ORIGINAL ARTICLE

Comparing Auditory Brain Stem Responses and Transient Otoacoustic Emissions in Premature Infants with Auditory Developmental Delay: Evidence of Temporary Auditory Neuropathy

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Abstract

Objectives
Premature birth causes some permanent or temporary abnormalities in the hearing system of the newborn. Inadequate development of the central auditory nervous system and balance, as well as the delay in the formation of the nerve myelin, can be the cause of many hearing disorders, including permanent or temporary auditory neuropathy spectrum disorder (ANSD). The present study aims to identify and understand developmental delay disorder in the hearing system of infants and investigate the possibility of temporary auditory neuropathy in infants.

Materials & Methods
In this comparative analytical study, twenty premature infants were randomly selected for hearing tests using auditory brainstem response and transient otoacoustic emissions at the time of discharge and three months after the first evaluation. The different components of these tests were analyzed and compared before and after developing the auditory system.

Results
The OAEs test showed a signal-to-noise ratio above six dB with appropriate amplitudes in all infants. The grand average waveform of the ABR showed a significant difference between the amplitudes of waves III and V before and after maturation in both ears ($p<0.05$). In addition, the absolute latency of waves, specifically III and V, showed a significant difference between the two assessment times (0.05).

Conclusion

The present study confirmed the occurrence of temporary ANSD or delayed maturation in premature infants following the lack of complete growth and myelination of auditory nerve fibers. There is a need to determine the hearing status of premature infants by frequent examinations and prevent any unnecessary prescription of amplifications.

Keywords: Premature Infant, Auditory Neuropathy, Developmental Delay

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Introduction

For many years, in infants, it was believed that the prevalence of hearing loss to be about 1 in 1000 live births, or 4, 000 per year. This prevalence has been underestimated because it is only related to congenital bilateral profound hearing loss (1). In addition, initial research overlooked infants susceptible to developmental disabilities. This oversight is significant considering the proven higher prevalence of hearing loss in these infants compared to those with typical development. (1). In infants admitted to the neonatal intensive care unit (NICU), the risk of hearing loss is 20-50 times higher than that in typical peers, approximately equal to 1 in 150 infants (1, 2). The risk factors for hearing loss have been classified by the Joint Committee on Infant Hearing (JCIH). Besides, audiologists have used these criteria for many years to identify infants with hearing loss. Auditory brainstem response (ABR) and otoacoustic emission (OAE) tests are suitable for the screening of hearing loss due to automatic response detection. Acceptance or rejection criteria have already been defined for ABR and OAE devices (1, 3). The infants with risk factors should be followed up and investigated more. It has a lot of variability, including the high latency that can be seen in the waves, a low amplitude wave V with poor morphology, and the large amplitude of wave III in relation to waves I and V, which according to various studies, is caused by the lack of proper growth and poor development of the neural generators that produce ABR (4-6). Consequently, in such cases, the screening devices settingto recognize wave V at the maximum intensity of 35-40 dB do not show a suitable response. The researchers believe that the absolute latency and the latency between the waves are significantly different between premature and full-term, indicating that the auditory maturation process influences the ABR results, and their characteristics differ between premature and mature babies (7, 8). This problem suggests the necessity of considering gestational age in the analysis of ABR waves and more frequent follow-up visits with frequent serial electrophysiological testing (4). In some studies conducted on low birth weight infants, an increase in latency of the wave I to V or III to V has been evident (7, 9).

Auditory neuropathy spectrum disorder (ANSD) is one of the types of hearing loss in which the communication between the cochlea and auditory afferent nerve fibers is interrupted. The primaryindicator to diagnoseANSD is the presence of evoked OAEs despite the absence or abnormal morphology of ABR (9-11). Despite numerous studies on ANSD, we have only achieved a partial understanding of its characteristics. The scientific community is yet to reach a consensus on the pathophysiology and risk factors of ANSD. (1, 4). This type of hearing impairment is usually seen in infants with risk factors and hospitalized in the NICU. Premature birth is one of the factors associated with some abnormalities that can have permanent or temporary effects on the hearing status of the infant (4). Undoubtedly, inadequate growth of the central nervous system, as well as the auditory nerve and balance systems, and delay in the formation of the myelin of the nerve can be the reason for many changes in the tests examiningdifferent levels of the auditory system (1, 7, 9). The inadequate development of the auditory nerve pathway and the lack of myelination in this pathway until sufficient growth leads to distortion of the waveforms and other ABR parameters (3, 5, 12, 13). This factor puts infants at risk of ANSD. So far, several studies have investigated some abnormalities caused by developmental immaturity in the auditory nerve pathway of infants and their effects on their hearing behaviors (7, 14). Premature birth often leads to several health complications, including delayed formation of ABR waves at the brainstem and associated higher levels. Additionally, there's an increase in the overlap of different waves and a disruption in their proper formation.. The dependence of infants' hearing and ABR waves on maturity has attracted the attention of many researchers, some of which have led them to investigate the necessity of behavioral study and using minimal auditory response level (MRL) instead of auditory threshold (7, 13). Therefore, in many studies, the necessity of repetition and follow-up, as well as conducting behavioral hearing tests, have been recommended due to the unresponsiveness of the auditory brainstem responses (1, 3, 5). In premature infants with low birth weight or hyperbilirubinemia, the mentioned symptoms are probably temporary and can improve with the development of the sensory nervous system (1, 5, 15). This is a reason for frequent follow-up for hearing tests in premature infants and emphasizes not judging early about hearing loss and using an amplification (1, 5, 12).

The study aims to examine the changes in the ABR test parameters in premature infants based on gestational age and then compare the findings after the maturation and development of their auditory system to understand betterthe role of auditory pathway maturation in auditory brainstem evoked responses. Assumedly, the disturbances in the auditory brainstem responses due to prematurity are temporary and not permanent, and the frequent follow-ups of the hearing tests and the acquisition of appropriate responses after maturation Can remove the infants from the classification as those with hearing loss and the need for an amplification.

Materials & Methods

Participants

This is a comparative analytical study with ethical approval obtained from the Ethics Committee of Iran University of Medical Sciences (Ethics code: IR.IUMS.REC.1399.404). At first, infants were examined by pediatricians and underwent clinical examinations. Then, by simple sampling method and according to gestational age and risk factors for hearing loss, twenty infants were selected. The inclusion criteria were gestational age <37 weeks and birth weight <1500 grams, and the risk factors for hearing loss including low Apgar score, mechanical ventilation, hyperbilirubinemia, and various infections (like sepsis or TORCH) (1, 2, 4). The infants were examined at the time of discharge or one month after discharge and two to three months after the first evaluation using ABR and OAEs. An infant might have been tested more than twice, but this study included only two evaluations (before and after the maturation of the auditory system).

Procedure

To perform objective tests, the infants needed to have a deep sleep. Therefore, the parents were requested to provide this by breastfeeding them before the tests and preventing the infants from deep sleep before the tests. The OAEs test was performed for each ear when the infant was sleeping using a Capella2 device (Madsen Co., Denmark). The acceptance criterion was a signal-to-noise ratio above six dB and appropriate amplitudes of OAEs. To ensure the correctness of the answers, double-checking was done. The ABR test was then performed using Charter EP 200 device (Madsen Co., Denmark), and based on the typical electrode placement pattern (non-inverting electrode on the forehead, and inverting electrode and the ground electrode on the right and left mastoids (M1 & M2). The click stimulus was used at the intensity of 80 dB nHL with the rate of 21.1 clicks per second and at the rarefaction polarity. The filter setting was 30-3000, and the number of sweeps was variable depending on signal-to-noise ratio (SNR). These stimuli were presented via an insert transducer (12). The morphology and amplitude of the waves, the absolute latencies of waves I, III, and V, the interval between the waves, and the hearing thresholds were examined. If there were no response in OAEs, the middle ear would be examined with a high-frequency tone probe tympanometry (Madsen, zodiac advance) to rule out otitis media.

Data analysis

Descriptive statistics (mean, standard deviation, minimum, and maximum) were used to describe data, and a paired t-test was used to compare the results of each recorded response. The significance level was set at 0.05. Most data had a normal distribution; however, in cases where the data distribution was not normal, non-parametric tests such as the Wilcoxon test were used. All statistical analyses were carried out in SPSS v.20 software.

Results

The infants had a mean age of 33±1.89 weeks and a mean birth weight of 1837.33±276.80 gr. The mean amplitude and absolute latency of waves I, III, and V, the inter-wave intervals, and the ratio of amplitude wave V to wave I at an intensity of 80 dBnHL at pre and post-developmental evaluations are presented in Table 1. The grand average waveforms of the ABR at pre and post-developmental evaluations for each ear at an intensity level of 80 dBnHL and near-the-threshold level are presented in Figures 1, 2, and 3, 4, respectively. In the period between the two evaluations, the amplitude and absolute latency of waves III and V increased in both ears. In the right ear, the difference in the absolute latency of wave III was significant between the two evaluation times (A and B, Fig 1). In the left ear, the difference was significant in the absolute latency and amplitude of the wave V ($p<0.05$) (C and D Fig 2). The interval between waves I and V in both ears and the interval between waves

Table 1. Means and standard deviations of ABR components in pre and post discharge evaluations

Components		Phase Mean	Right Ear			Left Ear		
			SD	P value	Mean	SD	P value	
Amplitude (microvolts)	Wave I	Pre	0.08	0.03	0.09	0.08	0.03	0.052
		Post	0.20	0.26		0.27	0.30	
	Wave III	Pre	0.25	0.50	0.01	0.25	0.06	0.055
		Post	0.28	0.08		0.28	0.08	
	Wave V	Pre	0.07	0.05	0.07	0.05	0.04	0.03
		Post	0.22	0.06		0.19	0.09	
Latency (ms)	Wave I	Pre	1.50	0.49	0.46	1.64	0.07	0.03
		Post	1.62	0.06		1.59	0.05	
	Wave III	Pre	4.12	0.19	0.49	4.10	0.18	0.04
		Post	4.36	0.26		4.03	0.11	
	Wave V	Pre	6.97	0.78	0.14	7.16	0.45	0.03
		Post	6.41	0.41		6.42	0.38	
Inter-wave Latencies (ms)	I-III	Pre	2.44	0.19	0.39	2.43	0.15	0.97
		Post	2.74	1.26		2.43	0.11	
	I-V	Pre	8.57	0.68	0.00	8.80	0.46	0.00
		Post	4.79	0.40		4.82	0.34	
	III-V	Pre	2.92	0.73	0.14	3.05	0.36	0.03
		Post	2.41	0.39		2.39	0.35	
V.I ratio	-	Pre	1.23	0.91	0.46	0.84	0.35	0.20
		Post	1.64	0.78		1.19	0.73	
TEOAE SNR (dB)		Pre	12.42	2.05	0.79	12.32	2.00	0.80
		Post	12.33	1.96		12.45	1.9	

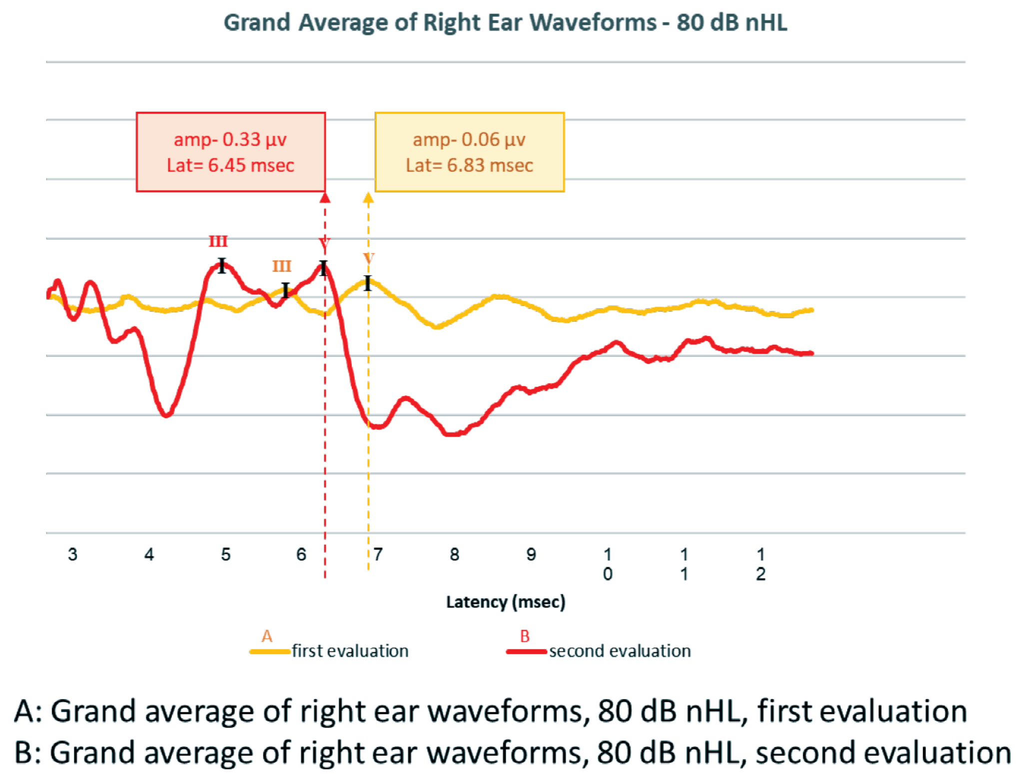

Figure 1.**pre** *and Post discharge ABR grand average responses of right ear at 80 dB nH..*

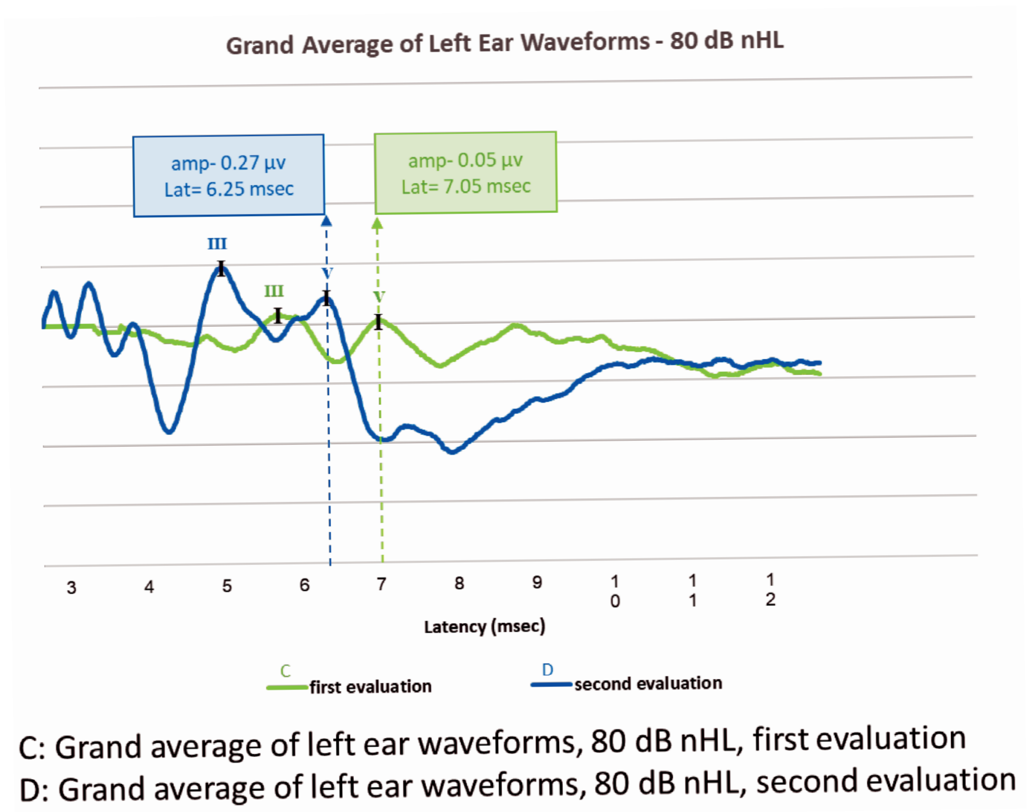

Figure 2.**pre** *and Post discharge ABR grand average responses of left ear at 80 dB nH..*

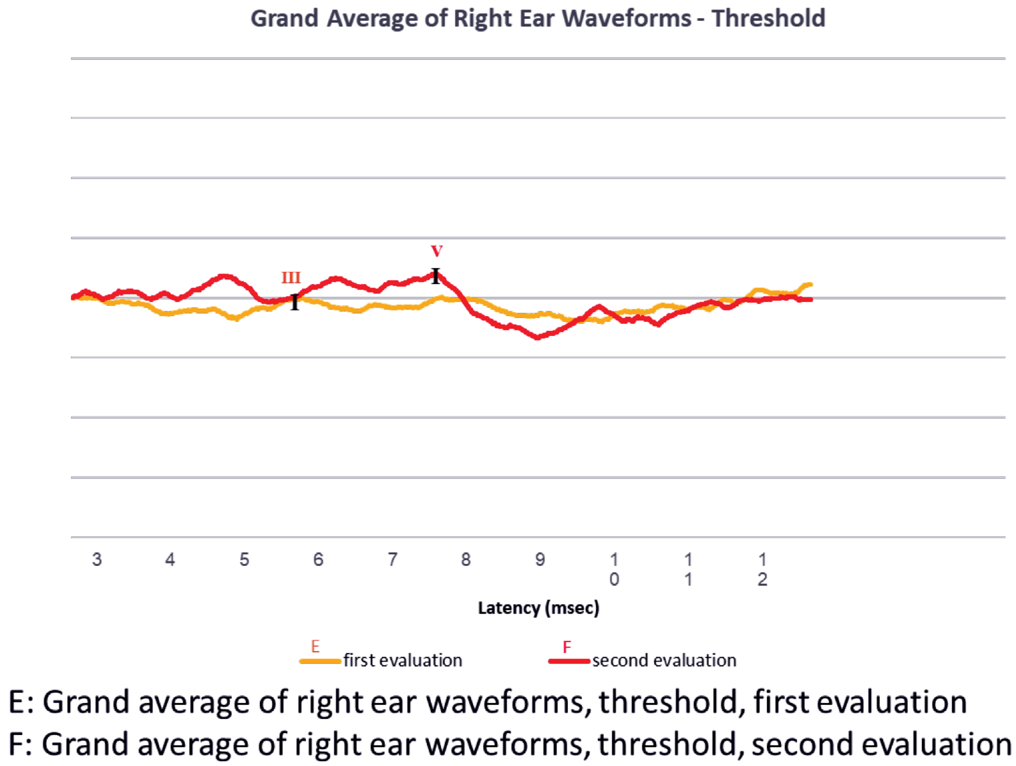

***Figure 3**. Post discharge ABR grand average responses of right ear at near threshold levels.*

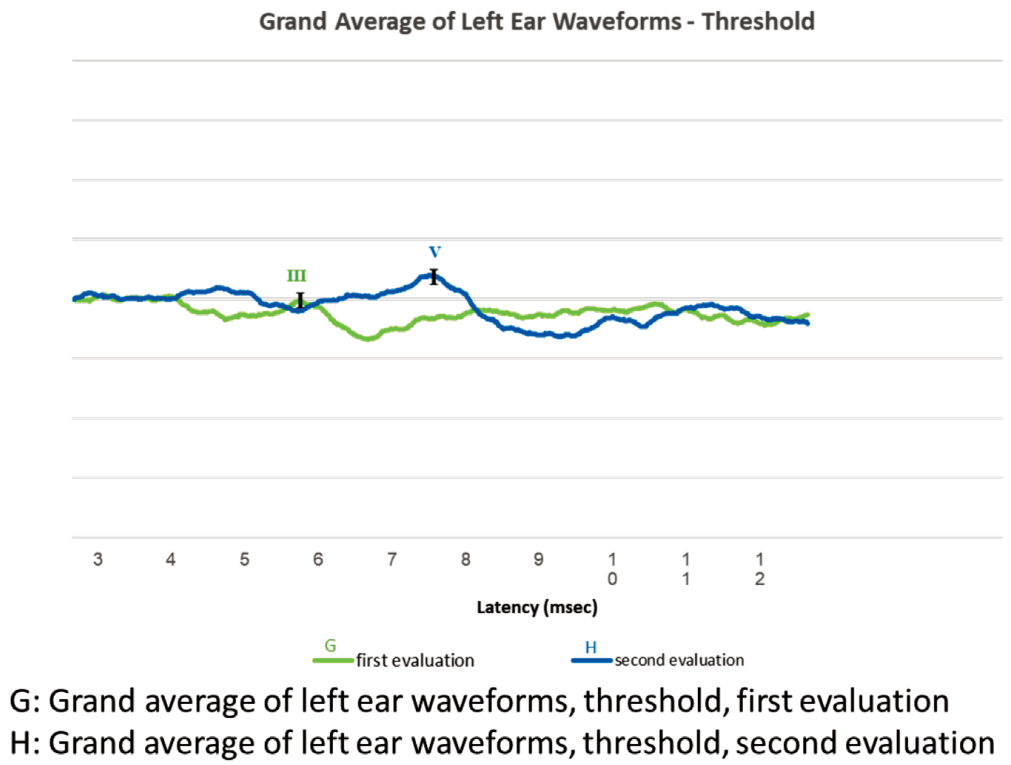

***Figure 4**. Post discharge ABR grand average responses of left ear at near threshold levels.*

III and V were significantly different between the two evaluations in the left ear ($p<0.05$). The difference in the amplitude ratio of V/I between the two evaluations was not significant in any ears ($P>0.05$) (Table 1).

Discussion

Prematurity and developmental delay are among the damages that can lead to auditory neuropathy. They are associated with some abnormalities that can have permanent or temporary effects on the auditory system. Inadequate growth of the central nervous system, as well as the auditory nerve and balance systems and delay in the formation of nerves' myelin can be the reasons for many changes in the evaluations examining different levels of the auditory system (1, 4, 7, 16). So far, some abnormalities caused by developmental immaturity in the auditory nerve pathway of infants and their effects on their hearing status have been investigated (1, 7, 14). The present study aims to investigate the changes in the parameters of ABR in premature infants at the time of birth and three months after birth. The results showed that the auditory brainstem responses are greatly affected by the synchronization of neural firings in the auditory nerve pathway, consistent with the results of previous studies (4, 7, 12). If this neural synchronization, derived from myelination and maturation of the system, is not provided, there will be a delay in the formation of brainstem auditory evoked waves, specifically waves III and V, or even higher centers. However, possibly, the more peripheral components of ABR, such as wave I, are less affected by the immaturity (7, 12). Therefore, in the absence of sharp wave V, it is possible to detect the threshold by using other ABR components, such as wave I or even wave III, whose maturity occurs faster (12). In cases where symptoms are similar to transient ANSD or brain stem dysfunction, especially in premature infants, the thresholds of evoked responses can be examined by wave III or I and carefully judged about the hearing status (12). In this regard, in the present study, due to the immaturity of the central auditory pathway, wave V did not have a good morphology. Besides, irregular and unrepeatable waves were seen after wave III in all cases, and the approximate hearing threshold was determined with wave III in many infants. By using the test battery approach, including the behavioral tests, and by applying MRL instead of the auditory threshold, it is possible to estimate the hearing thresholds of the infants (7, 12, 13). Observing impaired evoked responses can be related to several reasons: (a) sensorineural or mixed hearing loss, (b) ANSD due to reasons such as genetics or hyperbilirubinemia, and (c) ANSD due to auditory immaturities or developmental delay (5). In some studies, the absence of evoked responses (6, 10) or disturbances in their morphology (12), along with the presence of OAEs and cochlear microphonic responses (6, 15) were reported. Remarkably, any rehabilitation in the second and third groups (b, c) should be done with caution.

The researchers believed that the absence of ABR and OAEs is also confirmed by the absence of cochlear microphonic potential formation when the child enters the rehabilitation process (15, 17). Differentiating between permanent and temporary ANSD in cases with developmental delays or those admitted to the NICU is essential. This differentiation should preferably be done two months after receiving the first ABR. Improvement in auditory evoked responses with increasing age and frequent follow-up of the hearing status using behavioral tests can help the therapist to achieve stable conditions for the infants (12, 15, 18). After observing permanent or temporary

ANSD symptoms in infants, this study re-evaluated the ABRs three months after the first examination. A significant improvement in developing the auditory nerve pathway and the appearance of later waves with better morphology was evident in the grand average waveforms of infants. The results of the ABR re-examination showed that developmental maturation strengthened the myelination process of nerve fibers and led to synchronization firing in a set of auditory nerve fibers, such that, in addition to reducing wave latency, later waves with greater amplitudes emerged (18-20). Maturational changes and improvements in the central nervous system delay decision-making for the treatment and rehabilitation of infants. The final decision about using an amplification or cochlear implantation depends on repeating the behavioral test, stability in the test results, and rejecting the possibility of temporary neuropathy (1, 11, 15). In this study, following the observation of the general symptoms of neuropathy in the infant while informing the parents and explaining the situation, the necessary advice on providing a sound environment suitable for the infant, such as observing the face and lips of the parents while talking and communicating frequently with the infant, was emphasized (10, 21). The investigation results showed that the parents' exposure to many problems in these children may cause the parents to neglect their follow-ups, so the research team frequently followed up with all the infants and their families and periodically checked them.

In Conclusion

Hearing loss symptoms similar to ANSD can be common in premature infants, specifically in those with low birth weight. In this study, following the maturation and development of the central auditory nervous system, these symptoms were reduced in infants, and their ABR parameters reached the normal range three months later. Detecting hearing thresholds with the help of primary evolved waves (III or I), as well as repeating behavioral hearing tests and providing appropriate advice to parents, can prevent any errors in diagnosing and providing inappropriate rehabilitation.

Acknowledgment

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Authors' Contribution

Malihah Mazaheryazdi: study concept and design, development of original idea, data collection and writing the manuscript. MA sharafi: study concept and design, statistical analysis and interpretation of the result. M Akbari: study concept and design, interpretation of the result. FA Choobdar: design and development of original idea. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare no conflict of interest.

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