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BRAINSTEM EVOKED RESPONSE AUDIOMETRY (BERA) IN NEONATES WITH HYPERBILIRUBINEMIA: A PROSPECTIVE STUDY IN INDIAN TERTIARY CARE HOSPITAL

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Abstract- *Introduction*: Neonatal Hyperbilirubinemia is one of the most common clinical sign in neonatal medicine and is a common cause of sensory neural hearing loss and auditory neuropathy. If not controlled, hyperbilirubinemia can lead to hyperbilirubinemic encephalopathy, or neonatal death. Brainstem Evoked Response Audiometry (BERA) has expanded the possibility of objective testing of hearing functions. This is an effective and simple method and measures the specific part of the auditory pathway. Hence the present study was designed to determine the initial BERA abnormalities and hearing loss in term neonates with hyperbilirubinaemia, to compare the findings of BERA between the cases (hyperbilirubinemic neonates requiring treatment that is total Serum Bilirubin >15 mg/dl) and controls (hyperbilirubinemic neonates not requiring treatment that is total serum bilirubin < 12 mg/dL) and also to compare initial BERA findings with follow up BERA findings at two to four months. *Methods*: This is prospective Case control study conducted between July 2012 to Sept 2014 in Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune India. 120 neonates as cases and 120 neonates as controls were included in the study.

Conclusion: Hearing loss and BERA abnormalities was significantly more among cases with total serum bilirubin levels>15 mg/dL compared to neonates with total serum bilirubin < 12mg/dL in neonatal nursery unit. BERA is a simple, effective and reliable and non-invasive technique for determining auditory functions in the neonates with hyperbilirubinemia.

Keywords- Neonatal Hyperbilirubinemia, Brainstem Evoked Response Audiometry

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Introduction

Neonatal Hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg per dL (86 µmol per L) which is a frequently encountered problem [1,2]. It is one of the most common clinical sign in neonatal medicine. Infants without identified risk factors rarely have total serum bilirubin levels above 12 mg/dL. As the number of risk factors increases, the potential to develop markedly elevated bilirubin levels also increases [3-5]. Common risk factors for hyperbilirubinaemia include fetal-maternal blood group incompatibility, prematurity, and a previously affected sibling [6,7]. Cephaohematomas, bruising, trauma from instrumental delivery and delayed meconium passage also increases the risk of Hyperbilirubinemia. Infants with risk factors should be monitored closely during the first days to weeks of life [8].

The auditory pathway is known as one of the most susceptible parts of the central nervous system for the bilirubin related injury, which is a common cause of sensorineural hearing loss and auditory neuropathy. If not controlled, hyperbilirubinemia can lead to hyperbilirubinemic encephalopathy, or neonatal death. Moreover, surviving infants are at high risk of neurological damage, which can manifest as cerebral palsy, epilepsy, or cognitive deficits [8,9].

Sensorineural hearing loss is severe sensory sequelae in young infants and its early diagnosis depends on systematic hearing screening. Early diagnosis and intervention are crucial for improving linguistic development and prognosis of these children [10,11].

Hearing impairment is a condition wherein the ability to detect certain frequencies of sound is completely or partially impaired. The ability to hear during the early years of life is critical for the development of speech, language, and cognition. Early identification and intervention can prevent severe psychosocial, educational, and linguistic repercussions [10-12].

Brainstem Evoked Response Audiometry (BERA) has expanded the possibility of objective testing of hearing functions. This is an effective and simple method that requires less co-operation of the patient and measures the specific part of the auditory pathway. It is not significantly altered by the state of consciousness, drugs and environmental factors like the sensory input to the cortex.[10] Hence the present study was designed to determine the initial BERA abnormalities and hearing loss in term neonates with hyperbilirubinaemia, to compare the findings of BERA between the cases (hyperbilirubinemic neonates requiring treatment that is total Serum Bilirubin >15 mg/dL) and controls (hyperbilirubinemic neonates not requiring treatment that is total serum bilirubin < 12 mg/dL) and also to compare initial BERA findings with follow up BERA findings at

two to four months.

Materials and Methods

This is prospective Case control study conducted between July 2012 to Sept 2014 (One and a half years for collection of data and six months for analysis) in Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune India. A Total of 240 neonates were included in the study. 120 neonates as cases and 120 neonates as controls were studied.

Ethical Clearance

Institutional Ethical clearance was obtained from Review Board of Dr. D. Y. Patil Medical College and Hospital, Pimpri, Pune before the study was started. Informed written consent was obtained from parents of the children included in the study.

Inclusion Criteria

- Term neonates with appropriate for gestational age (born between 37 completed weeks to 42 weeks of gestation) with birth weight between 2.5 kg to 3.5 kg with clinical jaundice between 0 - 28 days of life were included in the study.
- Neonates with hyperbilirubinemia (total serum bilirubin more than 15mg/dL) presenting to the Neonatal Care Unit requiring treatment were taken as Cases.
- Neonates with total serum bilirubin less than 12mg/dL, not requiring treatment were taken as Controls.

Exclusion Criteria

Pre term neonates, Familial history of hearing loss, intrauterine infections (TORCH), craniofacial abnormalities including pinna anomalies and canal agenesis, Using ototoxic drugs like aminoglycosides for more than five days or using them with loop diuretics, Sepsis or meningitis, Conjugated hyperbilirubinemia, Birth asphyxia, Needing mechanical ventilation for more than 5 days, Manifestations of syndromes with hearing loss, such as Usher- RefsumSyndrome [13,14].

Procedure

A predesigned proforma was used to record the demographic data and risk factors of hyperbilirubinemia. Total and direct bilirubin estimation was done by Diazo method. Weight was recorded using digital weighing scale. Gestational age assessment was done by modified Ballard score. BERA was done between 0 to 28 days for all the neonates on the day following peak of serum bilirubin level. Follow up BERA was done in those neonates with abnormal initial BERA, between two to four months. BERA was interpreted by an audiologist. Those babies showing abnormal follow up BERA were sent to Otorhinolaryngologist for further evaluation and follow up.

The BERA test was performed in a dark quiet room in the afternoon, about 30 minutes post feeding and while they were in natural sleep. Those who remain awake were sedated with oral Triclofos 20mg/kg. Active electrode was attached to the mastoid region. Ground electrode was kept on fore head. The resistance was kept below 5000 ohms. Right and left ears were tested with refraction clicks of 0.1 m sec duration administered at the rate of 11 /sec, with masking noise on other ear from the 3A Insert Ear Phones, held lightly over the test ear. Two thousand responses were averaged with filter setting of 100-1500 Hz on the Non Destructive Interventions (NDI) equipment. BERA developed within 10 m sec time and were seen at a gain of 500nv/div. Initially the high intensity of 80 dBnHL (Decibels of hearing loss) was administered. Then the intensity was decreased in steps of 20 DB till 20 dBnHL click, which was taken to be the normal threshold for producing V. Wave V was identified by a prominent trough like deflection crossing well below the baseline on the oscilloscope after 7 msec. An infant was considered to have normal hearing threshold if wave v is present at 30dBnHL in both ears or in one ear at 45dBnHL [10,13-15].

Statistical Methods

Results were analyzed using descriptive statistics by Statistical Software's [PRIMER OF BIOSTATISTICS] (Epi – Info 7). For categorical data, rates, ratios, and percentages were calculated. Comparison between the two groups was done using Chi Square test. For continuous data, Mean ± SD was calculated. The two groups were compared using two sample t test with unequal distribution or Fischer Exact test. *p* value <0.05 was considered as statistically significant.

Results

A total of 240 neonates delivered in the hospital were included in the study. These neonates were divided into groups of 120 each as;

Group 1: Cases (Neonates with Total serum bilirubin >15mg/dL and requiring treatment)

Group 2: Controls (Neonates with Total serum bilirubin < 12mg/dL and not requiring treatment)

The data obtained was coded and entered into Microsoft Excel Worksheet and the data was analyzed and results were tabulated as below.

Majority of the neonates among cases 52(41.33%) attained peak serum bilirubin levels on day 3 of life, that is 51 between 15-20 mg/dL and 1 neonate reached >20 mg/dL. Among Controls, majority of neonates 40(33.33%) had peak serum bilirubin on 3rd day of life that is 25 between 10-12 mg/dL and 15 had <10mg/dL [Table-1] (*p*= 0.245).

Total serum bilirubin levels in 119 cases were between 15-20 mg/dL and in 1 neonate (0.83%) the values were > 20 mg/dL. Among controls, 80(66.67%) had total serum bilirubin between 10-12 mg/dL and 40(33.33%) <10 mg/dl. Mean total serum Bilirubin (mg/dL) among cases was 16.18 with SD of 0.95 and among controls was 10.20 with SD of 1.28. P value= 0.001. Mean Indirect bilirubin (mg/dL) was 14.75 with SD of 0.87 among cases and 8.95 with SD of 1.19 among controls [Table-1] (*p*<0.001).

BERA impression on severity of hearing loss in the right ear showed moderate hearing impairment significantly (38 subjects; 31.67%) in cases (*p*<0.001). BERA impression on severity of hearing loss in the left ear showed moderately severe hearing impairment significantly in 33 (27.50%) cases (*p*<0.00). In BERA findings in right ear, it was observed that, latencies of all the 3 waves I, III, V and all the 3 inter peak intervals between I –III, I-V, III-V were prolonged significantly in cases compared to controls (p=0.001). Mean DBnHL upto which wave V was indentified among cases was 48.58 with SD of 16.72 and among controls was 18.25 with SD of 4.84 (*p* <0.001).

In BERA findings in left ear, it was observed that, mean frequencies of latencies of all the 3 waves I, III, V and all the 3 interpeak intervals between I –III, I-V, III-V were prolonged significantly in cases compared to controls (p=0.001). Mean DBnHL upto which Wave V

was identified among cases was 50.13 with SD of 19.24 and among controls was 18.25 with SD of 4.84. (*P =0.001*). In this study among the cases, most of the neonates 37(31.09%) with total serum bilirubin levels between 15 to 20 mg/dL had moderate hearing loss in right ear. One neonate with total serum bilirubin >20mg/dL had moderate hearing loss [Table-1].

Table 1- Analysis of various parameters in relation to hyperbilirubinemia, initial BERA and follow up BERA in the present study

S No	Variables	Cases		Controls		P value	
1	Day wise distribution of peak serum bilirubin levels (Max on Day 3)	41.33%		33.33%		0.245	
2	Mean Total Serum Bilirubin levels	Mean 16.18mg/dl , S.D 0.95		Mean 10.20mg/dl, S.D 1.28		0.001	
3	ABO incompatibility	37.50%		9.10%		<0.001	
4	Day wise distribution of BERA. (Max on 4th day of life)	37.50%		43.33%		0.096	
		Right Ear	Left Ear	Right ear	Left Ear	Right Ear	Left Ear
5	Total Incidence of hearing loss	86.67%	86.67%	0%	0%	<0.001	<0.001
6	Incidence of commonest form of Hearing loss	(Moderate degree) 31.67%	(Moderately severe degree) 27.50%	0%	0%	<0.001	<0.001
7	Latencies of wave I	2.53, 0.46	2.58,0.42	1.76,0.57	2.06,0.54	0.001	0.001
8	Latencies of wave III	4.57,0.46	4.53,0.46	3.65,0.63	3.79,0.61	0.001	0.001
9	Latencies of wave V	6.55,0.55	6.61,0.57	5.38,0.60	5.58,0.57	0.001	0.001
10	Interpeak interval between I-III	2.04, 0.30	1.96,0.113	1.89,0.29	1.74,0.15	0.001	0.001
11	Between I- V	4.01,0.22	4.03,0.31	3.62,0.33	3.53,0.24	0.001	0.001
12	Between III- V	1.98,0.25	2.07,0.25	1.73,0.18	1.79,0.16	0.001	0.001
13	DBnHL upto which wave V was indentified	48.85,16.72	50.13,19.24	18.25, 4.84	18.25,4.84	0.001	0.001
		Cases		Cases at follow up			
14	Incidence of hearing loss	86.67%	86.67%	6.50%	6.50%		
15	Latencies of wave I	2.53,0.46	2.58,0.42	1.88, 0.20	1.86,0.15	<0.001	<0.001
16	Latencies of wave III	4.57,0.46	4.53,0.46	3.93,0.20	3.89,0.15	<0.001	<0.001
17	Latencies of wave V	6.55,0.55	6.61,0.57	5.87,0.17	5.88,0.16	<0.001	<0.001
18	Interpeak interval between I-III	2.04,0.30	1.96,0.13	2.05,0.07	2.03,0.05	0.631	<0.001
19	Between I- V	4.01,0.22	4.03,0.31	3.99,0.13	4.02,0.05	0.313	0.62
20	Between III- V	1.98,0.25	2.07,0.25	1.94,0.14	1.99,0.03	0.163	<0.001
21	DBnHL upto which wave V was indentified	48.58,16.72	50.13,19.24	16.36,10.64	17.50,9.62	<0.001	<0.001

Among the cases, most of the neonates (32 subjects, 26.89%) with total serum bilirubin levels between 15 to 20 mg/dL had mild hearing loss (32 subjects, 26.89%) had normal hearing in left ear and 1 neonate with total serum bilirubin >20 mg/dL had moderately severe hearing loss. The repeat BERA in those cases with abnormal initial BERA at follow up in right ear revealed 3(2.88%) of the neonates with mild,1(0.96%) with moderate and 2(1.92%) with moderately severe hearing impairment. In 86(82.69%) of cases BERA reverted to normal and 12(11.54%) of the cases with initial abnormal BERA were lost to follow up [Table-1].

118 neonates among the cases (98.33%) and all 120 controls (100%) had no family history of jaundice in siblings. 2(1.67%) of the neonates among cases had a positive family history (Fisher exact test: $p = 0.249$) [Table-2].

Most prevalent Blood group among the mothers in cases was O+ blood 35.83% and most prevalent blood group among mothers in controls was B+ 36.67% [Table-3].

Table 2- Family history with jaundice in previous siblings

Family history	Cases (n=120)		Controls (n=120)	
	Number	Percentage	Number	Percentage
Present	2	1.67	0	0
Absent	118	98.33	120	100
Total	120	100	120	100

Table 3- Mother's blood group

Blood group	Cases (n=120)		Controls (n=120)	
	Number	Percentage	Number	Percentage
A-	3	2.5	2	1.67
A+	30	25	34	28.33
AB-	2	1.67	4	3.33
AB+	9	7.5	12	10
B-	0	0	4	3.33
B+	32	26.67	44	36.67
O-	1	0.83	0	0
O+	43	35.83	20	16.67
Total	120	100	120	100

Table 4- Neonate's blood group

Blood group	Cases (n=120)		Controls (n=120)	
	Number	Percentage	Number	Percentage
A-	4	3.33	2	1.67
A+	33	27.5	22	18.33
AB+	6	5	8	6.67
B-	0	0	8	6.67
B+	57	47.5	70	58.33
O-	1	0.83	0	0
O+	19	15.83	10	8.33
Total	120	100	120	100

Most prevalent blood group in neonates among both cases and controls was B+ 47.5% in cases and 58.33% of the neonates in controls. ABO incompatibility between mother and neonate was found among 11 in controls (9.1%) and among 45 in cases (37.5%) [Table-4] (p<0.001). The Direct Coomb's Test was negative in all the 240 neonates in both cases and controls.

Discussion

There was no statistically significant difference in the Day wise distribution of peak serum bilirubin levels among cases and controls (p =0.245).

Mean total serum Bilirubin (mg/dL) among cases was 16.18 with SD of 0.95 and among controls was 10.20 with SD of 1.28. p=0.001. Mean Indirect bilirubin (mg/dL) was 14.75 with SD of 0.87 among cases and 8.95 with SD of 1.19 among controls (p<0.001). Thus among the cases mean total serum bilirubin levels and mean indirect serum bilirubin levels were significantly more among cases than compared to controls [Table-1].

Female to male ratio was 1.10:1 and 1.06:1 in cases and controls respectively (p=0.897). Thus Sex of the neonates was not found to be significant risk factor for hyperbilirubinemia. In terms of risk factors of jaundice, 118(98.33%) of the neonates among the cases and all 100% among the controls had no family history of jaundice in siblings. 1.67% of the neonates among cases had a positive family history [Table-2]. Thus family history of jaundice in siblings was not found to be a significant factor. Similar finding were reported from various investigators also [13-17].

Most prevalent blood group among the mothers in cases was O+ 43 (35.83%) and most prevalent blood group among mothers in controls was B+ 44 (36.67%). Most prevalent blood group in neonates among both cases and controls was B+ i.e. 32(47.5%) and 44 (58.33%) of the neonates respectively. Direct Coomb's Test was negative in all the 240 neonates in both cases and controls. ABO incompatibility was found to a significant risk factor among Cases 37.5% as compared to controls 9.1% (p<0.001). In fact, the cause of hyperbilirubinemia in 26.7%, neonates of Agrawal et al study is ABO incompatibility [13]. The cause of hyperbilirubinemia was idiopathic in 63.3% and ABO incompatibility in 26.7% cases. Deorari *et al* revealed 3(16.6%) neonates with ABO incompatibility out of 18 hyperbilirubinemic neonates [18].

38 (31.67%) had moderate hearing impairment (p<0.001) in the right ear and 33 (27.50%) had moderately severe hearing loss in the left ear (p<0.001), which was significantly more compared to controls. Only 16 (13.33%) cases had normal hearing as compared to control group in which all the neonates had normal hearing.

BERA abnormalities noted were prolongation in the latencies of all 3 waves I, III, V and all 3 inter peak intervals I-III, I-V, III-V. The mean latencies of waves I, III, V, interpeak intervals between I and III, I and V, III and V, and DBnHL up to which wave V was identified were significantly high among cases. Mean DBnHL up to which wave V was identified in the right ear among cases was 48.58 with SD of 16.72 and among controls was 18.25 with SD of 4.84. (p< 0.001). Mean DBnHL up to which Wave V was identified in the left ear among cases was 50.13 with SD of 19.24 and among controls was 18.25 with SD of 4.84 (p<0.001). That is, the DBnHL up to which wave V was identified was significantly raised in cases [Table -1]. These findings suggest that the incidence of hearing impairment and BERA abnormalities when compared to controls was significantly more among cases 104 (86.67%). In all cases with hearing impairment, bilateral affection of both right and left ears were noted. Sharma *et al* [18] in India 2006 studied 30 hyperbilirubinemic neonates and found abnormal BERA in 22 (73.3%) [10]. In the study by Agarwal *et al* [13] the frequency of BERA abnormalities in hyperbilirubinemia on initial testing was 17 (56.7%) comparable to some earlier reports [19,20] but higher than others (16-33%) [21,22]. Latencies of all the waves and intervals were significantly prolonged in hyperbilirubinemia as compared to controls showing affection of VIII nerve as well as brainstem [12,22-25].

Most of the neonates among cases 37 (31.09%) with total serum bilirubin levels between 15 to 20 mg/dL had moderate hearing loss in right ear. One neonate with total serum bilirubin >20mg/dl also had moderate hearing loss. 32 (26.89%) with total serum bilirubin levels between 15 to 20 mg/dL had mild hearing loss and 32 (26.89%) with bilirubin between 15 to 20 mg/dL had normal hearing in left ear and 1 neonate with total serum bilirubin >20 mg/dL had moderately severe hearing loss. There was no direct relation between severity of hyperbilirubinemia and degree of hearing loss. In the study of Hanko et al, it is unclear why some infants do not develop hearing loss or neurological injury with the serum bilirubin levels that other infant's do [20]. Sharma *et al* [10] studied mean latency of various waves and inter peak distance was compared at different serum bilirubin levels viz.12-18, 18-25 and more than 25 mg/dl and statistically significant correlation in prolongation of latency and the inter wave intervals was obtained with serum bilirubin levels more than 25 mg/dL. Agarwal *et al* [13] also found correlation with serum bilirubin more than 25 mg and but Gupta *et al* [20] found such correlation only at serum bilirubin > 30%. According to a study by Zamani *et al* [15] severe hyperbilirubinemia causes hearing loss. When indirect bilirubin passes the blood brain barrier, it will be deposited in the basal ganglia, and also in the vestibulo-cochlear nucleus and the consequence of this phenomenon will be sensorineural hearing loss. It was reported that 33% of newborns with blood bilirubin levels of 15 -25 mg/dL had loss of wave complexes IV and V in Auditory Brainstem Response.

In a study performed by Sheykholeslami & Kaga [25] for localization of the pathological aetiology of hearing loss in those with a history of hyperbilirubinemia, 3 cases had abnormal Auditory Brainstem Response. They found that in severe hyperbilirubinemia at least some defects exist in the cochlea and especially in the outer hair cells and even moderate forms of hyperbilirubinemia (< 20 mg/dL) would be able to cause sensorineural hearing loss

The pathophysiology of Sensorineural hearing loss secondary to severe hyperbilirubinemia is not well defined, although its toxicity can affect cochlear hair cells and neurons of the basal nuclei and of the central auditory pathways. A recent report of 30 infants with hearing loss and exposure to severe hyperbilirubinemia suggests that damage to the outer hair cells of the cochlea is very common; twenty-six infants (87%) out of 30 had cochlear damage and in four cases (13%) an auditory neuropathy was documented.

The comparison of initial BERA with follow up BERA, it was observed that the mean frequencies of latencies of all 3 waves I, III, V and DBnHL upto which wave V was identified was significantly low at follow up for both the ears. In right ear all 3 interpeak intervals I-III, I-V, III-V were reduced at follow up but were not statistically significant and in left ear reduction in interpeak intervals I–III, III–V was statistically significantly, however reduction in interpeak interval between I–V was not statistically significant. In the study by Pramod *et al* [10] after treatment BERA abnormalities in form of prolonged

inter wave interval persisted only in 7 cases while the latencies of various waves had normalized showing that in most cases with hyperbilirubinemia the deafness induced is transient and improves if treated in time and appropriately. Further follow up BERA tracing obtained at 2 to 4 months revealed that, responses improved in 2 more cases while 5 infants continued to show persistent abnormalities. Similar findings were reported by Deorari *et al* [18] while other author reported that on follow-up all neonates with abnormal BERA showed a reversion back to normal. Improved brain functions may be due to removal of bilirubin from the brainstem because of phototherapy and/or exchange transfusion thus postulating the hypothesis of transient bilirubin toxicity or the transient brainstem encephalopathy. But persistence of abnormalities in some cases may be due to permanent damage caused by axonal degeneration and loss of myelin rather than hair cell loss [10].

Conclusion

Hearing loss and BERA abnormalities was significantly more among cases with total serum bilirubin levels>15 mg/dl compared to neonates with total serum bilirubin <12mg/dl in neonatal nursery unit, emphasizing screening for hearing loss in all hyperbilirubinemic neonates and early detection of hyperbilirubinemia and immediate screening for hearing loss. Hence BERA is a simple, effective and reliable technique for determining auditory functions in the neonates especially changes of early bilirubin toxicity.

Conflicts of Interest: None declared.

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