. The risk of abnormal ABR is significantly higher among preterm and low-birth-weight infants, as well as those with haemolytic disorders such as ABO incompatibility, Rh incompatibility, and G6PD deficiency. Elevated peak bilirubin levels and the need for exchange transfusion were strong predictors of auditory abnormalities, underscoring the necessity for vigilant monitoring of bilirubin levels and timely intervention.

Early OAE screening proved to be a valuable predictor of abnormal ABR outcomes, supporting its integration into neonatal follow-up protocols to detect subclinical auditory damage. Timely and aggressive management of hyperbilirubinemia, alongside targeted follow-up of high-risk infants, is essential for preventing long-term hearing impairment and optimizing neurodevelopmental outcomes.

All the neonates who failed in OAE were having abnormal ABR, whereas, 2.9% of the neonates were found to be abnormal while they passed on OAE. Thus using the Oto-acoustic Emission (OAE) test alone in screening programs for high-risk neonates, before discharge from the hospital, is obviously inadequate. Since BERA wave changes have been associated with hyperbilirubinemia in newborn, BERA monitoring of jaundiced infants may be an important clinical tool for detecting early reversible bilirubin injury Future research should focus on longitudinal follow-up to determine the reversibility of ABR abnormalities and their impact on language and cognitive development. Moreover, integrating electrophysiological screening with newer biomarkers could enhance early detection of bilirubin-induced auditory injury.

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