AUDITORY BRAINSTEM RESPONSES IN NEONATAL HYPERBILIRUBINEMIA AND EFFECT OF THERAPY

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Abstract: Objectives; To determine the effect of neonatal hyperbilirubinemia on auditory brainstem responses (ABRs) and evaluate ABR responses to lowering of bilirubin levels. **Study Design:** prospective case control trial **Setting :** tertiary referral center. **Patients :** 60 neonates (40 cases & 20 controls). Term appropriate for date (AFD) neonates with uncomplicated birth history and bilirubin level of ≥ 13 mg/dL were included as cases, those with bilirubin value of < 13 mg/dL were taken as controls. **Interventions;** First BERA examination was carried out within 24 hrs of the diagnosis of hyperbilirubinemia and repeat examination was done when total serum bilirubin came down to < 13 mg/dL with treatment. Comparisons were made between cases (before & after therapy) and control **Results;** No abnormality in neonates with bilirubin < 18 mg/dL. Abnormal ABRs were observed in 24 (60%) of the 40 cases studied, with therapy it reverted back to normal in 15 (62%). The commonest abnormality noted was prolonged latency of wave V (42.5%), followed by prolonged latency of wave III (35%) and wave I (22.5%). Prolonged latency of wave I was found in only those with bilirubin > 20 mg/dL. Inter peak latency of wave I-V (Brain stem conduction time) was prolonged in 8 cases; it reverted to normal in all cases. Prolonged inter peak latency of wave I-III was observed in 7 cases, of which it reverted to normal in 6. Absent waves reappeared in 4 out of 5 cases, but abnormal amplitude ratios reverted to normal in only one of the 7 cases in which it was abnormal. **Conclusions;** about 60% of term AFD neonates with serum bilirubin of > 18 mg/dL will demonstrate ABR changes. Most of these changes revert to normal early after therapy, indicating need for aggressive therapy in this subgroup of neonates.

Keywords: Auditory brainstem responses, hyperbilirubinemia, kernicterus.

INTRODUCTION:

Neonatal hyperbilirubinemia continues to be a problem, responsible for neonatal morbidity and mortality. Unfortunately the estimation of bilirubin level alone is not specific to predict bilirubin neurotoxicity. Importantly however, the early features of bilirubin neurotoxicity are reversible^[1,2,3,4]. Early detection of neurotoxicity facilitates proper use of aggressive bilirubin lowering measures like exchange transfusions.

Auditory brainstem responses (ABRs) offer a noninvasive modality to assess neural integrity of the auditory pathway. Data from previous investigations suggests a correlation between hyperbilirubinemia and abnormal ABR waveforms^[1-7]. This study aims to determine the effect of neonatal hyperbilirubinemia on auditory brainstem responses and evaluate responses to lowering of bilirubin levels.

MATERIALS AND METHODS:

In this prospective study ABR testing was done in 60 neonates (40 cases & 20 controls). Term appropriate for date neonates with uncomplicated birth history and bilirubin level of ≥ 13 mg/dL were included as cases. Those with major congenital anomalies and complicated neonatal course or exposure to drugs influencing bilirubin binding, were excluded. Neonates meeting the above criteria but with a bilirubin value of < 13 mg/dL were taken as controls. Written parental consent was obtained in all cases and the study was approved by the institutional review board.

For the procedure the baby was sedated with Triclophos (50mg/

kg) orally. Four electrodes were applied as follows; two active electrodes on each mastoid, one reference electrode on the vertex and one neutral on the forehead. Neonatal headphones were applied and 2000 click stimuli, of 95 dB intensity, at the rate of 10dB/sec were generated and delivered mono aurally with masking noise of 55 dB intensity to the other ear. ABRs were recorded by standard technique on a brainstem evoked response audiometer (Nicolet compact four system), having a signal generating, processing and monitoring system.

Two runs were done each time and results were averaged. Each ear was tested separately. First BERA examination was carried out within 24 hrs of the diagnosis of hyperbilirubinemia and repeat examination was done when total serum bilirubin came down to < 13 mg/dL with treatment. Similar procedure was followed for controls.

For ease of presentation and comparison the following subgroups were analyzed;

I- Neonates with total serum bilirubin level 13-20 mg/dL.

II- Neonates with total serum bilirubin level 20-25 mg/dL.

III- Neonates with total serum bilirubin level > 25 mg/dL.

In the above subgroups "a" signifies the group without treatment and "b"- after therapy.

C- Neonates with total serum bilirubin level < 13 mg/dL taken as controls. Mean and standard deviations were calculated using standard methodologies and students 't' test was used to compare the means in different groups. Significance was taken at 5% level ($p < 0.05$).

RESULTS:

The control group consisted of 20 neonates, and of the 40 cases, 18 belonged to group I, 12 to group II and 10 to group III. The range of bilirubin among cases, controls and post treatment group (b) was 15-29 mg/dL, 3-7 mg/dL and 7-12.8mg/dL respectively. Abnormal auditory brainstem response (ABR) was observed in 24(60%) of the 40 cases studied, with therapy it reverted back to normal in 15(62%). Significant differences were observed in wave latencies and inter peak latencies in group II and III compared to controls (Table 1 & 2). Amplitude ratio was significantly different in only group III. The commonest abnormality noted was prolonged latency of wave V (42.5%), followed by prolonged latency of wave III(35%) and wave I (22.5%). Following therapy and lowering of bilirubin levels to below 13mg/dL the statistical differences observed during initial analysis disappeared in all but one group i.e., amplitude ratio in group III b versus controls. Inter peak latency of wave I-V (Brain stem conduction time) was prolonged in 8 cases, it reverted to normal in all cases. Prolonged inter peak latency of wave I-III was observed in 7 cases, of which it reverted to normal in 6. Absent waves reappeared in 4 out of 5 cases, but abnormal amplitude ratios reverted to normal in only one of the 7 cases in which it was abnormal.

DISCUSSION:

Since ABR wave changes have been associated with hyperbilirubinemia in newborns, ABR monitoring of jaundiced infants may be an important clinical tool for detecting early, reversible bilirubin injury. Normally waves I, III and IV-V complex are present in the full term neonates. Wave I represents the auditory nerve, wave III the superior olive, and wave IV-V complex the lateral meniscus and inferior colliculi, respectively [8]. Deviant wave latencies and/or amplitude in ABRs indicate disturbance in brainstem function and serial ABRs are useful to follow up the course of dysfunction detected on initial assessment. We took neonates who were free from other pathological processes; thereby the alteration in ABRs can be implicated in all probability to raised bilirubin levels.

Most of the studies have identified an effect of hyperbilirubinemia on central conduction time, although some studies suggest an effect on peripheral auditory nerve as well. The reported

differences may be due to inclusion of both preterm and term infants, the use of different definitions of hyperbilirubinemia and variations in technique [6]. We observed that about 60% of term AFD neonates with serum bilirubin of > 18mg/dL demonstrated ABR changes. The incidence of ABR abnormalities reported by others is comparable [1,3], although lower values have also been found [4].

The latency of wave III, V and interpeak latency of wave I-III, I-V (central and brainstem conduction time) are prolonged earlier in response to moderate increase in bilirubin levels and latency of wave I (peripheral conduction time) becomes abnormal in infants suffering from severe hyperbilirubinemia [5,6]. In accord with earlier reports, [1,3,5] we observed, significant correlation between total serum bilirubin level and brainstem conduction time (Inter peak latency of wave I-V); the group with bilirubin levels of > 25 mg/dL had significantly increased inter peak latency of wave I-V (Brain stem conduction time) as compared to controls, group I & II (Table.2). However, this association has not been consistently observed [2,4].

Most of the previous workers [2,3,4] have shown the transient nature of the bilirubin encephalopathy with reversal of changes in almost all patients after therapy. However we observed reversal of abnormalities in most but not all after phototherapy and or exchange transfusion, possibly because of early second ABR examination.

The reversibility of changes encourages consideration for aggressive measures to lower bilirubin in neonates with hyperbilirubinemia and ABR wave changes.

ABRs have potential to serve as immediately available end point of bilirubin toxicity in neonate at risk of neurotoxicity. Rapid reversibility of changes is heartening, but an underlying subtle neurotoxicity cannot be entirely excluded. So long term studies with serial neurodevelopment assessment are required.

In conclusion, about 60% of term AFD neonates with serum bilirubin of > 18mg/dL will demonstrate ABR changes. Most of these changes revert to normal early after therapy, indicating need for aggressive therapy in this subgroup of neonates.

Table 1:
Findings on brainstem audiometry in cases and controls

	Groups						
	Ia (No.18)	Ib	IIa (No.12)	IIb	IIIa (No.10)	IIIb	C (No.20)
Mean Bilirubin mg/dL	16.1	9.4	22.4	10.3	26.6	9.9	4.7
Latencies* wave I	1.55 ± 0.18	1.54 ± 0.18	1.72 ± 0.27	1.54 ± 0.25	1.70 ± 0.39	1.55 ± 0.25	1.51 ± 0.25
Latencies wave III	3.27 ± 0.68	3.07 ± 0.63	3.96 ± 0.53	3.55 ± 0.26	3.70 ± 0.22	3.46 ± 0.35	3.32 ± 0.27
Latencies wave V	5.28 ± 0.62	5.28 ± 0.62	5.72 ± 0.62	4.95 ± 0.41	5.92 ± 0.83	5.13 ± 0.17	5.15 ± 0.34
Inter peak latency* I-III	2.03 ± 0.43	1.93 ± 0.24	2.23 ± 0.53	1.95 ± 0.37	2.08 ± 0.44	2.03 ± 0.43	1.92 ± 0.30
Inter peak latency III-V	2.43 ± 0.88	2.35 ± 0.85	2.39 ± 0.94	2.26 ± 0.83	2.57 ± 0.92	2.41 ± 0.87	2.43 ± 1.00
Inter peak latency I-V	4.31 ± 0.64	4.12 ± .57	4.52 ± 0.72	3.98 ± 0.53	5.62 ± 0.72	4.63 ± 1.36	4.22 ± 0.59
Amplitude Rate**, V/I	1.46 ± 0.62	1.48 ± 0.37	1.47 ± 0.18	1.47 ± 0.18	0.96 ± 0.21	1.07 ± 0.10	1.50 ± 0.17

*-latencies & interpeak latencies are given as milliseconds (mean ± SD). **-amplitude rate given as millivolts (mean ± SD).

Table 2: Comparison of brainstem audiometry findings among the various groups.

Groups compared	Latencies			Inter peak latency			Amplitude Ratio V/I(ms)
	Wave I	Wave III	Wave V	I-III	III-V	I-V	
Ia vs c	0.608	0.356	0.122	0.331	0.996	0.671	0.231
Ib vs c	0.703	0.322	0.122	0.884	0.781	0.612	0.451
IIa vs c	0.031*	0.001*	0.002*	0.004*	0.904	0.211	0.608
IIb vs c	0.735	0.143	0.152	0.807	0.628	0.257	0.608
IIIa vs c	0.041*	0.025*	0.001*	0.245	0.704	0.001*	0.000*
IIIb vs c	0.699	0.432	0.866	0.331	0.661	0.265	0.000*
Ia vs IIa	0.004*	0.003*	0.002*	-	-	0.498	-
Ia vs IIIa	0.019*	0.048*	0.001*	-	-	0.001*	-
IIa vs IIIa	0.733	0.170	0.519	-	-	0.001*	-

Values denote P-value based on students "t" test, *signifies P<0.05

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