ONE YEAR OUTCOME OF BABIES WITH SEVERE NEONATAL HYPERBILIRUBINEMIA AND REVERSIBLE ABNORMALITY IN BRAINSTEM AUDITORY EVOKED RESPONSES

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ABSTRACT

Brainstem auditory evoked responses (BAER) were longitudinally recorded prospectively in 18 term infants with neonatal hyperbilirubinemia (NHB) (total serum bilirubin >15 mg/dl). Seven neonates had abnormal BAER. Wave complex IV-V was absent in eight recordings in NHB group while they were normal in the control group (p <0.001). Prolongation of latency of waves I and V and interwave conduction time (wave I-V) occurred in jaundiced infants especially when unconjugated serum bilirubin level rose above 22 mg/dl. The abnormalities in BAER reversed to normal in all seven neonates after exchange blood transfusion indicating transient nature of bilirubin toxicity to the brain. All seven neonates in the study and control group had normal hearing, development quotient and were free of neurological sequelae on follow up for one year.

Key **words:** *Brainstem auditory evoked responses (BAER), Neonatal hyperbilirubinemia (NHB), Development quotient (DQ).*

Neonatal hyperbilirubinemia (NHB) is a common problem affecting 5-6% of newborn babies. Persistence of high levels of unconjugated bilirubin for a long duration may lead to neurologic sequelae among the survivors(l). There is no single level of bilirubin which warrants active intervention in the form of phototherapy or exchange blood transfusion.

Brainstem auditory evoked responses (BAER) provide useful information regarding the neuro-physiological status of the 8th nerve, the cochlear nucleus, superior olivary nucleus, lateral leminiscus and the inferior colliculus in the brainstem(2-4). Bilirubin damage classically involves superior olive, lateral lemniscus and inferior colliculus(5). None of the previous studies have looked prospectively for developmental and neurological outcome of neonates with reversible abnormal BAER. In the present study BAER were recorded longitudinally to document pathophysiglogic changes that occur in association With neonatal hyperbilirubinemia. Neonates with abnormal BAER were subjected to exchange blood transfusion. These neonates were followed up for developmental, hearing and neurological examination till 1 year of age.

Material and Methods

The study group comprised of 18 term neonates born between April 1988 to May

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Received for publication: July 27, 1993; Accepted: April 5, 1994

1989 who developed hyperbilirubinemia (serum bilirubin >15 mg/dl). The following subjects were excluded from the study: *(i)* Gestation <37 weeks or >42 weeks; *(ii)* Apgar score of <6 at 1-minute; *(iii)* Presence of congenital malformations; *(iv)* Complicated neonatal course such as respiratory distress syndrome, hypoglycemia, septicemia, *etc;* and (v) Birth weight and/or head circumference less than 10th percentile or more than 90th percentile for the gestation.

The control group comprised of 20 term neonates without clinical jaundice. They were selected to standardize the test and served as an internal ethnic control for the developmental assessment. The exclusion criteria were similar to those of the study group. Informed consent was obtained from the parents of the newborns who served as subjects for the study. They were explained the need for follow up study for evaluation of development quotient and hearing.

BAER were recorded on the day when neonatal hyperbilirubinemia was detected and subsequently every 24-48 hours till serum bilirubin level fell below 15 mg/dl. BAER was performed in a dark quiet room by computerized electric response audiometer Nicolette 1170. Click acoustic stimuli, alternating in polarity were presented by an earphone to each ear alternately at an intensity of 75 decibles (db) hearing level at a rate of 20 clicks/second. The electrical activity was recorded as the potential difference between a mastoid electrode and a scalp vertex electrode. This was filtered between 150 and 3000 Hz and averaged to 2048 stimuli. Recordings were made in duplicate from each ear. A built in chart recorder provided tracings of the response.

The following parameters were evaluated: (0 The presence or absence of wave complexes III and IV-V; *(ii) Latency of wave I, III and V:* It was measured from the time of click stimulus to the peak of a particular wave; and *(iii) Interwove conduction time wave* V *to I:* Also known as brainstem transmission time (BTT), it is the conduction time for stimulus to travel brainstem.

The BAER was considered as abnormal: *(a)* if no definitie wave form III and/or IV-V complex were seen at 75 db; and *(b)* if brainstem transmission time (interpeak distance between wave I and IV-V complex) was greater than + 2 SD for the gestational age.

Babies with jaundice (>15 mg/dl) were treated with phototherapy. If the BAER was identified abnormal (based on above criteria) in addition to raised serum bilirubin levels, double volume blood exchange transfusion was performed.

Babies were followed up in the special high risk babies clinic for evaluation of development quotient (DQ) by Nancy Bayley Scale at 6 months and 12 months(6). Repeat BAER were done at 1 month ± 7 days, 6 months ± 15 days and 12 months ± 15 days. At 6 months and 12 months, hearing was evaluated by parental questioning, behavioral audiometery and impedance audiometry(7).

A detailed clinical examination was done in all the follow up cases.

Statistical analysis was done using Students 't' test and Fisher's exact test.

Results

The mean gestational age of jaudiced infants (eight boys, ten girls) was 39.0 ± 0.41 weeks (median 39 weeks) and their birth

weight ranged from 2.3 kg to 3.3 kg. Thirteen were born by uncomplicated spontaneous vaginal delivery while five were delivered by elective cesarean section. Apgar score was >6 at 1 minute. The causes of jaundice included Rh iso-immunization in two, ABO incompatibility in five, G-6-PD deficiency in two, and idiopathic in nine. The mean age of onset of jaundice was 4±2 days. The control group consisted of 20 neonates (9 boys, 11 girls) with mean age at the time of BAER as 3 ± 2 days. Mean gestational age was 39 ± 0.3 weeks and birth weight ranged between 2.6 to 3.4 kg.

Latency, interwave conduction time in control group and neonates who underwent exchange blood transfusion are shown in *Table I.* The following abnormalities in BAER were recorded in patients with neonatal hyperbilirubinemia before exchange blood transfusion.

Loss of waves: Five of 18 jaundiced neonates demonstrated loss of waves, I, III and wave complex IV-V whereas these waves were present in all the recordings in control infants ($p < 0.001$ by the Fisher exact test). In eight of the recordings in the infants with hyperbilirubnemia, the wave complex IV-V were absent. Wave complex IV-V was absent bilaterally in 3 and unilaterally in 2. It was accompanied by absence of wave III and wave I in four and two occasions, respectively. All these neonates had serum bilirubin levels above 24 mg/dl.

Latencies and interwave conduction times: In four neonates (included two neonates with unilateral wave complex IV-V absence) I-V conduction time in six recordings were +2 SD more than the mean when compared to control infants *(Table II).* These neonates had serum bilirubin levels above 22 mg/dl.

Relationship of abnormal BAER to bilirubin levels: The mean ± SD maximum

TABLE I - *Latency and Interwave Conduction Time Before/After Exchange Blood Transfusion (Mean±SD)*

Group	Serum bilirubin mg/dl	Latency (msec) I	ill	V	Conduction time (msec) I to V (BIT*)
(a) Control infants (n = 20)		1.86 ± 0.02 (36)	5.11 ± 0.31 (40)	7.01 ± 0.30 (40)	5.13 ± 0.23 (36)
(b) Before exchange blood transfusion (n=7)	24.56 ± 1.59	2.07 ± 0.46 (12)	5.53 ± 0.54 (10)	8.06 ± 0.73 (6)	6.02± 0.73 (6)
(c) After exchange blood transfusion (n=7)	14.89 ± 2.13	1.83 ± 0.32 (14)	5.44 ± 0.37 (14)	7.39 ± 0.48 (14)	5.56 ± 0.53 (14)
p value (b *vs* C)	<0.001	NS	NS (t=2.06)	NS (t=1.39)	NS

Total number of measurements are' shown in parentheses.

* Brainstem transmission time.

TABLE II—*Clinical and BAER Findings in Exchange Transfusion Neonates*

Birth wt (kg)	Gestation (weeks)	Age (hours)	Cause of NHB	Serum bilirubin (mμ/dl)	BAER measurements (msec)			
					Latency I Rt/Lt	Latency III Rt/Lt	Latency V Rt/Lt	Interval I-V Rt/Lt
3.250	38	48	Idiopathic	23.0	1.48/1.40	5.76/4.56	8.78/7.24	7.40/5.76
		56		17.0	1.40/1.40	5.62/4.40	8.50/7.00	7.10/5.60
2.345	38	84	Rh incomp.	22.8	2.80/2.80	6.60/5.80	8.88/8.28	6.08/5.48
		98		14.0	1.64/2.60	5.84/5.60	7.72/8.20	6.08/5.60
2.900	37	70	ABO incomp.	27.0	1.68/1.80	5.62/5.28	NI*/7.20	NI/5.46
		82		18.0	1.60/1.80	5.58/5.20	7.00/7.00	5.80/5.16
2.600	38	60	Idiopathic	25.2	1.68/2.20	5.76/5.24	NI/NI	NI/NI
		80		16.1	1.68/2.16	5.72/5.28	7.08/7.16	5.40/5.00
3.100	39	128	ABO incomp.	26.2	2.24/2.00	5.28/5.40	NI/8.00	NI/6.00
		136		13.7	2.00/1.92	5.88/5.36	7.80/7.08	5.80/5.16
2.650	38	96	Idiopathic	24.0	NI/NI	NI/NI	NI/NI	NI/NI
		108		11.7	1.68/2.16	5.72/5.28	7.08/7.16	5.40/5.00
2.860	37	56	G-6PD	24.8	1.80/1.80	NI/NI	NI/NI	NI/NI
		64	deficiency	13.1	1.76/1.84	5.40/5.32	7.26/7.40	5.52/5.56

* Wave complex not identified.

bilirubin concentration in jaundiced neonates with abnormal BAER was 24.56 ± 1.59 mg/dl which decreased to 14.84 ± 2.13 mg/dl within 24 hours following exchange blood transfusion. Abnormal *BAER (vide supra)* occurred only if serum bilirubin values were above 22.8 mg/dl.

Seven neonates with abnormal BAER and high serum bilirubin levels were subjected to double volume exchange blood transfusion. The wave complexes reappeared in all jaundiced infants in whom they were absent initially. The amplitude and latency as well as interwave conduction time improved following exchange blood transfusion (*Table I)*. The clinical and BAER details before and after exchange blood transfusion are as in *Table II* and *Fig.1*.

Hearing evaluation: Seven infants with neonatal hyperbilirubinemia who underwent exchange blood transfusion and sixteen control infants reported for follow up. Hearing was normal as assessed by parental questioning, behavioral and impedance audiometery at 12 months of age.

Development Quotient (DQ): The mean Development Motor Quotient (DMQ; 118 ± 6.3 *vs* 124 ± 6.2) and Deve-lopment Mental Quotient (DMeQ; 111 ± 6.8 *vs* 116 ± 8.6) in the study control groups were comparable and normal at 1 year of age.

Neurological sequelae: None of study and *control group babies* developed seizures, motor deficits or features of cerebral palsy on follow up till 1 year of age.

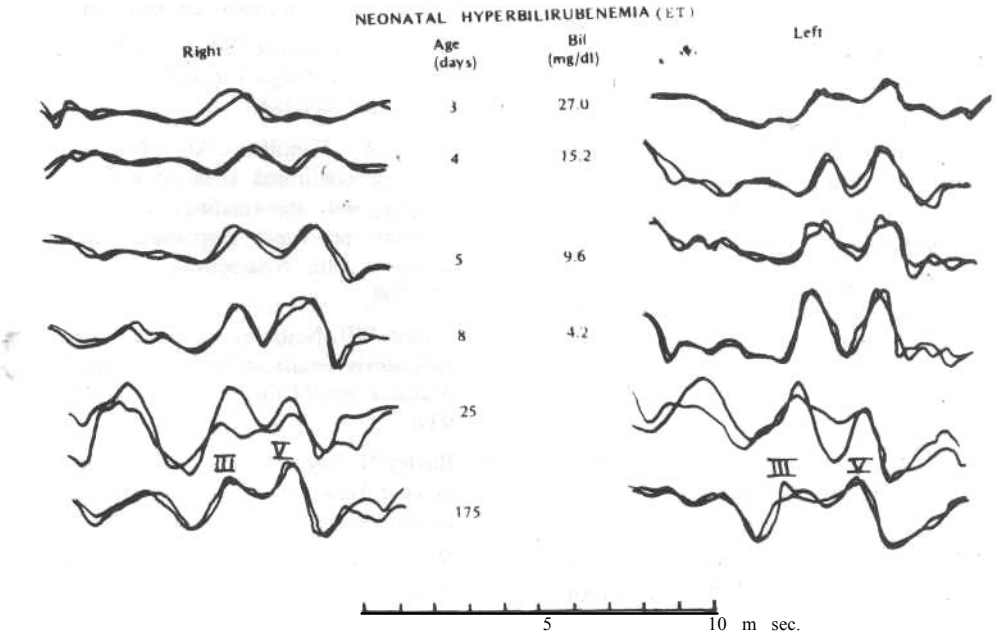

Fig. 1. BAER record on follow up in a neonate with NHB of 27 mg/dl at the age of 3 days. Note absence of wave complex IV-V in Right ear and increased complitude of waves following exchange blood transfusion at the age of 4 days. Note progressive improvement on day 5 and 8 with serum bilirubin levels of 9.6 mg/dl and 4.2 mg/dl. Follow up normal record at 25 and 175 days.

Discussion

The BAER consists of series of waves which represent the electrophysiologic response to auditory stimuli recorded by scalp electrodes. These waves are considered to represent electrical events evoked by auditory stimulation of the eighth nerve, the superior olive, and the inferior colliculus, respectively(2,3). Abnormalities of BAER following neonatal hyperbilirubinemia have been described earlier(8,10). Prolongation of brainstem conduction time occured at auditory nerve and brain stem level in NHB. In addition, aberrations of wave complexes IV-V and III appeared at higher bilirubin levels. These changes reverted to normal following exchange blood transfusion. The waves reappeared and latencies decreased following exchange blood transfusion. This indicates improved brainstem functioning following exchange blood transfusion. Similar observations have been reported by other workers(11-13). Hearing deficit is the commonest sequelae of bilirubin encephalopathy, due to brainstem dysfunction(14). Hearing evaluation and DQ on follow up was within the normal range in all babies in whom abnormalities reverted back to normal following exchange blood transfusion. Minor neurological deficits were not observed in any infant with NHB during first year of life.

The abnormal BAER, which is reversible following timely exchange blood transfusion, is consistent with the concept of transient bilirubin encephalopathy. Bedside BAER may provides a useful additional tool to serum bilirubin levels while deciding the need for exchange blood transfusion in neonatal hyperbilirubinemia.

The neurological outcome of NHB with serum bilirubin values ranging between 22-30 mg/dl is uncertain but it is recommended that unconjugated serum bilirubin level should not be allowed to cross 22 mg/dl in term infants. Our observations suggest that when facilities for BAER recording are not available, it is recommended that a term infant with NHB should be exchanged if total serum bilirubin approaches a level of 20 mg/dl.

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