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CASE REPORT

Outcome Of Neurodevelopment And Bera In Neonatal Hyperbilirubinemia.

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ABSTRACT

Neonatal hyperbilirubinemia is a significant burden in the childs development and the effect of bilirubin neurotoxicity has a greater impact on the neurodevelopment and hearing abnormalities of the growing child. This study was conducted to evaluate long term consequences of bilirubin toxicity on both neurodevelopment and hearing. A total of 34 neonates with bilirubin levels more than 20mg/dl were enrolled during the period of 3 years in Dr.D.Y.Patil Medical College. Neurodevelopmental assessment using TDSC and Hearing assessment using BERA was done on all 34 neonates at birth and at 1 year of age to see the changes in abnormalities. Out of the 34 neonates 22(64.7%) had abnormal BERA at the time of diagnosis with abnormality of wave V(61%), abnormality of wave III(35%) and prolonged interpeak latency(3%) and all the neonates(34) had normal BERA at followup of 12 months of age (p value <0.0001). Among 34 neonates all the subjects had normal neurodevelopment at the time of diagnosis and 12 months of age. **Conclusions:** Neonates with hyperbilirubinemia (bilirubin levels more than 20mg/dl) should be screened for neurotoxic effect of hyperbilirubinemia causing damage to neurodevelopment and auditory pathway. Early evaluation by BERA and TDSC scale is necessary to prevent permanent neurological and hearing damage.

Keywords: Neonatal Hyperbilirubinemia, BERA, Neurodevelopment, bilirubin encephalopathy.

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INTRODUCTION

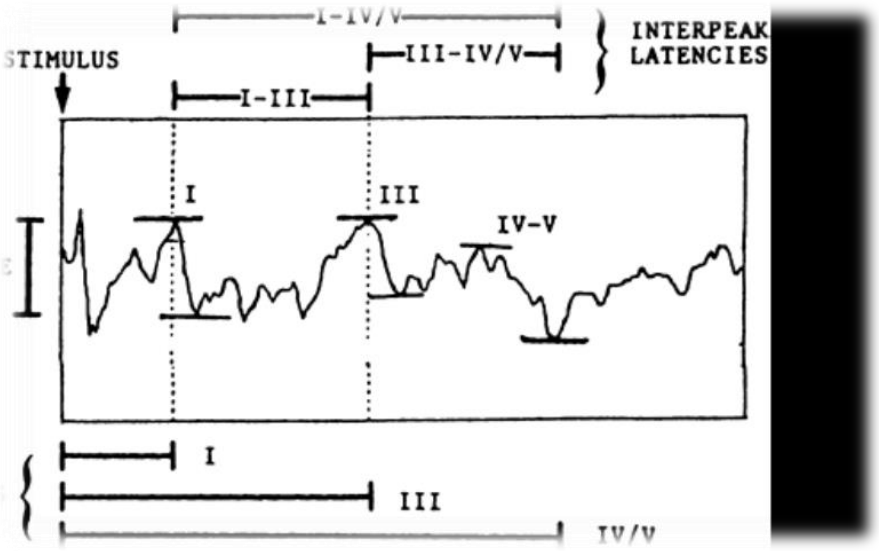
Neonatal hyperbilirubinemia is an adverse perinatal state which increases the risk of auditory impairment and neurodevelopment. Jaundice is a common finding in neonates affecting 70% of term and 80% of near term neonates in the first week of their life. After the neonate enters the environment, it is immediately exposed to a state of increased oxygen concentration and rapid elevated production of bilirubin. Due to limited availability of albumin, indirect bilirubin concentrations rise alarmingly and this unconjugated bilirubin can cross the blood brain barrier and precipitate in various parts of the brain like basal ganglia, brainstem, cerebellum, or the hippocampus. Although the hyperbilirubinic state is very transient in normal physiological conditions, even short-term increase can have adverse effects of the neurologic condition of the neonate. In altered states where the bilirubin levels crosses 15mg/dl the increased levels of bilirubin in the brain results in exaggerated adverse effect on the neural development.

In clinical setting, kernicterus denotes the chronic and permanent sequelae of bilirubin toxicity. Acute bilirubin encephalopathy is the clinical manifestation of bilirubin toxicity in the neonatal period. It has been well established that once "acute bilirubin encephalopathy" develops, babies sustain a varying degree of neurodevelopmental sequelae. Hyperbilirubinemia in term infants has been associated with abnormalities in Brainstem evoked response audiometry (BERA), cry characteristics and neurobehavioral measures. There has been conflicting evidence regarding the proportionate association of peak bilirubin levels with the future neurodevelopmental delays. The level of bilirubin associated toxicity in healthy term infants or preterm infants is uncertain and appears to vary among infants and in different clinical circumstances [1].

Bilirubin in healthy term neonates especially free bilirubin could enter brain cells and cause damage which is perceived by BERA. Studies identify that free bilirubin is more associated with BERA abnormalities. Early detection and rehabilitation of hearing loss is important for the development of speech and language skills in hearing impaired children [2]. BERA is an effective and non-invasive means of assessing the functional status of auditory nerve and brainstem auditory sensory pathway. It is not significantly altered by drugs, state of consciousness and variety of environmental factors [3]. The BERA changes in response to hyperbilirubinemia includes loss of one or more peaks of waves I-V, raised threshold, increase in latency of waves I,III or V or increased interpeak interval[3]. This acute change seen in BERA can be reversed by early bilirubin lowering measures, thereby explaining the transient nature of bilirubin encephalopathy. But persistent elevation of bilirubin can cause neuronal degeneration and thereby persistent changes in BERA.

BERA is generated by the auditory nerve and subsequent structures within the auditory brainstem pathways. *(Illustration 1)*

Illustration 1



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

- Informed written consent (parents/guardians) of all the subjects was taken before the start of the study.
- Detailed Antenatal and Postnatal history was taken in each case and physical examination was done for all term jaundiced neonates as per proforma.
- Clinically yellowish discolouration was examined by kramers rule [4] and those babies who had severe hyperbilirubinemia were enrolled into the study.
- With all aseptic precautions 2 ml of venous blood was drawn. The liver function test was done by autoanalyzer using "Continuous flow analysis(CFA)" in laboratory of Dr.D.Y.Patil Medical College and Hospital and Research centre.
- The bilirubin levels in neonates according to hours of life was estimated [5].
- BERA was done of all the enrolled subjects by using CLARITY OCTOPUS 2CH with silver electrodes of 10mm diameter. Sweep velocity of 10mm/s and click acoustic stimulus rate of 10/s with intensity 90dB and further evaluation was done.
- Complete neurological assessment was done.
- Further evaluation and management of all the cases was done in NICU of Dr.D.Y.Patil Medical College and Hospital with Intensive phototherapy [6].
- Followup for neurodevelopmental assessment was done at 3.5 months, 9 months and at 12 months of age in Dr.D.Y.Patil medical college and hospital by Trivandrum Development Screening Chart[7] and further evaluation was done.
- Follow up BERA was done at 12 months of age and further evaluated.
- Those babies who had abnormal neurodevelopment/ abnormal BERA were referred for the further management.

RESULTS

Distribution of cases according to gestational age and gender (Table 1)

Table 1: Distribution of cases according to gestational age

Gestational age	Male	Female	Total
36-38 weeks	03	04	07
38-40 weeks	08	07	15
>40 weeks	07	05	12
Total	18	16	34

A total of 34 neonates were enrolled into the study of which 18 were male and 16 female. Out of the 34 neonates 7(20%) belonged to gestational age between 36 to 38 weeks, 15(44%) belonged to 38-40 weeks and 12(35.3%) were more than 40 weeks.

Distribution of cases according to mode of delivery (Table 2)

Table 2: Distribution of cases according to mode of delivery

Mode of delivery	Male	Female	Total
Normal Vaginal	14	09	23
LSCS	04	07	11
	18	16	

Out of 34 neonates, 23(67%) were delivered by vaginal and 11(32%) were delivered by caesarean section. P value 0.002

Distribution of cases according to Risk factors (Table 3)

Table 3: Distribution of cases according to Risk factors

	PV Leak	GDM	PIH	Thyroid
Male	07	02	05	04
Female	05	01	02	0
Total	12	03	07	04

In this study 14(41%) out of 34 neonates had antenatal risk factors like GDM, PIH or Thyroid disorders and 12(35%) neonates had history of PROM.

Distribution of cases according to Bilirubin levels (Table 4)

Table 4: Distribution of cases according to Bilirubin levels

	18-20	20-22	>22
Male	01	06	11
Female	0	08	08

Out of the 34 neonates 19(55%) subjects had peak bilirubin levels greater than 22mg/dl, 14(41%) belonged to bilirubin levels 20-22mg/dl and 1(4%) subject had bilirubin levels 18-20mg/dl. P value 0.04

Distribution of cases according to BERA findings at peak bilirubin levels(4^{th}-5^{th} day of life) (Table 5)

Table 5: Distribution of cases according to BERA findings at peak bilirubin levels(4^{th}-5^{th} day of life)

	Normal	Abnormal
Male	07	11
Female	05	11

Out of the 34 neonates, at the peak of hyperbilirubinemia, 22(67%) neonates had abnormal BERA and 12(35.3%) neonates had normal BERA findings. P value 0.029

Distribution of cases according to Wave Abnormalities in BERA (Table 6)

Table 6: Distribution of cases according to Wave Abnormalities in BERA

BERA abnormality	Male	Female
Prolonged wave V	10	11
Prolonged wave III	07	05
Prolonged interpeak latencies	01	0

Out of the 22 subjects with abnormal BERA waveforms 21 neonates (61%) had prolonged latency of wave V and 12 subjects(35%) had prolonged latency of wave III and 1(2.9%) had prolonged interpeak latencies.

Distribution of cases according to follow up BERA(12 months of age) (Table 7)

Table 7: Distribution of cases according to follow up BERA(12 months of age)

	Normal (n=cases)	Abnormal (n=cases)
Male	18	0
Female	16	0

Out of the 22 subjects with abnormal BERA findings at peak hyperbilirubinemia, all 22 babies had normal BERA waveform findings at 12 months of age (p value <0.00001)

Distribution of cases with Neurodevelopmental Assessment(TDSC scale) (Table 8)

Table 8: Distribution of cases with Neurodevelopmental Assessment(TDSC scale)

	Male	Female
Birth	Normal	Normal
3.5 months	Normal	Normal
9 months	Normal	Normal
12 months	Normal	Normal

Out of the 34 neonates, all the subjects had normal neurodevelopment at 3.5 months, 9 months and 12 months of follow up visits.

Table 9: Analysis of this study

Gestational age(weeks)	Gender Male	Female	Risk factors	Abnormal BERA at birth	Neurological assessment at birth	BERA at 12 months	Neurodevelopment at 12 months
36-38wks	03	04	04	05	Normal	Normal	Normal
38-40 weeks	08	07	10	09	Normal	normal	Normal
>40weeks	07	05	07	08	Normal	Normal	Normal

The present study revealed that 5 out of 7(71%) neonates belonging to gestational age less than 38wks had abnormal BERA waves at peak bilirubin levels and 17 neonates out of 27(63%) with gestational age more than 38 weeks showed abnormal BERA at diagnosis.

DISCUSSION

The Incidence of neonatal hyperbilirubinemia in India is approximately 4.3% to 6.5% [8] although recent studies in tertiary centres have shown an incidence of 10.5% in term live births [9].

Timely detection and early intervention is crucial for prevention of neurological abnormality and hearing disability. BERA is a useful and non-invasive tool in the assessment of bilirubin toxicity on the auditory pathway.

The incidence of hyperbilirubinemia in my study revealed a slightly higher incidence in the male group 18 (52%) compared to female 16(48%) **with P value of 0.029**, similar to the findings of the study by Sahoo M et.al [10] and Keshwani et.al [11]. My study also revealed an increase in cases of hyperbilirubinemia in neonates with gestational age between 38-40 weeks and above (79%) as compared to neonates with gestational age less than 38wks(21%) similar to the study by Keshwani et.al [11] which also showed 59% incidence in term neonates compared to near term neonates.

The present study showed an increase in the number of cases of hyperbilirubinemia in neonates delivered by normal vaginal delivery 23(67%) as compared to Caesarean section 11(33%) **with P value of 0.0023**. This data is at par with the 2015 study by Keshwani et.al [12] which concluded that two thirds cases of hyperbilirubinemia were delivered through normal vaginal delivery. This maybe a correlation to the increased fetal stress in vaginal delivery and a decreased exposure of maternal bacterial flora in caesarean sections. However no significant correlation could be drawn that normal vaginal delivery increases the risk of hyperbilirubinemia.

In this study revealed no significant association of hyperbilirubinemia and maternal risk factors like PIH, GDM and thyroid disorders 14(41%) similar to the study by Debasis Kr. Samanta et.al[12]. This elucidates that the maternal risk factors like gestational diabetes mellitus, pregnancy induced hypertension or thyroid disorders in the mother has no influence on the occurrence and severity of hyperbilirubinemia in term neonates. Although these risk factors play an important role in the outcome of NICU admissions but has no direct effect of neonatal bilirubin metabolism.

This study includes neonates belonging to 2 major groups based on their peak bilirubin levels. 55%(19) neonates belonged to the group with bilirubin level >22mg/dl and 41% (15) belonged to the group with bilirubin levels between 20-22mg/dl [13].

Comparing the two groups with BERA abnormalities revealed an increased effect of bilirubin on the central nervous system once bilirubin levels crosses 22mg/dl. 13 neonates(68%) out of 19 belonging to the group with bilirubin >22mg/dl showing changes in BERA as compared to 9(64%) of the 14 subjects with bilirubin levels between 20-22mg/dl with **P value of 0.041.** This above result is consistent with previous studies which also demonstrate the effect of bilirubin on CNS above 22mg/dl [14, 15]

In this study the most common wave abnormality was prolonged Wave V(61%) followed by prolonged wave III(35%) and prolonged interpeak latencies of wave V and wave III(3%). The study of Ravi Sharma et.al in 2006[16] also showed similar abnormalities of prolonged latency of wave V(42.5%) more than wave III(35%) abnormalities. The study by A.K.Gupta[13] also had similar wave abnormalities in hyperbilirubinimic subjects.

Neurological assessment was done at the peak of hyperbilirubinemia and the neurodevelopment was followed up at 3 and half months, 9 months and 12 months of age. In my study all 34 neonates(100%) had normal neurological findings at the time of diagnosis and all the subjects had normal neurodevelopment by TDSC at 3.5 months, 9 months and 12months of followup. This shows that the neurotoxicity of bilirubin is readily reversible and the impact of peak bilirubin levels in healthy term neonates is transient at best if treated as per protocol with phototherapy and exchange transfusions [16-19].

The present study found that the outcome of hyperbilirubinemia and BERA abnormalities were completely reversible with early and vigilant therapy by either Phototherapy or exchange transfusion. The above result was drawn after followup BERA in all the neonates at 12 months of age revealed normal. Neonates with Wave abnormalities in BERA at peak of hyperbilirubinemia had BERA findings and neurological development at par with non hyperbilirubinimic neonates at 12 months of age. Numerous studies by Deorari et.al [17], A K Gupta [18], Ravi sharma [16], M Vinod [19] all showed the reversible nature of bilirubin toxicity and emphasised on early intervention.

Abnormal BERA waveforms were more common in jaundiced neonates belonging to gestational age less than 38wks(71%) than the neonates with gestational age more than 38 wks. The study conducted by Newman in 1993 also showed a similar result where near term neonates with hyperbilirubinemia showed more predominance for abnormal BERA findings [20].

All the 34 cases were followed up both for neurodevelopmental outcome and persistence of BERA abnormality at 3 months, 9 months and 12 months and BERA was repeated at 12 months of age to look for persistence of BERA abnormality similar to studies by A.K gupta and Deorari et.al. Out of the 22 cases with abnormal BERA findings at diagnosis all 22 had normal BERA report at 12 months followup which shows 100% reversibility of the bilirubin toxicity on auditory pathway and all 22 cases had normal neurodevelopment all throughout the followup. Studies like A.K.Gupta and Deorari also showed 100% reversibility in bilirubin encephalopathy similar to my study although studies by Ravi sharma and

M.Vinod showed 60% reversibility in BERA abnormalities at follow up. All the studies showed normal neurodevelopmental outcome of all subjects with hyperbilirubinemia at birth through followup. This clearly correlates that the bilirubin toxicity in neonatal hyperbilirubinemia is completely reversible by early treatment and the nature of transient bilirubin encephalopathy.

CONCLUSION

Neonates with physiological hyperbilirubinemia (bilirubin levels more than 20mg/dl) should be screened for neurotoxic effect of hyperbilirubinemia causing damage to neurodevelopment and auditory pathway. Early evaluation by BERA and neurological assessment through TDSC scale is necessary to prevent permanent neurological and hearing damage.

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