Audiological Assessment of Neonates with Hyperbilirubinemia

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Abstract: Background: Neonatal hyperbilirubinemia is a very common problem of newborn and can lead to serious neurological squeal. Transient otoacoustic emission (TOAE) and auditory brain stem response (ABR) are most widely used devices to assess newborns peripheral auditory sensitivity and pathway integrity respectively. Objective: to assess the auditory function in neonates suffering from hyperbilirubinemia, correlate different levels of bilirubin in neonates with ABR findings and to identify the effect of treatment of hyperbilirubinemia on neonates, auditory functions. Patients and Methods: 70 full term newborns with no risk factors for hearing loss; other than having hyperbilirubinemia with different bilirubin levels; requiring phototherapy and/ or exchange transfusion, compared to 30 normal neonates who were delivered normally or by caesarian section were included in this study. All were subjected to TOAE and ABR testing. Cases were tested before and after phototherapy and / or exchange transfusion. Results: our study revealed a referral rate of 18% by TOAE and 36% by ABR testing for the cases. The overall higher referral rates tended to occur more frequently in neonates with higher levels of total serum bilirubin (TSB) than in those with lower levels of TSb. After treatment of jaundiced newborns, 9 out of 25 refer cases (36% of ABR referral) showed improvement by AABR; which means that hearing affection may be transient. Conclusion. ABR is a sensitive tool to assess reversible bilirubin neurotoxicity and AABR is a time and cost effective device to be used for hearing screening neonates with hyperbilirubinemia.
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Key Words: Hyperbilirubinemia- Jaundice – Phototherapy- Exchange transfusion – Auditory brain stem response – Transient otoacoustic emission.

1. Introduction:

Hyperbilirubinemia is one of the most common neonatal transitional syndromes occurring in 60 to 70% of term infants and virtually all premature infants, with 1-2% of term or near term infants reaching total serum bilirubin levels of 20 mg/dL. It may reach extreme levels with a significant potential for irreversible brain damage and kernicterus **(Seoud et al., 2007a).**

Bilirubin is known to inhibit mitochondrial enzymes and affect DNA synthesis and ion exchange. It disturbs neuro-excitatory signals, and impairs nerve conduction (Dennery et al., 2001 and Sharpio, 2003). Some authors reported that the site of lesion in auditory impairment caused by hyperbilirubinemia may be retrocochlear, with the cochlea unaffected (Sano et al., 2005). Others reported that lesions may include the organ of Corti, especially at the outer hair cells and the cochlear nerve. In any case, it is presumed that neonatal ABR, which reflects functional integrity and the development of the auditory pathway up to the brainstem level, can be affected by hyperbilirubinemia (Rhee et al., 2001).

ABR has been proposed as an objective tool to evaluate acute bilirubin encephalopathy, not only because it is technically feasible to use at the bedside but also because the auditory system is probably the most sensitive neural system to clinically overt bilirubin injury. Early reports of the use of ABR described changes in ABR before and after exchange transfusion in term neonates with hyperbilirubinemia. These bilirubin – induced ABR changes progress from reversible prolongation of absolute wave latencies followed by loss of wave amplitude and ultimately the inability to detect an identifiable wave **(Sanjiv and Amin, 2004).**

Bilirubin can produce behavioral changes and alteration in ABR at total serum bilirubin below 20mg/dL. Wave I abnormalities, which reflects auditory nerve function, may be seen at higher bilirubin levels and in Kernicteric infants with hearing loss **(Wennberg et al., 2006).**

Aim of the study: To assess the auditory function in neonates suffering from hyperbilirubinemia, correlate different levels of bilirubin in neonates with ABR findings and to identify the effect of treatment of hyperbilirubinemia on the neonates' auditory functions.

2. Patients and Methods:

The study was performed on 100 neonates (200 ears) classified into 2 main groups: group, of cases; neonates with hyperbilirubinemia, they include 70 cases (140 ears) both males and females selected from neonatal intensive care units, El- Mounira Children Hospital and Children Hospital Cairo University. All of them were full term newborns; having hyperbilirubinemia with different bilirubin levels, with some requiring exchange transfusion and / or phototherapy.

Group of healthy neonates (control group) included 30 neonates, matched by age and sex to group of cases. Neonates with any risk factors for hearing loss as prematurity, intake of ototoxic drugs, encephalitis, septicemia, meningitis, TORCH infections, mechanical ventilation > 10 days and birth weight < 1500 grams will be excluded from the study.

All cases and controls were subjected to the following: Full history taking (pregnancy, antenatal. perinatal and postnatal). Clinical examination including otologic examination by inspection and otoscopic examination of the ear and the auditory meatus , noting size of the canal, any debris, wax or vernix. Total and direct serum bilirubin levels were done and audiological testing: otoacoustic emission using portable TEOAEs Screener and automated auditory brain stem response (AABR); by the Echoscreen device. (After the parents' consent).

Statistical Methods:

All the above data were collected and statistically tested by analysis of variance or students' t-test. Correlations were studied by simple persons coefficient. Significance was defined as $P< 0.05$.

3. Results:

A total number of 100 neonates (59 males and 41 females) were screened in this study, their gestational age ranging from 35-41 weeks with a mean of 38.5 wks ± 1.72 SD. Their age ranged from 1-4 days and birth weight was between 2000-4000 grams with a mean of 2953.3 grams ± 468.84 SD.

Based on the level of TSB, obtained just before the start of TEOAE and AABR recording, neonates were divided into 4 subgroups: neonates with TSB less than 15 mg/dL (n=10; 14.2%) those with TSB 15-20 mg/dL (n=16; 22.8%), those with TSB 20-25 mg/dL (n=20;28.5%) and those with TSB greater than 25 mg/dL (n=24; 34.2%).

The device used for hearing screening (portable TEOAE and AABR screener, Echo-screen plus TDA by Natus) uses a binomial statistical test to give either pass or refer results, by calculating the statistical probability that an emission or on ABR has recorded at a succession of sampling points ranging from 6 to 12 ms after the stimulus; this algorithm repeats until the acquired data fit with a template composed of auditory brainstem responses obtained at 35 dB from normal hearing newborns. Failure of an ear to attain this likelihood is reported as a refer result (versus a pass result), which indicates that the infant needs follow-up hearing testing (Fig. 1,2,3,4).

For this study, we considered bilateral refer results as abnormal and bilateral pass results as normal and so results are illustrated per subject, not per ear (unilateral pass or refer results were excluded); to maintain consistency in analyzing the data and ease of presenting and illustrating the results (Ahlfors and Parkers, 2008).

Table (1): Shows the overall results of TEOAE testing for cases and control groups where referral percentage was 18.6% in cases and 16.7 in controls; relative to the total number of neonates in each group. Chi-square test was not statistically significant ($P > 0.05$).

Table (2): Shows the over all results of AABR testing for cases and control groups where referral rate for jaundiced cases is much higher than that for controls, Chi-Square test was statistically significant ($P< 0.05$).

Table (3): Shows TEOAE testing results for different TSB groups where there is a statistically insignificant difference in Chi-Square test ($P < 0.05$) for the Pass and Refer results, but still highest referral percentage was in the group with highest TSB levels (> 25 mg/dL)= 29.9%; relative to the other groups.

Table (4): Shows AABR testing results for different TSB groups where there is a statistically significant difference in Chi-Square test ($p< 0.05$) for the Pass and Refer results. Moreover, the highest referral rates were in the group with highest TSB levels (> 25 mg/dL) = 87.5% relative to the other groups (indicating hearing affection).

Our results showed statistically significance for the AABR test duration, i.e AABR testing duration was longer for groups with higher TSB levels. Automatic retesting takes longer time for groups with high TSB levels; as the algorithm repeats until the acquired data fit, with the saved template of auditory brainstem responses on the device.

Table (5): Shows TEOAE results after management by phototherapy and / or exchange transfusion which is statistically significant i.e; Refer results for the groups that under went 3 times exchange transfusion (the group with highest TSB levels > 25 mg/dL) were highest. Group with TSB level < 15 mg/dL; all of them gave Pass results; as they under went phototherapy only and not exchange transfusion.

Table (6): Shows AABR results after management by phototherapy and / or exchange transfusion which is statistically significant; i.e; Refer

results by AABR for the group that underwent 3 times exchange transfusion were highest. Thus the more the number of exchange transfusion, the fewer the pass results for jaundiced neonates.

Table (7): Shows the overall AABR testing results before and after management where before management Pass = 19 and Refer = 25, after management Pass = 28 and Refer = 16 i.e after management 9 cases (20.4%) changed from Refer to Pass which indicates that after phototherapy or exchange transfusion, some of the AABR results in neonates with hyperbilirubinemia recovered quickly.

Our results showed that TSB groups were not statistically significant according to the gender distribution. Also TEOAE and AABR results with gender distribution showed statistically insignificant difference ($p > 0.05$).

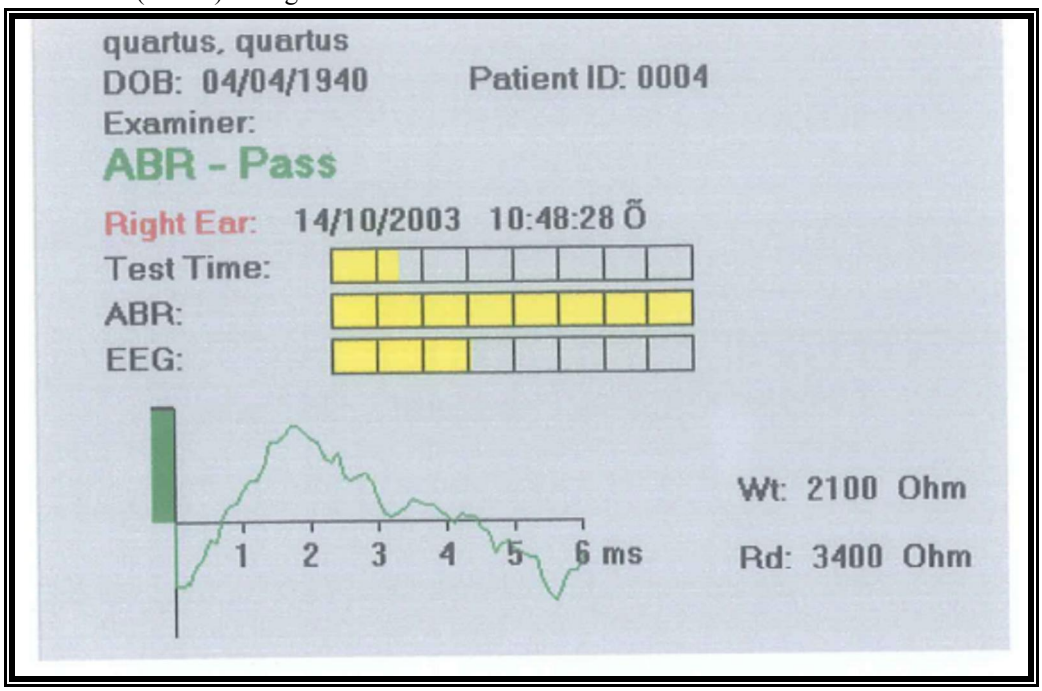

Fig. 1. Showing the Echo-screen ABR " PASS" result display.

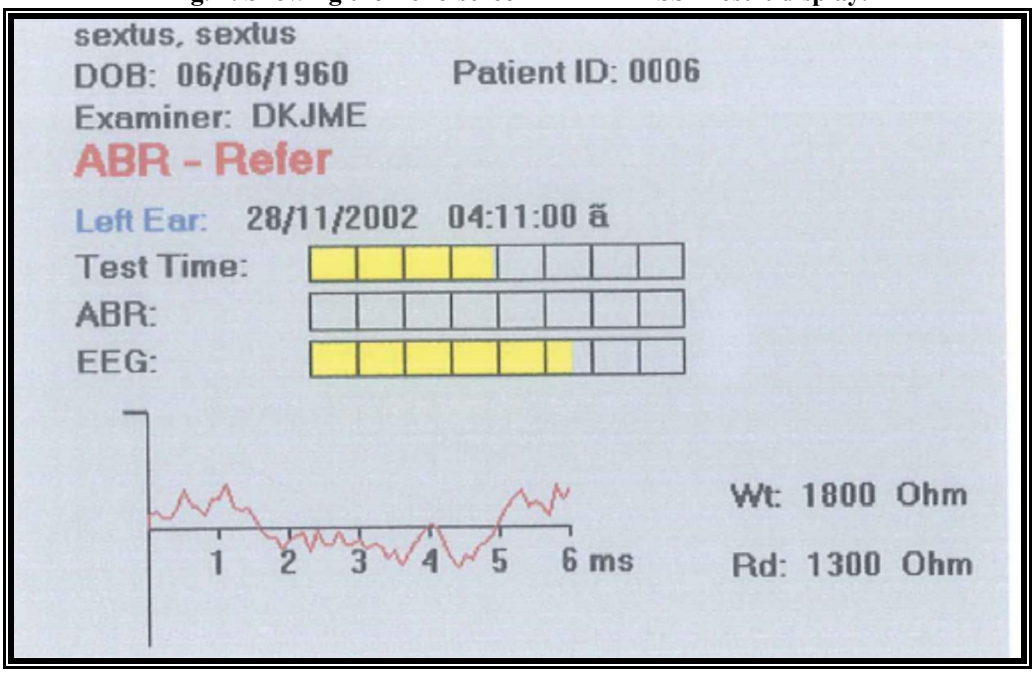

Fig. 2. Showing the Echo-screen ABR " REFER" result display.

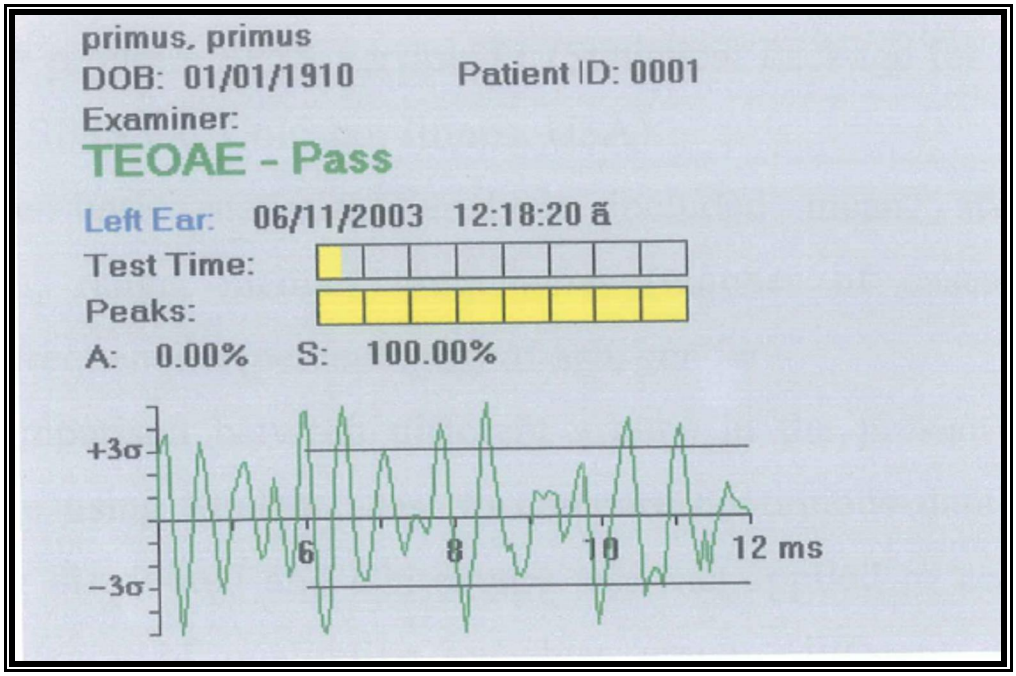

Fig. 3. Showing the Echo-screen TEOAE "PASS" result display.

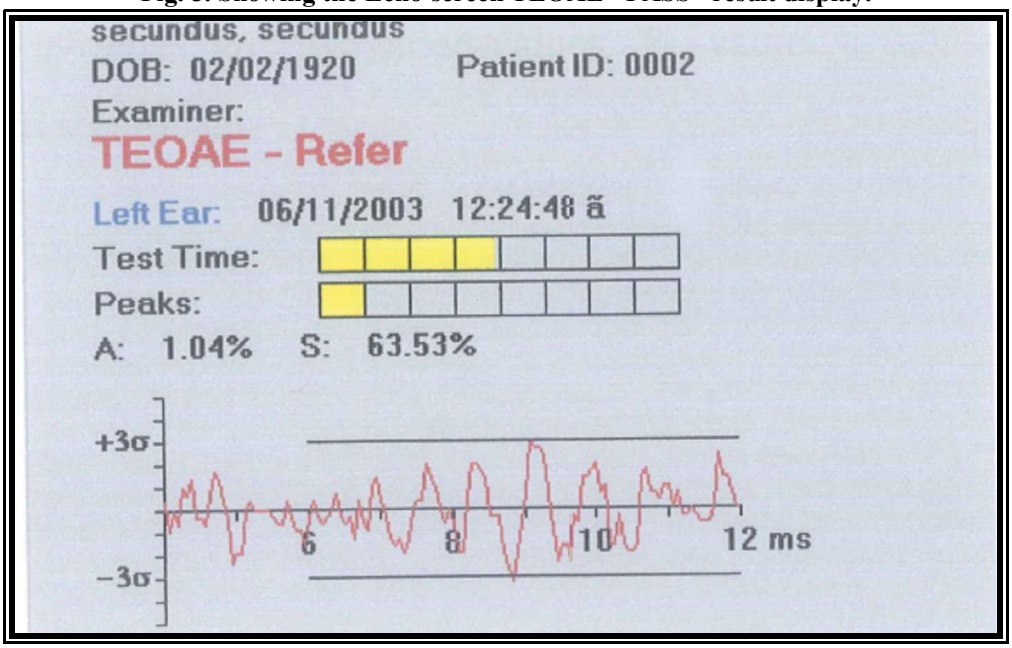

Fig. 4. Showing the Echo-screen TEOAE "PEFER" result display.

Table (1): Overall results of TEOAE testing for Cases & Control groups.

			GROUPS		Total cases
			Cases	Controls	
TOAE	Refer	Count	13	5	18
		% within GROUPS	18.6%	16.7%	18%
	PASS	Count	57	25	82
		% within GROUPS	81.4%	83.3%	82%
Total		Count	70	30	100
		% within GROUPS	100%	100%	100%

Table (2): Overall results of AABR testing for Cases & Control groups.

			GROUPS		Total cases
			Cases	Controls	
AABR	Refer	Count	28	8	36
		% within GROUPS	40%	26.7%	36%
	PASS	Count	42	22	64
		% within GROUPS	60%	73.3%	64%
Total		Count	70	30	100
		% within GROUPS	100%	100%	100%

Table (3): Showing TEOAE testing results for different TSB groups for the study group.

			TSB-GROUPS (mg/dL)				Total TSB
			TSB < 15	15-20	20-25	> 25	
TEOAE	PASS	Count	10	14	16	17	57
		% within TSB GROUPS	100%	87.5%	80.0%	70.8%	81.4%
	Refer	Count	0	2	4	7	13
		% within TSB GROUPS	0%	12.5%	20.0%	29.2%	18.6%
Total		Count	10	16	20	24	70
		% within TSB GROUPS	100%	100%	100%	100%	100%

Table (4): Showing AABR testing results for different TSB groups for the study group.

			TSB-GROUPS (mg/dL)				Total TSB
			TSB < 15	15-20	20-25	> 25	
AABR	PASS	Count	10	13	16	3	42
		% within TSB GROUPS	100%	81.3%	80.0%	12.5%	60%
	Refer	Count	0	3	4	21	28
		% within TSB GROUPS	0%	18.8%	20%	87.5%	40%
Total		Count	10	16	20	24	70
		% within TSB GROUPS	100%	100%	100%	100%	100%

Table (5): TEOAE results after management by Exchange transfusion & / or Phototherapy.

			Management				Total
			1E.T	2E.T	3 E.T	Phototherapy	
TEOAE	PASS	Count	7	12	0	38	57
		% within treatment	77.8%	85.7%	0%	90.5%	81.4%
	Refer	Count treatment	2	2	5	4	13
		% within treatment	22.2%	14.3%	100.0%	9.5%	18.6%
Total		Count	9	14	5	42	70
		% within treatment	100%	100%	100%	100%	100%

Table (6): AABR results after management by Exchange transfusion & / or Phototherapy.

			Management				Total
			1E.T	2E.T	3 E.T	Phototherapy	
AABR	PASS	Count	1	2	0	39	42
		% within treatment	11.1%	14.3%	0%	92.9%	60%
	Refer	Count	8	12	5	3	28
		% within treatment	88.9%	85.7%	100%	7.1%	40.%
Total		Count	9	14	5	42	70
		% within treatment	100%	100%	100%	100%	100%

Table (7): Showing the overall AABR testing results before & after management (by Phototherapy & / or exchange transfusion)

			Management	
			Before	**After**
AABR	PASS	**Count**	**19**	**28**
		%	43.2%	63.6%
	Refer	Count	25	16
		%	56.8%	36.4%
Total		Count	44	44
		%	100%	100%

4. Discussion:

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in newborns. Its clinical manifestation occurs in 60% of normal newborns and nearly all preterm neonates; as the serum bilirubin rises, the skin becomes more jaundiced in a cephalopedal manner (Watson, 2009).

In our study; the range of total serum bilirubin level was 12-55.2 mg/dL with mean of 33.6 ± 8.2mg/dL; compared to a study by Seoud et al., (2007b), where the range was between 8-55 mg/dL with mean of 23.6 ± 8.2 mg/dL and El-Hawary et al. (2009), the range of TSB was from 6.5-65.5 mg/dL with mean value of 24.5 ± 9.16 Sgro et al. (2006) found that mean peak of TSB level reported was 27.5 ± 4.4 mg.

In our study, phototherapy was used for almost all cases. Cases that did not respond to phototherapy having markedly elevated TSB levels (> 25 mg/dL) at presentation were managed mainly by exchange transfusion (40% of cases). Similar results were reported by Seoud et al. (2007b), where 30.3% required exchange transfusion on the other hand, a study done in San Francisco, USA by Newman et al. (2006), reported that 3.5% only required exchange transfusion, which is lower compared to our Egyptian results. Delayed seeking of medical advice may contribute to high levels of serum bilirubin requiring exchange transfusion in our country.

Hyperbilirubinemia during the neonatal period is known to be an important risk factor for neonatal auditory impairment. Previous researches on hearing impairment effect of neonatal jaundice concentrated on peripheral auditory (sensory, cochlear or sensorineural) impairment and gave little attention to central auditory impairment (Wilkinson and Jiang, 2006).

In most of the studies performed on jaundiced neonates; testing was usually done by using either automated or diagnostic ABR, as that of Sharma et al. (2007), Ze Dong et al. (2007) and Ahlfors and Parker, (2008). However, in our study we used both TEOAE and AABR screeners for hearing screening of all our subjects as neonatal jaundice cases are more likely to develop central rather than peripheral hearing loss. Hearing screening in this study was done between 2-7 days of life, a time by which the vernix and amniotic fluid have cleared spontaneously from the ear, and inspection was done before screening to check the external ear canal in order to decrease failure rate and also the test was carried out while the newborn was in a state of quiet sleep or at least alert and quiet, no sedatives were used in this study.

Another important factor in assessing feasibility is the duration needed to accomplish the test. In this work the average time needed for recording TEOAE was 50.44 sec per ear and 274.89 sec per ear for ABR. The average registered time was 4.5 minutes ± 2 minutes. Ng and Yun; (1992), reported 3.6 minutes, and 3.3 minutes by Maxon et al. (1993).

El-Dansoury et al. (2003), reported longer time, 13.5 ± 6 minutes, most probably due to recording in awake babies.

Our preliminary data indicated that after phototherapy or exchange transfusion, some of the ABR results (Refer) in neonates with hyperbilirubinemia recovered quickly, suggesting that the auditory impairment is largely transient and may improve if treated appropriately and in time. This is similar to findings by other investigators (Wong et al., 2006). Thus; ABR was a more sensitive test than TOAE.

All these variables only correlated weakly with the level of TSB, in spite that our study did not include any ABR traces, showing the absolute or the interwave latencies of the waves and how they are affected by hyper bilirubinemia. However, it further revealed that there were no major differences in

AABR results between the neonates with different levels of TSB, except for the significant affection in the neonates with TSB greater than 25m/dL, when compared with those with TSB at 10-15 mg/dL, which is close to the results reported by Ze Dong et al. (2007), where there was a significant increase in wave V latency and I-V interval in the neonates with TSB greater than 20 mg/dL when compared with those with TSB at 11-15 mg/dL.

Bilirubin has specific predilection for the auditory neural pathways, therefore, early detection of bilirubin-induced neuronal injury may be possible by the use of auditory brain stem responses (ABR). ABR changes induced by bilirubin progress from reversible prolongation of the absolute latencies of waves III and V follwed by loss of wave amplitude and ultimately the inability to detect on identifiable wave. These reversible changes may persist for up to 24 hours after the decrease in total serum bilirubin concentrations. Furthermore, prolonged bilirubin toxicity may cause irreversible sensorineural hearing loss (Sanjiv et al., 2001).

An Automated ABR (AABR) refer results of one or both ears occurs in perhaps 4% of new born hearing screening tests, while congenital hearing loss occurs in just 1-2 babies per 1000. Many of the screening refer results of AARB are therefore not due to congenital hearing loss and the "false positives" are usually attributed to technical (movement) or anatomical (ear canal obstruction) difficulties (Ahlfors and Parker, 2008).

Our study revealed 18% (refer) results by TEOAE and 36% (refer) results by AABR for the study group, which were higher than the percentage of Ze Dong et al. (2007), who found that 28% of neonates had BAER abnormalities, suggesting auditory impairment peripherally or centrally, but the BAER abnormalities tended to occur more frequently in neonates with higher levels of TSB than in those with lower levels, which was the same conclusion of our results.

Salvago et al. (2013), found high sensorineural hearing loss percentages (9.52%) in NICU babies suffered from hyper bilirubinemia. Also Nickisch et al. (2009), detected hearing function disorders in 87% (13/15) of the neonatal hyperbilirubinemia group ranging from total deafness to normal behavioral audiometry. On the other hand Heimler and Sasidharan, (2010), found that none of the children had a neurosensory hearing deficit or any significant neurological deficiency.

Our results showed that, after treatment (phototherapy and / or exchange transfusion) of jaundiced newborns, some of them (9 out of 25 Refer cases = 36% of AABR referral); showed improvement by AABR (changed into Pass). Sharma et al. (2007), reported similar findings, where improvement (normalized waves latencies) was recorded in 15 cases out of 22 jaundiced neonates. Improved brain functions may be due removal of bilirubin from the brain stem by phototherapy and / or exchange transfusion, thus postulating the hypothesis of transient bilirubin toxicity or transient brain stem encephalopathy. However, persistence of abnormalities in some cases may be due to permanent damage peripherally caused by axonal degeneration and loss of myelin rather than hair cells loss.

5. Conclusion:

Highest level of referral rates was among the group with highest TSB levels (>25mg/dL) either by TEOAE (29.2%) or by AABR (87.5%); which is even a more sensitive tool to detect hearing affection for neonates with hyperbilirubinemia. Using TEOAE and AABR screeners for hearing screening of jaundice cases was a time and cost effective screening test.

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