Brainstem Evoked Response Audiometry (BERA) in Neonates with Hyperbilirubinemia

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Abstract (1) To study the BERA changes in neonates with unconjugated hyperbilirubinemia. (2) To compare the BERA changes in the neonates with unconjugated hyperbilirubinemia before and after therapy. Thirty consecutive term appropriate for gestational age (AGA) neonates presenting to NICU with total serum bilirubin requiring intervention (using the American Academy of Pediatrics guidelines) were included in the study as cases and thirty normal term AGA neonates with uneventful peri-natal period and a maximum measured serum bilirubin <12 mg/dl in case of term baby were included as controls after obtaining informed consent. Initial BERA was done within 3–24 h of hospitalization after obtaining informed consent from parents, at the time of discharge and at 3 month followup. Machine used for recording BERA was intelligent hearing system version 3.3. In our study out of the 30 cases 10 (33.3 %) cases were found to have BERA changes in the form of absent wave forms, raised threshold, prolonged latencies or prolonged inter peak latencies. In our study, it was observed that there was statistically significant correlation (p value < 0.005) between increasing bilirubin level and BERA changes. Correlation of the findings of this study with previous few studies indicates that BERA can be used as a useful non invasive tool to determine auditory functions in the neonate especially changes of early bilirubin toxicity.

Keywords Brainstem evoked response audiometry (BERA) · Bilirubin toxicity · Auditory functions · Neonatal hyperbilirubinemia

Introduction

Neonatal jaundice is a common problem seen in the newborn. It is observed during the first week of life in approximately 60 % of term and 80 % of preterm [1, 2].

Bilirubin in healthy term neonates especially free bilirubin (Bf) could enter brain cells and cause damage which is perceived by brainstem evoked response audiometry (BERA). Studies identify that Bf is more associated to abnormal BERA.

Early detection and rehabilitation of a hearing loss is important for the development of speech and language skills in hearing impaired children [3].

BERA is an effective and non-invasive means of assessing the functional status of the auditory nerve and brainstem auditory sensory pathway. It is not significantly altered by the state of consciousness, drugs and variety of environmental factors [4].

The BERA changes in response to hyperbilirubinemia include loss of one or more peaks of waves I–V, raised threshold, increase in latency of waves I, III or V or increased inter peak interval [4].

It is worth mentioning that BERA can detect subclinical bilirubin encephalopathy even before the appearance of any signs or symptoms of kernicterus.

The present study was undertaken to evaluate the effect of hyperbilirubinemia in term newborns on BERA and change, if any, in BERA after therapy.

The acute changes seen in BERA can be reversed by early bilirubin lowering interventions, thereby explaining

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the transient nature of bilirubin encephalopathy. But persistent elevation of bilirubin can cause neuronal degeneration and thereby persistent changes on BERA.

Some studies have found correlation between the bilirubin level and BERA changes, whereas some have disproved it.

Thus serial BERA can be used as a tool to detect neuro developmental delay secondary to neonatal hyperbilirubinemia.

Neural Generators of the BERA [5]

BERA is generated by the auditory nerve and subsequent structures within the auditory brainstem pathways. Information regarding the origin of individual wave components of BERA was provided by Moller and Janetta.

Wave I It is the representation from the compound action potential in the distal portion of cranial nerve VIII. The response is believed to originate from afferent activity of cranial nerve VIII fibres as they leave cochlea and enter the internal auditory canal.

Wave II It is generated by the proximal VIII nerve as it enters the brainstem.

Wave III Generated mainly in the cochlear nucleus (second order neuron).

Wave IV It arises from pontine third order neuron. Mostly located in superior olivary nucleus, but additional contributions may come from cochlear nucleus and nucleus of lateral lemniscus.

Wave V Generation of wave V reflects activity of multiple anatomic auditory structures. Sharp positive peak of wave V arises mainly from the lateral lemniscus, following slow negative wave represents dendritic potential in the inferior colliculus.

Wave V is the component analysed most often in the clinical application of the BERA.

Wave VI and VII These waves appear to be generated in the inferior colliculus, perhaps in the medial geniculate body.

Materials and Methods

Methodology

This study was conducted in the Department of ENT and PEDIATRICS. The study period was between December 2011–October 2013 after approval from institutional ethical committee and informed consent from guardians.

Inclusion Criteria

Thirty consecutive term appropriate for gestational age (AGA) neonates presenting to the NICU of GSVM

Hospital, with total serum bilirubin requiring intervention (using the American Academy of Pediatrics guidelines) [2] were included in the study as cases and thirty normal term AGA neonates with uneventful peri-natal period and a maximum measured serum bilirubin <12 mg/dl in case of term baby were included as controls after obtaining informed consent.

Exclusion Criteria

- Neonates born with birth asphyxia with poor APGAR score
- Intrauterine infections
- Sepsis
- Meningitis/encephalitis
- Drug like amino glycoside administration
- Craniofacial malformation
- Conjugated hyperbilirubinemia
- External and middle ear pathology
- Kernicterus

Mode of Collection of Data

All neonates presenting with icterus to the NICU of Hospital were subjected to total bilirubin estimation. Patient was subjected to ENT and pediatric examination prior to test. If the neonate was awake, it was sedated by 20 mg/kg of triclofos orally.

Preparation of Patient

Skin was prepared with abrasive skin preparatory paste, which is chloride and acetone free, electrolyte gel was applied which is non staining, non irritant to skin.

Electrode Placement

Silver electrode were used and applied in following fashion according to double channel using four electrode montage system.

Vertex—+ve
Left mastoid—-ve
Right mastoid—-ve
Forehead—neutral

Machine Setting

Click acoustic stimuli with a click rate of 20–40/s, rarefaction in polarity was presented by insert ear phone to each ear at an intensity from 90 to 30 dBnHL. Time window was 15 ms; with a filter setting of 30–3,000 Hz. The

Table 1 Distribution of cases in different bilirubin range

Maximum measured bilirubin in mg/dl		Case (n = 30)
Group I	15–20	20 (66.6 %)
Group II	20–25	5 (16.6 %)
Group III	25–30	5 (16.6 %)

presence of wave V at the Intensity of 30 dBnHL was taken as the normal threshold.

BERA measures considered for diagnosis were

- Loss of one or more peaks of I–V at 90 dBnHL
- Raised threshold
- Absolute latencies of wave I, III, V peaks

- Inter peak intervals of I–III, III–V and I–V

Neonates were treated for hyperbilirubinemia according to the standard treatment protocol (using the American Academy of Paediatrics guidelines) [2]. Repeat BERA was done in all cases after therapy at the time of discharge and after a follow-up period of 3 months.

The mean age of babies among the cases was 8 days and among the controls was 7 days in our study (Tables 1, 2).

Latency of different waves and intervals decreased (returned towards normal) after therapy. When serum bilirubin levels came down, the abnormalities on initial BAER reverted back to normal in most cases. p value was significant for wave I, III, V and interpeak latency I–III and

Table 2 Number of cases with different BERA changes at peak levels of bilirubin

BERA changes	Cases		
	Group I	Group II	Group III
Absent wave forms	0 (0 %)	0 (0 %)	4 (13.3 %)
Raised threshold	1 (3.33 %)	4 (13.3 %)	5 (16.6 %)
Prolonged latencies I	0 (0 %)	1 (3.33 %)	2 (6.66 %)
Prolonged latencies III	0 (0 %)	1 (3.33 %)	3 (10 %)
Prolonged latencies V	0 (0 %)	2 (6.66 %)	2 (6.66 %)
Prolonged inter peak interval I–III	1 (3.33 %)	2 (6.66 %)	3 (10 %)
Prolonged inter peak interval III–V	0 (0 %)	0 (0 %)	0 (0 %)
Prolonged inter peak Interval I–V	0 (0 %)	1 (3.33 %)	3 (3.33 %)

Table 3 Comparison of latencies of I, III, V & inter peak latencies of cases at peak level of bilirubin, at the time of discharge and follow-up at 90 Dbnhl

Waves	At peak level (A) in msc mean $\pm$ S.D.	At discharge (B) in msc mean $\pm$ S.D.	At followup (C) in msc mean $\pm$ S.D.	p value A versus B	p value B versus C	p value A versus C
I	2.06 $\pm$ 0.29	1.76 $\pm$ 0.01	1.58 $\pm$ 0.01	0.0001	0.0001	0.0001
III	4.55 $\pm$ 0.35	4.41 $\pm$ 0.20	4.16 $\pm$ 0.27	0.08	0.26	0.0001
V	6.79 $\pm$ 0.36	6.66 $\pm$ 0.29	6.34 $\pm$ 0.22	0.12	0.0001	0.0001
I–III	2.48 $\pm$ 0.31	2.65 $\pm$ 0.20	2.60 $\pm$ 0.35	0.011	0.09	0.16
III–V	2.23 $\pm$ 0.27	2.24 $\pm$ 0.18	2.18 $\pm$ 0.05	0.98	0.19	0.33
I–V	4.71 $\pm$ 0.37	4.89 $\pm$ 0.29	4.76 $\pm$ 0.22	0.05	0.003	0.53

Table 4 Comparison of BERA changes at peak level of bilirubin at the time of discharge and follow-up

BERA changes	At peak level of bilirubin (no. of cases)	At discharge (no. of cases)	At follow up (no. of cases)
Absent wave forms	4 (13.3 %)	3 (10 %)	1 (3.3 %)
Raised threshold	10 (33.3 %)	8 (26.6 %)	1 (3.3 %)
Prolonged latencies I	3 (10 %)	0	0
Prolonged latencies III	4 (13.3 %)	2 (6.6 %)	2 (6.6 %)
Prolonged latencies V	4 (13.3 %)	2 (6.6 %)	2 (6.6 %)
Prolonged interpeak interval I–III	6 (20 %)	1 (3.3 %)	0
Prolonged interpeak interval III–V	0	0	0
Prolonged interpeak interval I–V	4 (13.3 %)	0	0

Table 5 Correlation of bilirubin level with BERA changes

Maximum measured bilirubin in mg/dl	No. of cases	Cases with BERA changes	% of cases showing BERA changes
15–20	20	1	5
20–25	5	4	80
25–30	5	5	100

I–V when latency at peak level was compared with that at discharge and follow-up (Table 3).

Result

In our study out of the 30 cases 10 (33.3 %) cases were found to have BERA changes in the form of absent wave forms, raised threshold, prolonged latencies or prolonged inter peak latencies (Tables 4, 5).

The commonest abnormality observed in our study was raised threshold seen in 10 (33.3 %) cases which was comparable with other studies.

The other commonest abnormalities noted was prolonged latencies (13.3 %) and absent wave forms (13.3 %) which were also comparable with other studies. Prolonged latencies of waves and inter peak interval indicated prolongation of nerve conduction at auditory nerve and brain stem level.

Among the 10 cases with raised threshold it was found that 8 (26.6 %) cases had raised threshold even at discharge but on follow up only 1 (3.3 %) case had persistently raised threshold. Of the 3 cases with prolonged latencies of wave I on follow up all were found to have improved latencies. Of the 4 (13.3 %) cases with prolonged latencies III and V, 2 (6.66 %) had persistent changes at discharge, as well as at follow up whereas in 2 cases it was found that latencies improved. Similarly it was found that of the 6 cases with prolonged I–III and 4 cases with prolonged I–V when followed up all had normal latencies.

All cases were reviewed with a follow up BERA at the time of discharge and after a period of 3 months in our study and in other studies by Sharma et al., Gupta et al. and Agrawal et al. Whereas Deorari et al. followed up the cases till 1 year. Bhandari et al. did not follow up the cases [4, 6–9].

Out of the 10 cases with significant BERA changes, it was found that 8 cases had persisted abnormalities at the time of discharge and 3 cases were found to have persistent abnormalities at the time of follow up after 3 months.

In our study, it was observed that there was statistically significant correlation (p value < 0.005) between increasing bilirubin level and BERA changes.

Conclusion

10 (33.3 %) out of 30 cases in our study had BERA changes. The most common BERA change noted in our

study was raised threshold seen in 10 cases (33.3 %). BERA changes persisted in 8 (26.6 %) cases at the time of discharge of which in 3 (10 %) cases, changes persisted even at follow up after 3 months. The precise blood level above which indirect reacting or free bilirubin will be toxic for an individual infant is unpredictable [10]. In our study, it was found that all the 5 cases with bilirubin >25 mg/dl had BERA changes and out of these 5, 3 cases had persistent BERA changes at follow up thus there was significant correlation between BERA changes and maximum measured bilirubin indicating that higher the level of bilirubin, higher the risk of toxicity to auditory pathway.

However, this study need further validation by conducting it on a large sample size.

Studies by Sharma et al., Agrawal et al., Deorari et al., Gupta et al. [4, 6–8], also found statistically significant correlation of BERA changes with Serum Bilirubin >25 mg. Indicating that higher the level of bilirubin there is increased risk of bilirubin toxicity but with active intervention, it is possible to reverse the changes.

Correlation of the findings of this study with previous few studies indicates that BERA can be used as a useful non invasive tool to determine auditory functions in the neonate especially changes of early bilirubin toxicity.

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