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RESEARCH ARTICLE

Relationship between auditory brainstem response and neonatal hyperbilirubinemia before and after treatment

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Abstract

Background and Aim: Neonatal jaundice is one of the common causes of early sensorineural hearing loss and an important cause of deafness in children. Auditory responses are the most sensitive parts of the nervous system to the toxic effect of bilirubin. This study was aimed to examine the effect of neonatal hyperbilirubinemia and its treatment on auditory brainstem responses (ABR).

Methods: In this before-after and experimental study, a total of 44 term neonates who were admitted to the neonatal ward due to bilirubin level of ≥15 mg/dl after the third day of birth were entered to the study. The first ABR examination was carried out within the first day of admission and repeated after treatment if it was abnormal. Comparisons were drawn to examine the correlation between ABR changes and the level of bilirubin and ABR changes before and after treatment of hyperbilirubinemia. $p<0.05$ was considered significant, and statistical power of the study was 90%.

Results: ABR was abnormal in 45% of the understudy population. The most common abnormality was prolonged latency of wave V (90%, p=0.0001). Other abnormalities were prolonged interpeak latencies (IPL) of wave I-III (85%, p=0.692), prolonged latency of wave III (65%, p=0.0001), prolonged IPL of wave I-V (25%, p= 0.087) and prolonged wave I (4%, p=0.0149). ABR was repeated on six neonates, four cases (67%) of which had normal ABR and the other two (33%) were abnormal.

Conclusion: ABR evaluation should be routinely performed in neonates with hyperbilirubinemia regardless of the presence of bilirubin-induced encephalopathic findings.

Keywords: Acute bilirubin encephalopathy; auditory brainstem response; hyperbilirubinemia

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Introduction

Unfortunately, bilirubin level on its own is not a specific criterion to predict the incidence of bilirubin-induced neurotoxicity. Since neurotoxicity is reversible in early stages, early diagnosis and appropriate treatment modalities to reduce the level of bilirubin play a crucial role to lower the rate of morbidity and mortality [1]. Neonatal jaundice is one of the common causes of early sensorineural hearing loss (SNHL) and an important cause of deafness in children. In fact, auditory tracts are the most sensitive parts of the nervous system to the toxic effect of bilirubin [1,2]. Kernicterus, especially in most of the premature neonates, occurs in lower

levels of bilirubin, and the total serum bilirubin in these neonates is not a reliable predictor for hyperbilirubinemia-induced encephalopathy [3], hence, a better criterion is needed to predict the probability of encephalopathy. Bilirubin has a specific correlation with auditory neural tract; therefore, early detection of the bilirubin-induced damage via auditory brainstem response (ABR) is an appropriate way to diagnose encephalopathy before the incidence of the classic signs of kernicterus. Hearing defect in infants leads to life time obstacles in language learning and speaking, learning problems during academic education, impaired social relationship and mental and emotional problems [4]. ABR is known as a non-invasive, sensitive, useful and effective method in diagnosis of early neural complications induced by hyperbilirubinemia in neonates [1,2]. Different studies have been indicative of the absence or latency of waves and interval between waves in ABR test if nervous complications occur due to hyperbilirubinemia [1,2,5]. Measurable and comparable variables which can be indicative of the abnormality in ABR results consist of wave I and III latencies, wave V mean latency, interpeak interval of III-V, I-III, I-V waves, or lack of each wave in ABR as well as its emergence after treatment of hyperbilirubinemia [1,2,5]. Though many authors have repeatedly stressed the necessity of performing ABR on all infants with high bilirubin levels, for various reasons, this recommendation is not routinely carried out in Iran [1,2]. One reason is that there is often no ABR equipment close to neonatal units, and in some cases, hospitals do not have them altogether.

Ethnicity is another important factor influential in the increase of bilirubin. A high level of bilirubin (approximately 17-18 mg/dl) is used as standard for over three days of phototherapy in term infants [1,2]. However, since eastern and Mediterranean races have a higher risk of hyperbilirubinemia, we studied bilirubin levels of 15 mg/dl and above to gather information about ABR in lower levels of bilirubin as well to determine whether there is ABR abnormality in infants with lower levels of bilirubin, who frequently undergo phototherapy in Iran. The present study aimed to evaluate the effect of hyperbilirubinemia and its treatment on ABR.

Methods

This before-after and experimental study was performed during 2010-2011 in the neonatal ward of Vali-e-Asr Hospital. 44 term neonates who were admitted to the neonatal ward due to bilirubin level of ≥ 15 mg/dl after the third day of birth entered the study. Premature neonates, neonates with asphyxia (Apgar score < 3 at 5 min), history of sepsis, anomalies of the nervous system, family history of hearing loss, chromosomal abnormalities, craniofacial malformations, history of using of ototoxic medicine, and drugs affecting the bonding of bilirubin and direct hyperbilirubinemia did not enter the study.

All understudy neonates were examined by a resident and a fellowship of neonatology, and signs of the nervous system involvement were recorded. Given the level of the non-conjugated bilirubin, phototherapy or blood exchange were performed as an appropriate treatment according to the protocols of the neonatal ward. All neonates underwent routine tests for evaluation of jaundice, complete blood count (CBC), coombs, reticulocyt count, bilirubin total and direct, Glucose-6-phosphate dehydrogenase (G6PD), blood group of mother and neonate, urine analysis. Moreover, OAE was routinely performed according to the screening program. The first ABR was carried out within the first 24 hours of the admission. If it was normal, repeating the test was not recommended by neonatologists and audiologists. Hence, the second ABR would be performed after treatment, if bilirubin decreased to less than 10 mg/dl and the first ABR was abnormal. An auditory evoked potential system (Charter ICS, Denmark) was used to record ABR. A click type stimulus was used twice with rarefaction polarity, with Intensity of 35-80 dB nHL, under 21/1 pulse which was set based on 1500 trials and analysis time of 10-15ms.

All of the neonates had been sedated by oral chlorate hydrate, 50mg per kg of body weight half an hour before the test. Four electrodes were applied as follows: two active ones were placed on mastoid bones, the reference electrode on vertex, and the ground electrode on the forehead. Recorded waves were analyzed and interpreted by an expert audiologist. Measurable and comparable variables consisted of mean latency of V, III and I waves, interpeak interval of I-III, III-V, I-V waves and no waves.

Neonates were divided into two groups according to the normal and abnormal results of the ABR, and they were compared in terms of bilirubin level and ABR changes before and after treatment.

Given the moral and ethical considerations, all of the recorded data remained completely confidential. All of the participants were clearly informed about the study objectives and how to participate in the study. Parents gave informed consent. All under study cases received adequate care and treatment, and no extra cost was imposed on patients. No intervention inconsistent with the trend of treatment was done. This study was ethically approved by the Research Committee of Tehran University of Medical Sciences.

Although this is a referral center and a lot of patients come from other cities, unfortunately, ABR test was repeated only on six neonates (30%), since others did not refer to the hospital after discharge.

Data were collected and analyzed by SPSS 19, birth weight, age, parity, bilirubin level, gestational age, reticulocyte count, hemoglobin, prolonged latency of waves and prolonged interpeak latencies, between two groups were analyzed using t-test.

Frequencies of prolonged latencies of auditory responces were compared between before and after treatment by McNemar test. To compare. Bilirubin levels in each group before and after treatment paired t-test was used. Gender effect was analyzed by chi-square test. $p<0.05$ was considered significant, and statistical power of the study was 90%.

Results

Demographic data of 44 neonates are shown in Table 1. 36% of deliveries were vaginal and 64% were done by cesarean section.

All neonates had negative coombs, and all neonates G6PD were sufficient. Mean reticulocyte count was 3.6 (SD=1.64), mean hemoglobin was 15.2gr % (SD=1.69), mean bilirubin level on the day of admission was 18.9 mg with SD 2.7, (range: 15.7-27), mean bilirubin level after treatment was 8.9 (SD=2.7) mg/dl [4,8-10]. Minimum and maximum levels of bilirubin in neonates with abnormal ABR were 15.8 and 26 mg/dl, respectively. No significant relationship was seen in terms of reticulocyte count and hemoglobin between the two groups ($p=0.506$, 0.481). No significant difference was found in the level of bilirubin before and after treatment in the two normal and abnormal groups of ABR ($p=0.452$, 0.922). However, when the two groups were divided into smaller groups in terms of wave and interpeak abnormality, and no abnormality, significant wave abnormality was found in higher level of bilirubin ($p=0.005$).

All neonates (100%) underwent phototherapy; however, three of them (6.8%) had blood exchange besides phototherapy which was due to the high level of bilirubin and therapeutic indications. OAE was normal in both ears of 43 neonates (97%), and repeated test was normal for other three percent. Abnormal ABR (prolonged latency in waves and interpeak latencies) was reported in 20 neonates (45%) before intervention. ABR waves was shown in Fig. 1, before and after treatment (abnormal and normal ABR) in one of the neonates (A was before and B was after treatment).

Neonates were divided into two groups according to normal and abnormal ABR, results of which are compared and shown in Table 2.

The most common abnormalities noted in 20 cases of ABR are as follows:

Prolonged latency of wave V (90%) followed by prolonged interpeak latencies I-III (85%), prolonged latency of wave III (65%), prolonged interpeak latencies of waves I-V (25%), and prolonged latency of wave I (4%). No absence

Table 1. Demographic data and bilirubin levels in normal and abnormal ABR groups

		Normal ABR		Abnormal ABR		Total		p
		Mean (SD)	Percent (n)	Mean (SD)	Percent (n)	Mean (SD)	Percent (n)	
Gestational age (week)		38.6 (0.83)	-	37.8 (1.15)	-	38.2 (1.06)	-	0.012
Parity		1.6 (0.83)	-	1.2 (0.4)	-	1.4 (0.7)	-	0.046
Gender Percent (n)	**Female**	-	12-52.2%	-	6-28.6%	-	18-40.9%	0.099
	Male	-	11-47.8%	-	15-71.4%	-	26-59.1%	
Birth weight (gr)		3135 (315)	-	3308.80 (436)	-	3217.95 (383)	-	0.135
Age at admission (days)		6.2 (2.8)	-	5.0 (1.5)	-	5.6 (2.3)	-	0.088
Weight (gr) at referring to the hospital		3058 (356)	-	3055 (371)	-	3056 (359)	-	0.977
Bilirubin levels (mg/dl) on the day of admission		18.6 (2.5)	-	19.2 (3.0)	-	18.9 (2.7)	-	0.452
Bilirubin levels (mg/dl) after treatment		11.0 (2.9)	-	11.0 (1.8)	-	11.0 (2.4)	-	0.922
Type of treatment	**Phototherapy percent (n)**	-	23-56.1%	-	18-43.9%	-	41-93.2%	0.583
	Blood transfusion percent (n)	-	1-33.3%	-	2-66.7%	-	3-6.8%	0.430

of waves was reported.

Although this is a referral center and many patients come from other cities, unfortunately, ABR was repeated only on six neonates (30%), four of which (67%) had normal ABR after treatment and two (33%) were abnormal who were referred to an ENT specialist for follow up.

Discussion

ABR is a suitable test for early detection of the bilirubin-induced nerve damage. Normally, I, III, V waves are seen in term neonates. Wave I is related to the initial part of the auditory nerve near the cochlea, wave III is related to the superior olivery complex (SOC), and wave V is related to the lemniscus of the upper pons and the colliculus of the midbrain. Latency between the waves in ABR test is indicative of brainstem dysfunction.

Similar to other studies, results of the current study showed a significant correlation between the waves and prolonged latency of waves with increased level of bilirubin. Increased level of bilirubin in 45% of cases has been associated with ABR impairment, and the minimum level of bilirubin associated with abnormal ABR has been 15.8 mg/dl, higher levels of which have been reported in different studies [1,2,3,6].

Zahed Parsa et al. [2] showed that severe jaundice leads to acute brainstem dysfunction which is reversible after blood exchange. In their study, similar to most of the other studies, bilirubin-induced encephalopathy is transient, and ABR impairment has been resolved in most cases. However, it is notable that 10% of abnormal cases of ABR, even after two times, have remained abnormal which have been referred to ENT specialists. According to the results of previous studies, ABR is a high-potential test for early diagnosis of neuro-toxicity in neonates. Rapid reversibility of changes is really promising, but it is hard to completely rule out the probability of neurotoxicity. This issue is indicative of para-mount importance of timely and immediate treatment of hyperbilirubinemia. Hence, scr-eening test and early diagnosis of nerve

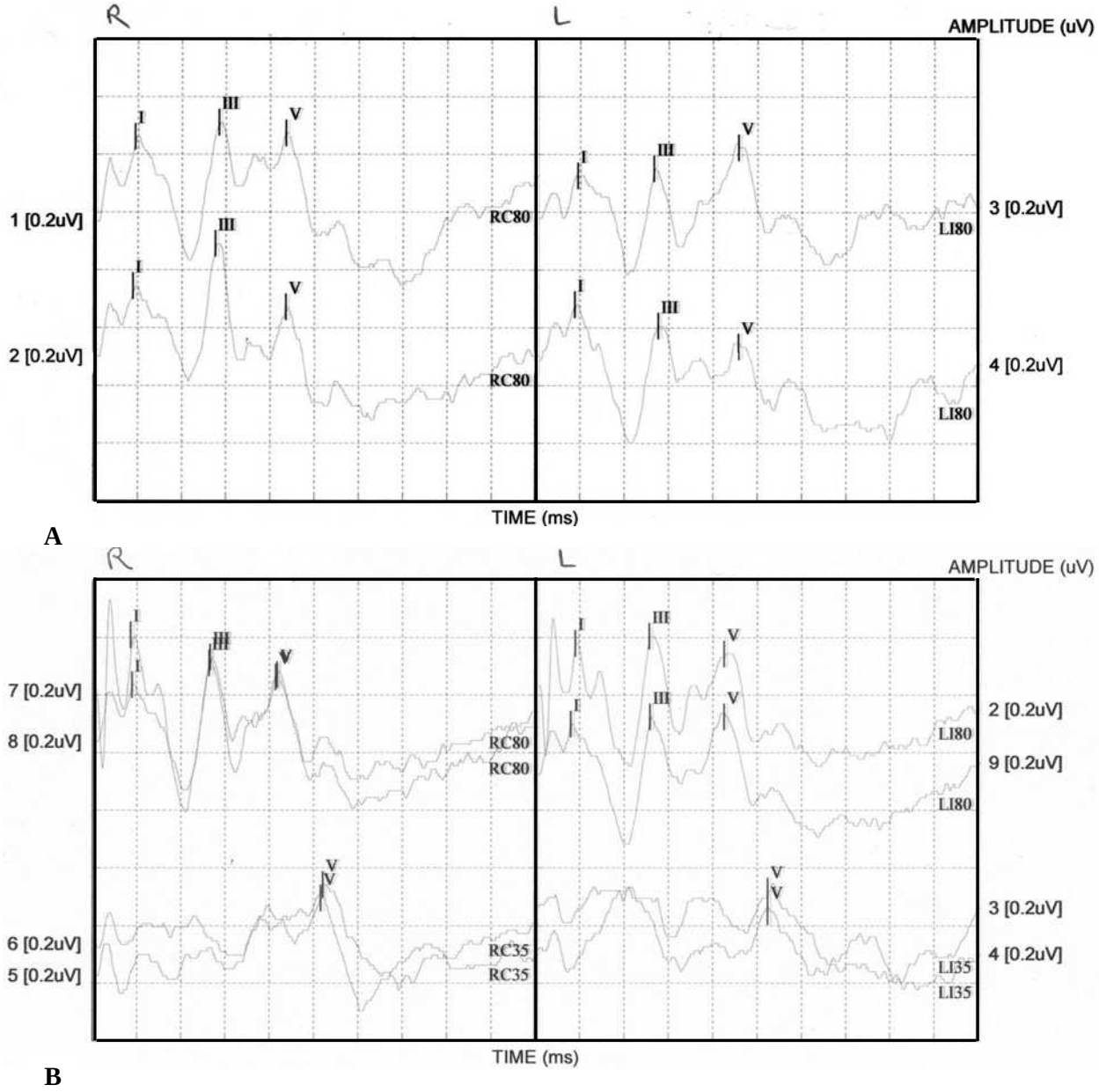

Fig. 1. ABR waves before and after treatment, A) before and abnormal, B) normal and after treatment.

damage induced by bilirubin is necessary in all cases of severe jaundice to diagnose auditory impairment and initiate appropriate interventions accordingly.

Prolonged mean latency of waves I, V and prolonged interpeak interval of waves III-V were compatible with those in Kaga et al. [7].

There is strong evidence to confirm auditory nervous system as the most sensitive part of the nervous system to bilirubin-induced neurotoxicity, which is one of the most common manifestations of acute bilirubin-induced neurotoxicity in neonates [8].

Different studies have revealed a number of auditory neuropathies despite the absence of signs of acute bilirubin-induced encephalopathy [3]. Having ruled out other predisposing factors associated with auditory neuropathy, the relationship between hyperbilirubinemia and auditory neuropathy could be studied on the participants of this study.

No sign of clinical encephalopathy was seen in

Table 2. Comparison of mean (standard deviation) waves prolonged latency and interpeak latencies in normal and abnormal ABR groups

	Normal ABR	Abnormal ABR	p
Prolonged latency of wave I	1.3 (0.03)	1.536 (0.2)	0.0149
Prolonged latency of wave III	4.17 (0.13)	4.51 (0.41)	0.0001
Prolonged latency of wave V	5.38 (0.13)	6.85 (0.13)	0.001
lnterpeak latencies I-III	2.3 (0.2)	3.1 (0.2)	0.692
lnterpeak latencies I-V	4.83 (0.4)	5.7 (0.4)	0.087
lnterpeak latencies III-V	2.42 (0.33)	2.43 (0.25)	0.859

understudy population. Several studies have revealed that serum bilirubin, especially in a long period of time, is not an appropriate predictor for bilirubin-induced neurotoxicity [9,10]. In this study, OAE was not abnormal in any of abnormal cases of ABR, also ABR was abnormal in most of the normal cases of OAE. This result confirms the high level of OAE testing error which is known to all ENT specialists, and that is why the ABR test is required in all patients with hyperbilirubinemia. Also 45% of neonates with bilirubin range of 15.8-26 mg/dl had abnormal ABR. ABR remained abnormal in one case despite the absence of indications for blood exchange. Mukhopadhyay et al. showed a significant relationship between abnormal ABR and developmental impairment in nervous system of neonates who underwent blood exchange [11].

According to Satish et al. [12], bilirubin-induced neurotoxicity occurs in a level of bilirubin which does not need blood exchange, and it is suggested that until determining neurotoxic level of bilirubin, decision making about blood exchange should be done with more caution. In this study, when the level of bilirubin is so high that blood exchange turns to a necessary choice of treatment, probability of ABR to remain abnormal is significantly more than that in the group of neonates undergoing phototherapy. However, there were no difference between them in incidence of abnormality before treatment.

Conclusion

Bilirubin level on its own is not a specific criterion to predict the incidence of bilirubin-induced neurotoxicity. Having known that neurotoxicity in initial stages is reversible, early diagnosis and implementation of appropriate diagnostic methods (e.g. ABR) are really necessary. Due to the high testing error of OAE, it is suggested that neonates undergo ABR examination from the beginning.

Given the probable incidence of bilirubin-induced neurotoxicity in lower levels of bilirubin which blood exchange is required, it is suggested that blood exchange should be postponed until determining non-neurotoxic level of hyperbilirubinemia.

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