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Original Research Article

Clinicoetiological profile, immediate outcome and short-term follow-up of term babies with hyperbilirubinemia

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ABSTRACT

Background: Neonatal jaundice is a common cause of admission of newborns. Since bilirubin is potentially toxic to the central nervous system, early detection and appropriate management is of paramount importance. We therefore undertook this study with an objective to assess the causes, clinical correlation, immediate outcome and short term follow up for hearing and neurodevelopmental assessment in term babies with jaundice admitted in our NICU.
Methods: This study was done in NICU in Bapuji Child Health Institute and Research center attached to JJMMC, Davangere. This study included 100 term infants admitted for jaundice during November 2013 to May 2015 and 6 months follow up of these infants for hearing and neurodevelopmental outcome was done. A proforma was used to collect relevant information.
Results: Physiological jaundice (50%) and Blood group incompatibility (36%) were the most common causes of hyperbilirubinemia in the study. During a short term follow up i.e. 6 months, majority (97%) of the jaundiced infants had normal hearing and neurodevelopmental outcome except for 3 infants who had sensorineural hearing loss and BIND. In severe group the percentage of abnormal BERA and unfavourable neurological outcome was more when compared to moderate group, which was statistically significant. All the 3 infants who had abnormal BERA had developmental delay.
Conclusions: Neonatal jaundice is a common cause of admission of newborns. Physiological jaundice was the commonest cause of neonatal hyperbilirubinaemia followed by blood group incompatability. Majority of the infants had normal BERA and normal neurodevelopmental outcome on short term follow up. A close association was found between BERA and neurodevelopmental outcome in the study. BERA is an useful neurophysiological tool for monitoring neurological complications, however it is not a useful tool to predict final neurological outcome.

Keywords: BERA, Hyperbilirubinemia, Neurodevelopmental outcome, Term neonates

INTRODUCTION

Neonatal Jaundice is one of the most common conditions requiring medical attention in newborn babies. Approximately 60% of term babies and 80% of pre- term babies develop jaundice in first week of life.[1] Neonatal jaundice refers to yellowish discolouration of skin and sclera of newborn babies that results in accumulation of unconjugated bilirubin in skin and mucous membrane. This is associated with a raised level of bilirubin in the circulation, a condition known as Hyperbilirubinemia.

In most infants unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However in some infants serum bilirubin levels may excessively rise, due to certain risk factors like blood group and Rh incompatibility, G-6-PD deficiency, sepsis etc.,which can be cause for concern because unconjugated bilirubin is

neurotoxic.[2] If left untreated, bilirubin can accumulate and cross the blood brain barrier, leading to number of adverse neurodevelopmental outcomes including Acute encephalopathy, diminished auditory response and in extreme cases Kernicterus. The wide variation in etiology and neurological outcome in jaundice from various studies has been documented. We therefore undertook the present study to assess etiology, immediate outcome and short term follow up for hearing and neurodevelopmental assessment in term babies with jaundice admitted in our NICU.

METHODS

Inclusion criteria

- Term babies (birth weight >2500 g, and gestational age >37 weeks).
- Indirect hyperbilirubinemia with bilirubin levels above the physiologic values (above 5 mg/dl).

Exclusion criteria

- Conjugated hyperbilirubinemia
- Babies with congenital anomalies or metabolic or syndromal disorders
- Babies already admitted for various causes; birth asphyxia, meconium aspiration syndrome, etc
- IUGR babies

100 term neonates with hyperbilirubinemia admitted in NICU during a period from November 2013 to May 2015 and a short term i.e. 6 months follow up of these babies is done.

Methodology

Of the 100 term neonates with jaundice that have met the inclusion criteria, as per the unit protocol are throughly examined, evaluated and treated as follows: A pretested proforma was used to collect data. Informed consent is obtained from the parent before evaluating each neonate. A detailed history with respect to onset of jaundice, risk factors, feeding history, previous sibling with history of jaundice, mothers blood group and antenatal history is taken followed by a through clinical examination. TSB value that is obtained at admission is evaluated based on AAP normograms. The severity of hyperbilirubinemia was classified according to peak TSB level into two sub-categories:

- Moderate hyperbilirubinemia (15 to < 20 mg/dl) (257 to < 342 µmol/L) and
- Severe hyperbilirubinemia (>20mg/dl) (>342 µmol/L).

Thus, the 100 cases in the study group were further divided into two sub-groups based on severity of hyperbilirubinemia as follows:

- Moderate group: Total 84 cases were recruited with average peak TSB level of 18.8mg/dl (320.7 µmol/L) (range = 17.5 to <20 mg/dl) (300 to <342 µmol/L).
- Severe group: Total 16 cases were recruited with average peak TSB level of 21.6mg/dl (369.0 µmol/L) (range ≥20mg/dl) (>342 µmol/L).

Serial estimates of bilirubin done as per unit protocols

- Term non-hemolytic jaundice: once in 24 hours
- Term hemolytic jaundice: once in 6-12 hours.

At the time of discharge a physical and neurodevelopmental assessment is done using Amiel Tison method and these infants are followed up for a period of 6 months. During follow up visits: BERA is done at 3rd month if BERA is abnormal a repeat BERA done at 6th month and physical and neurodevelopmental assessment done up to 6 months of age.

RESULTS

Out of 100 clinically jaundiced neonates, exaggerated physiological jaundice (50%) was the most common cause of neonatal hyperbilirubinemia followed by blood group incompatibility. Blood group incompatibility was seen in 36% cases (ABO incompatibility 22% Rh incompatibility 11%, combined Rh and ABO incompatibility 3%), sepsis 10%, blood group incompatibility with sepsis 2%, large cephalhematoma 2%. Long-term follow-up in this study would have evaluated the morbidity and mortality of these cases

Table 1: Etiology of neonatal jaundice (n=100).

Etiology	No. of patients	%
Exaggerated physiological jaundice	50	50
Abo incompatibility	22	22
Rh incompatibility	11	11
Combined Rh and ABO incompatibility	3	3
Sepsis	10	10
Blood group incompatibility with sepsis	2	2
Cephalhematoma	2	2

Table 2: Two groups based on TSB levels at admission.

Serum bilirubin(total)	
Severity	**Frequency**
Moderate	84
Severe	16

The mean TSB levels in the study was 17.50 mg/dl. The 100 cases in the study were divided into 2 groups based on severity of hyperbilirubinemia (Table 2).

Moderate group: 84 cases were recruited with average peak TSB level of 18.8mg/dl (range = 15 to <20 mg/dl).

Severe group: 16 cases were recruited with average peak of 25mg/dl (range ≥20mg/dl). All subjects in the study received phototherapy with 9 individuals (9%) receiving exchange transfusion 1 in moderate group; 8 in Severe group.

Among the 9 infants receiving exchange transfusion 3 had abnormal outcome in BERA and neurodevelopment during regular follow-up and all the 3 cases had blood group incompatibility either ABO or Rh incompatibility as risk factor with peak TSB level >20mg/dl. The BERA outcome of 100 neonates of average age 3.2 months (range = 1-6 months) is shown in Table 3.

Table 3: BERA outcomes.

Follow-up	BERA	
	Normal	Abnormal
At 3 months	97	3
At 6 months	97	3

97% of the infants had Normal BERA. 3 (3%) out of 100 infants had abnormal BERA at initial assessment. These 3 cases with initial abnormal BERA had a repeat BERA at 6months of age. All the 3 cases had blood group incompatibility either ABO or Rh incompatibility as risk factor with peak TSB level >20 mg/dl. The Outcome of BERA of 3 neonates with initial Abnormal BERA remained abnormal at 6 months of age. out of the 3 infants with an abnormal BERA and blood group incompatibility, 2 cases in Severe group had profound bilateral sensorineural hearing loss and 1 case in moderate group had slightly elevated hearing threshold (50 dB nHL).

Table 4: Neurological evaluation.

Follow-up	Neurological evaluation	
	Normal	Abnormal
At discharge	97	3
At 3 months	97	3
At 6 months	97	3

Neurodevelopmental outcome

97% of neonates had a normal neurodevelopmental outcome during short term follow up. 3% of neonates had BIND as shown in Table 4.

There was significant difference in the rate of abnormalities of neurodevelopment among the moderate and, severe groups.

3 cases (1 in moderate group; 2 in severe group) with initial abnormal BERA had motor delay, hypotonia, gaze palsy, microcephaly on follow at the age of 6 months.

Table 5: Comparison of neurological outcome between moderate and severe groups.

Measurement		Neurological evaluation		Fisher's exact test
		Normal	Abnormal	
Serum bilirubin (total)	Moderate	83	1	P<0.01
	Severe	14	2	

2 cases in the severe group had statistically significant abnormal neurological outcome when compared with moderate group).

DISCUSSION

Our study has shown the short term neurophysiological (BERA) and neurodevelopmental effects of hyperbilirubinemia. In our study cohort are favorable, if early close surveillance and intervention approach were followed. The studies of short-term effect of hyperbilirubinemia on BERA are summarized in Table 6.

Table 6: Studies of short-term effect of non-hemolytic or haemolytic hyperbilirubinemia on BERA.

Authors/ geographic location	BERA test age	BERA outcomes (abnormal rate)
Non-hemolyticetiology		
Gupta et al[3]	3 months	0/25 (0%)
Sabatino et al[4]	3 months	0/48 (0%)
Wong et al[5]	3.1 months (mean age)	9/99 (9.1%)
Agrawal et al[6]	2-4 months	7/30 (23.3%)
Sharma et al[7]	2-4 months	7/30 (23.3%)
Gupta et al[8]	6 months	4/60 (6.7%)
Rhee et al[9]	6 months	2/11 (18.2%)
Funato et al[10]	6 months	2/10 (20%)
Yilmaz et al[11] (Only 5/22 with non-hemolyticetiology	6 months	2/22 (9%)
Katona et al[12]	12months	7/39 (17.9%)
Pallotta et al[13]	12months	0/23 (0%)
Hosono et al[14]	12months	3/58 (5.2%)
Hemolyticetiology		
Yilmaz et al[11] (17/22 with hemolyticetiology)	6 months	2/22 (9%)
Chen et al[15]	3.2 months (mean age)	3/29 (10.4%)

There was significant association between the peak TSB and BERA in the present study. Two Indian studies reported that neonatal jaundice was associated with significant transient abnormalities of BERA.[3,8] However, Thoma et al and Ogun et al have found no significant correlation between these parameters.[16,17] An Italian study recruited 48 term non-hemolytic hyperbilirubinemic infants with peak TSB of 14 to 26 mg/dl (238 to 442

µmol/L).[4] Acute phase BERAs and serial BERAs until 3 months of age were performed. The initial BERA for patient group was significantly higher than the control group, but post-therapy, none of cases in patient group had abnormal BERA, which was interpreted that hyperbilirubinemia can alter central neurotransmission in auditory brainstem pathways, but the effect was only transient. Indian studies found 4 patients out of 60 (6.7%) and out of 30 (23.3%) had persistent BERA abnormalities over 2-4 months or 6 months serial assessments.[7,8] However, one Indian study reported that none of 25 cases with hyperbilirubinemia had BERA abnormalities within 3 months of age follow-up and concluded that a transient toxic effect of bilirubin on the brainstem.[3]

Hosono et al revealed 3 infants in a study of 58 (5.2%) term infants had abnormal BERA in serial tests until 12 months of age, while Katona et al claimed 7 out of 39 (17.9%) had BERA abnormalities assessed at age of 1 year, with 2 infants of the 7 found suffering serious hearing loss and therefore needing hearing aid, while 5 others had sub-clinical BERA changes.[14,12] Other studies that recruited a small number of subjects (<11 subjects) reported up to 20% patients with abnormal BERA within 6 months follow up.[9,10]

Present study has shown that 97% of the studied cases had normal neurodevelopmental outcome over 6 months serial evaluations with the exception of 3 cases (3 %) with abnormal BERA at 3- and 6-months assessment and these 3 cases had abnormal neurodevelopment, signs of BIND having motor delay and hypotonia at age of 3 and 6 months. BERA and neurodevelopmental outcome were significantly correlated in the study.

Funato et al revealed that delay in improvement of BERA abnormalities might be used as an early predictor for chronic bilirubin encephalopathy.[10] A study done by Agrawalet al proposed that serial BERA was a useful noninvasive tool to detect neurodevelopmental delay secondary to neonatal hyperbilirubinemia.[6] However, one Italian study also reported that there was no subsequent neurodevelopmental abnormality for all patients with serial neuropsychological evaluations over a 3-year follow-up.[4] A long-term Turkish study by Ozmert et al, reported 9 children with neonatal hyperbilirubinemia with prominent neurological abnormalities having abnormal BERA.[18]

There are three main limitations to the present study. One limitation is that we did not have any untreated cases as a control group due to ethical reasons, although few studies have recruited control cases.

A second limitation was that we did not explore the relationship between the outcome of BERA or neurodevelopment and the duration of exposure to hyperbilirubinemia, since the level of bilirubin in the brain and the duration of exposure to bilirubin are both important determinants of the neurotoxic effects of bilirubin.

A third limitation of our study is that it is a very short-term study of 6 months duration and we did not perform psychometric assessments such as DQ test for recruited cases as children with transient auditory neuropathy and BERA abnormalities may be at risk for later developing central auditory processing disorders.

CONCLUSION

The prevalence, aetiology and the outcome of neonatal hyperbilirubinemia varies from country to country, even in different areas of same country. Several studies regarding neonatal hyperbilirubinemia have been conducted in different countries. Neuroimaging studies and BERA combination would have been appropriate choice in predicting short term and long-term outcome. Long term follows up (up to 18 months) would be more appropriate in these cases in predicting long term neurodevelopmental outcome.

Recommendations

It is recommended that a future study be carried out on the children recruited in the current study to further evaluate the more long-time effects of hyperbilirubinemia on neurophysiological and neurodevelopmental outcomes, especially for those who had suffered from abnormalities either in BERA or in neurodevelopment. More evaluations including psychometric assessments are recommended for future research.

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