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Assessment of hearing in newborns with hyperbilirubinemia using otoacoustic emmisions and brainstem evoked response audiometry

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***Abstract*---**The early linguistic age when language and speech skills develop is between 3-5 years. Speech is essential for communication and hence an important part of a normal life. Permanent hearing loss in children remains a public health problem and hence its prevention is an utmost important public health programme -The National Programme for Prevention and Control of Deafness. Neonatal hyperbilirubinemia is seen in about 2.3% of newborns. It is a common adverse effect that puts neonates at a high risk for hearing impairment. Bilirubin encephalopathy is due to raised unconjugated (indirect) bilirubin. Unconjugated bilirubin crosses the blood-brain barrier and, because it is lipid soluble, it penetrates neuronal and glial membranes too. Most of the tests used for assessing the hearing status in an individual require the cooperation of the subjects which is obviously not found in infants. Therefore, objective tests not requiring the infant's cooperation can be used effectively. This study uses oto acoustic emissions (OAE) test as a screening test, and brain stem evoked response audiometry test (BERA) as a definite test for assessment of hearing in newborns with hyperbilirubinemia. To assess hearing impairment in newborns with hyperbilirubinemia. To study the incidence of hearing loss using OAE and BERA in newborns with hyperbilirubinemia. This was a prospective observational study conducted in 234 patients during the period November 2019 to April

2021 in all patients being treated for hyperbilirubinemia in the department of ENT and Paediatrics of a tertiary care teaching hospital. After obtaining clearance from the institutional ethics committee and prior informed consent, all clinically diagnosed patients of hyperbilirubinemia were included in the study. Out of 234 neonates with hyperbilirubinemia 13 (5.55%) had hearing impairment. 57 (24.35%) out of 234 neonates showed hearing impairment on OAE at the time of inclusion in the study. Out of these 57, 48 (20.5%) were having additional comorbidities like preterm birth in 30 (12.82%), low birth weight in 8 (3.41%), meconium aspiration syndrome in 11 (4.70%), sepsis in 3 (1.28%) had hearing impairment and 13 (5.55%) had persistent hearing impairment during follow up at 6 months and requiring further management. A significant association was noted with cases of hyperbilirubinemia in pre term neonates and neonates with sepsis. 97 (41.45%) preterm neonates were suffering from hyperbilirubinemia. Out of 97, 30 (12.82%) had Refer on OAE at enrolment and 8 (3.41%) had abnormal BERA at 6 months. The p value was <0.0001 and therefore statistically significant. Out of 234 neonates 9 (3.846%) had sepsis and of these 9, 3 (1.28%) had refer on OAE at enrolment and abnormal BERA at 6 months. The p value is <0.0001 and therefore statistically significant. Only hyperbilirubinemia was seen in 9(3.84%) neonates with hearing impairment. Out of these 57, 52 (91.22%) required exchange transfusion and 5 (8.77%) required phototherapy. To summarize, 5.55% of neonates suffering from hyperbilirubinemia had hearing impairment. 3.41% of the newborns were preterm and 1.28% had sepsis. A significant association of hyperbilirubinemia and hearing impairment found in neonates. Also, a significant association of hearing impairment and hyperbilirubinemia was seen amongst neonates born preterm and having perinatal sepsis. The significant hearing improvement, post treatment and during follow up using chi square test was found to be 26.807.

***Keywords*---**assessment, newborns, hyperbilirubinemia, otoacoustic emmisions, brainstem evoked.

Introduction

Speech is essential for communication and hence an important part of day to day life. The early linguistic age when language and speech skills develop is between 3-5 years. About 5.3% of the world population suffers from disabling deafness and 9% of those are children. Therefore, the problem of permanent hearing loss during early age in children has been a part of a major government public health programme i.e. The National Programme for Prevention and Control of Deafness, started in 2007.(1). Neonatal hyperbilirubinemia is commonly encountered in about 2.3% of newborns and having adverse effect on hearing. Hyperbilirubinemia is seen to involve about 70% of term babies and 80% of preterm babies during first week of life.(2)

The auditory pathway, including the inner hair cells, cochlea and the auditory nerve are one of the most sensitive parts of the nervous system to toxic agents. Severe neonatal hyperbilirubinemia is a common cause of Sensorineural hearing loss in neonates along with some level of auditory neuropathy. Bilirubin encephalopathy and auditory neuropathy are the two ways in which hyperbilirubinemia may lead to hearing impairment. Bilirubin encephalopathy is due to unconjugated (indirect) bilirubin. Unconjugated bilirubin crosses the blood-brain barrier and, because it is lipid soluble, it penetrates neuronal and glial membranes. Microscopically, they show necrosis and loss of neurons along with gliosis and atrophy. Bilirubin binds to cell membranes and is toxic to neurons and oligodendroglia. It damages mitochondria, inhibits oxidative phosphorylation, and causes calcium release promoting apoptosis. It also stunts axonal and dendritic growth. The acute toxic injury is aggravated by inflammatory reactions of microglia and astrocytes.[3-5] Auditory Neuropathy spectrum disorder has been described secondary to other co-morbid conditions that are common during the neonatal and post-neonatal period. It is caused due to toxic substances that reduce the neurotransmitter release from the inner hair cells causing disruption in the activation of dendrites of the auditory nerve.[6]

Most of the tests used for assessing the hearing status in an individual require the cooperation of the subjects which is obviously not possible in infants. In this study, we have used Oto Acoustic Emissions (OAE) test as a screening test, and Brain Stem evoked response audiometry test (BERA) as a definite test for assessment of hearing. These tests are objective tests and obviates patient's cooperation during testing, thus can be used effectively in infants. Otoacoustic Emissions or OAE are a part of a biological process that involves waves generated by movement of the basilar membrane and are measured in the external auditory canal. Stimulus invokes movement of the basilar membrane, which in turn causes the outer hair cells to move, or be deflected. Specifically, when the outer hair cells move, their stereo cilia bend in one direction or the other. Ions rush in and rush out, changing the membrane potential within the hair cell. The changes in voltage across the plasma membrane lead to OHC length changes (shortening and lengthening), which are called electro motility. The electro motility of the outer hair cells has a feedback effect on the basilar membrane, causing it to vibrate. Therefore, the electro motility of the outer hair cells is thought to be the mechanism which underlies OAE.This activity can be elicited either spontaneously or can be evoked and are measured by electrodes kept in the external auditory meatus. It is indicative of a healthy cochlea and functional tympanic cavity. It is also cost effective and easy to conduct, therefore repeatable.(6)

Brainstem Evoked Response Audiometry (BERA) is an alternative audiometric test of assessment of auditory function. It is an electrophysiological test and hence it essentially determines the anatomical and physiological integrity and hence the functionality of the auditory system. It ascertains the response of the auditory pathway to a stimuli either click or a narrow band chirp. The waves in response are recorded using electrodes placed over the scalp at fixed positions and studied. It is similar to a study of brainwaves as seen on Electroencephalogram (EEG). It is an effective and non invasive method of assessment that is not affected by state of consciousness and hence now become a popular method of audiological

assessment. (7). This study of hearing impairment has been conducted amongst the newborns with hyperbilirubinemia, at tertiary care hospital of rural western Maharashtra. This type of study has not been conducted in this population, and hence, is unique. This is a prospective observational study conducted in all patients being treated for hyperbilirubinemia in the department of Paediatrics at a tertiary care teaching hospital by their audiological assessment at the time of diagnosis and on follow up with OAE and BERA and thus find out the incidence of hearing impairment in these neonates.

Materials and Methods

This is a Prospective Observational study was conducted in 234 patients during the period November 2019 to April 2021 in all patients being treated for hyperbilirubinemia in the Department of Paediatrics and ENT of a tertiary care teaching hospital. After obtaining clearance from the institutional ethics committee and prior informed consent, all clinically diagnosed patients of hyperbilirubinemia were included in the study. The following patient parameters were also taken into consideration:

- Age
- Sex
- Gestational age at birth
- Comorbidities

Accordingly:

- OAE was done in all cases at enrolment that were receiving treatment.
- At follow up BERA was done at 3 and 6 months of age.

Based on the data of observation of OAE, BERA, co morbidities and the statistical analysis, result and conclusions were drawn.

Analysis of data

All the data tabulated was entered into MS-Excel. The Statistical Packages for Social Sciences (SPSS 24.0) was used. The present study was a prospective observational study in which the results were expressed as mean and standard deviation. Unpaired t-test was used for intergroup comparisons; association was done by using chi-square test. The $p \leq 0.05$ was considered as statistically significant.

Inclusion criteria

All neonates with hyperbilirubinemia being treated in Department of Paediatrics.

Exclusion criteria

- Neonates born with birth asphyxia
- Amino glycoside administered patients,

- Patients with Craniofacial malformations,
- Syndromic causes of deafness
- All causes of conductive deafness
- A family history of deafness

Observation

This is a prospective observational study was conducted in 234 patients during the period November 2019 to April 2021 in all patients being treated for hyperbilirubinemia in the Department of ENT and Paediatrics of a tertiary care teaching hospital. It was observed that minimum age of the babies was 5 days whereas maximum age was 31 days on the day of enrolment to study. The average age of the babies was 17.48±5.42 and among the 234(100%) subjects 151(64.53%) were females and 83(35.47%) were males. The male and female ratio was 1:1.819. On considering the co morbidities associated with the presenting symptoms, it was found that majority i.e. 137(58.54%) subjects was term and remaining 97(41.46%) subjects were preterm and 167(71.37%) of subjects were low in birth weight and 67(28.63%) of subjects were normal in birth weight.

Meconium aspiration was observed in 38(16.24%) of subjects and 15(6.41%) of subjects had sepsis. OAE was done in all cases at enrolment that were receiving treatment and at follow up at 3 months. Of the 234 neonates included in the study at the time of diagnosis the 177 (75.64%) had pass and 57 (24.34%) had refer and all the neonates of that had refer at the time of enrolment underwent OAE at 3 months and 15 (6.41%) showed refer and 38 (16.24%) showed pass. 4 (1.71%) neonates failed to follow up. The reduction of hearing impairment seen on OAE at 3 months on students t test had chi square test was 26.807 and p value <0.0001, which is significant. BERA at 3rd month, among the 51(100%) subjects 38(75.64%) were normal and 13(25.5%) were abnormal. BERA at 6th month, among the 51(100%) subjects 38(75.64%) were normal and 13(25.5%) were abnormal.

Among 234 (100%) 182 (77.78%) were given phototherapy and 52 (22.22%) and 5 (2.74%) out of 182 (100%) that were given phototherapy had OAE Refer on OAE at diagnosis. On follow up at 3 months 1 (00.54%) had OAE Refer and abnormal results on BERA. Out of 234 (100%) 52(22.22%) were given Exchange transfusion and 52 (22.22%) and all 52 that were given exchange transfusion had OAE Refer on diagnosis. On follow up at 3 months 14(26.92%) on OAE had Refer and abnormal results on BERA. At 6 months 13 (25%) of the 52 (100%) had abnormal results on BERA. Overall 13(5.55%) of 234 (100%) neonates suffering from hyperbilirubinemia, suffered from long term hearing impairment.

Discussion

Occurring in about 1–2 infants every 1000 births (8,9), prelingual sensorineural hearing loss (SNHL) is more frequent than other congenital pathologies. This value can raise 10- to 50-fold in presence of risk conditions associated with SNHL, particularly among NICU babies.Neonatal jaundice is a common disease that presents in 60% of term newborn and 80% of preterm ones during first week of life [10]. Hyperbilirubinemia at birth is a risk factor associated with hearing

loss that is usually further linked to other factors that might influence hearing synergistically, also, if left untreated, it may cause cerebral damage [11].

Prevalence of severe hyperbilirubinemia has increased in the past 2 decades. Studies have proposed causes for this increased incidence as decreased anxiety about birth time icterus and early discharge of the infants after birth (before 24–48 h) [12]. Hyperbilirubinemia is more prevalent in premature infants and remains more severe, in its course than in term neonates [74]. In this study, amongst all babies, 97(41.46%) were preterm and 137(58.54%) full term. In a similar study by Arora et al. (13-14), 41.42% neonates were also preterm. The newborns when studied according to their birth weight and it was observed that it was seen that majority 167(71.37%) of subjects were low birth weight and 67(28.63%) of subjects were normal in birth weight. This is similar to a study conducted by Sankar et al. in 2018 where a majority patients of LBW and needed phototherapy. (15).

It was also seen that 6.41% of the neonates had sepsis. This is in congruence with a study by Martines et al in 2013 where 5.9% of neonates had perinatal sepsis. (16). Of the 234 neonates included in the study at the time of diagnosis the 177 (75.64%) had pass and 57 (24.34%) had refer and all the neonates of that had refer at the time of enrollment underwent OAE at 3 months and 15 (6.41%) showed refer and 38 (16.24%) showed pass. 4 (1.71%) neonates failed to follow up. The significant reduction in impairment of hearing was seen on OAE at 3 months using students t test with chi square test value 26.807 -p value <0.0001**.** This was in congruence with various studies published over the years by Narden et al, Davis et al, Sutton et al, SHiu et al, Fortnum et al and Pitt et al. (17-22)

Also Steiner et al [23] measured the efficacy of phototherapy in reduction of exchange transfusion in NICU and found 3 out of 107 newborns required exchange transfusion. The previously mentioned studies agree with the findings of this study as very few severely affected subjects had undergone exchange transfusion. Significant hearing loss was seen in neonates at 6 months on BERA in 13 (5.55%) newborns. This is congruent to the study by Bhatt et al. Our study was also similar to those reported by Ohl et al. (4.55%), Meyer et al. (5.3%), Robertson et al. (3.1%) and Elahi et al. (7.9%). [85-88] This is also in congruence with the a study by Dwarkanath et al. [24] in which the distortion product OAE amplitude and signal-to-noise ratio improved significantly after phototherapy and BERA evaluation revealed in that study that 19 neonates had significantly prolonged wave V latency compared to normal, whereas no peaks were identified among other neonates.

Conclusion

In this study, hyperbilirubinemia and hearing impairment was found in 13 (5.55%) neonates which was significant. Also, a significant number of neonates having hearing impairment and hyperbilirubinemia and associated perinatal sepsis was found in 9(3.846%) neonates and in 97(41.45%) preterms. The hearing improvement, post treatment and during follow up was significant. Therefore, in all neonates having hyperbilirubinemia, a screening for hearing impairment is essentially required for early detection and timely intervention to prevent

resultant non development of speech. The study duration of 18 months may be looked upon as limitation.

Tables

Table 1
Descriptive statistics of age of baby (in days)

N	Minimum	Maximum	Mean	Std. Deviation
234	5.00	31.00	17.4786	5.42384

Table 2
Gender wise distribution of subjects

Gender	Frequency	Percent
Female	151	64.53
Male	83	35.47
Total	234	100

Gestational Age	Frequency	Percent
Preterm	97	41.46
Term	137	58.54
Total	234	100

Birth Weight	Frequency	Percent
LBW	167	71.37
Normal	67	28.63
Total	234	100

Meconium Aspiration Present	Frequency	Percent
No	196	83.76
Yes	38	16.24
Total	234	100

Sepsis Present	Frequency	Percent
No	219	93.59
Yes	15	6.41
Total	234	100

Table 5
OAE at Birth. (n=234)

OAE at Birth	Frequency	Percent
Pass	177	75.64
Refer	57	24.36
Total	234	100

Table 6
OAE at 3rd month. (n=234)

OAE at 3rd Month	Frequency	Percent
Pass at Birth	177	75.64
Defaulter	4	1.71
Pass	38	16.24
Refer	15	6.41
Total	234	100

OAE at Birth	Gestation Age			
	Preterm	Term	Chi-square	p-value
Pass	67(28.63%)	110(47.01%)	3.87	0.049
Refer	30(12.82%)	27(11.54%)		

BERA at 3rd months	Frequency	Percent
Normal	38	74.5
Abnormal	13	25.5

BERA at 6th months	Frequency	Percent
Normal	38	74.5
Abnormal	13	25.5

Study Variables	Hyp. Bil.+Preterm (n=38)	Hyp. Bil.+LBW (n=10)	Hyp. Bil.+No MAS (n=11)	Hyp. Bil.+No Sepsis (n=6)	Hyp. Bil. (n=11)
OAE at Birth	30(12.82%)	8(3.42%)	11(4.7%)	3(1.28%)	9(3.84%)
BERA at 6th Month	8(3.42%)	2(0.85%)	0	3(1.28%)	2(0.85%)
Chi-square Value	42.68	1.98	0.011	16.34	1.62
p-value	<0.0001*	0.16	0.91	<0.0001*	0.2

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