RESEARCH ARTICLE

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Auditory Brainstem Response in Children with Thalassemia Major under Chelating Therapy

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ABSTRACT

The present study compared the Auditory Brainstem Response (ABR) of children with thalassemia major and typically developing children. A total of 16 children participated in this study. Group I included 8 children with thalassemia major regularly undergoing blood transfusions and chelating therapy. Group II included 8 age and gender-matched typically developing children. All children in both groups had hearing sensitivity within normal limits. The Auditory Brainstem Response (ABR) was recorded monaurally for click stimuli from both ears. Results showed that the mean latencies of peaks of ABR were similar in both groups. The mean peak amplitude of peaks I and V of the ABR were different between groups, but it was not statistically significant. The present study showed no abnormality in the latency and amplitude of peaks of the ABR in children with thalassemia major with hearing sensitivity within normal limits.

Keywords: Auditory brainstem response, Thalassemia major, Chelating agent.

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INTRODUCTION

Beta-thalassemia syndromes are "a group of hereditary blood disorders characterised by reduced or absent beta globin chain synthesis, resulting in reduced Hb in Red Blood Cells (RBC), decreased RBC production and anaemia"[1]. Management of thalassemia major includes regular blood transfusions, iron chelation therapy, and management of secondary complications of iron overload. Deferiprone, deferasirox, and Deferoxamine (DFO) are the most commonly used iron chelators. The side effects associated with iron chelating agents include ophthalmic and renal complications, neurologic and skeletal changes, hearing loss, headache, and infection[2]. Chelation therapy is known to cause ototoxicity, depending on the type of iron chelator used, the dose and duration of therapy, and the average ferritin and haemoglobin levels[3,4]. The incidence of ototoxicity in patients using iron chelators such as Deferoxamine (DFO) varies from 3.8%–57%. However, deferiprone and deferasirox are reported to be not associated with ototoxic effects[3]. On the other hand, a study explained the presence of SNHL as having a positive significance in 50% of the study sample due to deferasirox[4].

Audiological assessment in individuals with thalassemia major has revealed the presence of hearing loss in one or both ears at more than one frequency. Various studies have reported the incidence of hearing loss between 3.5% to 52.1% in individuals with thalassemia major[5–10]. In a systematic review, the prevalence of hearing loss is found to be 32.3% in individuals with thalassemia major[11]. Further, studies have documented conductive, sensorineural, and mixed hearing loss among individuals with thalassemia major[10, 11]. Similarly, several studies have investigated Otoacoustic Emissions (OAE) in individuals with thalassemia major treated with chelating agents. Results have shown a reduction in the amplitude of OAE[7, 12] and absent OAEs in individuals with thalassemia major[6, 13] indicating an outer hair cell dysfunction in the cochlea.

A limited number of studies have investigated the ABR in individuals with thalassemia major[13–17]. Few studies have reported no abnormalities in the ABR among individuals with beta-thalassemia major[14, 16, 17]. In contrast, one study reported abnormalities in 43.7% of individuals with thalassemia major receiving long-term transfusion therapy[15]. Similarly, Chao et al. reported abnormal ABR in 61.9% of individuals (bilateral=28.6%; unilateral=33.3%) receiving long-term transfusion therapy[13]. On the other hand, hearing loss is known to affect the latency, amplitude, and morphology of the ABR[18-20]. However, majority of studies investigating the effect of thalassemia major on the ABR have not controlled the presence of hearing loss. Further, participants in the study were reported to have conductive or sensorineural hearing loss[13, 15]. Thus, abnormalities in the ABR which is reported in the literature in individuals with thalassemia major could be a consequence of hearing impairment. The present study investigated the ABR findings of children with beta-thalassemia major having hearing sensitivity within normal limits.

METHOD

Participants: A total of 16 children aged between 6 to 12 years participated in the study. Group I included eight children (two female, six male) with thalassemia major undergoing blood transfusions regularly (mean age=12.1 years, SD=3.3). All children had received oral iron chelating agents (deferiprone or deferasirox, 400-500 mg per month). The mean haemoglobin level was 8.36 gm/dl (SD=0.93), and the mean serum ferritin level was 5089.83 ng/ml (SD=2815.43). Group II included eight age and gender-matched typically developing children with no history of ear pain, ear discharge or other ear-related complaints. All children in both groups had hearing sensitivity within normal limits. The pure-tone hearing threshold was less than 25 dB HL at octave frequencies from 250 Hz and 8000 Hz. Ethical approval was obtained from the institutional ethics committee to conduct the study.

Recording of the Auditory Brainstem Response: The ABR was recorded using the IHS Smart EP version 3.92 (Intelligent hearing systems, Florida, USA) evoked potential system. During the recording of the ABR, participants were made to sit comfortably on a reclining chair in a sound-treated room. The electrode sites were cleaned using Nu-prep Skin Prep Gel. Gold-plated disc electrodes were placed on the electrode sites using conduction paste and secured using adhesive tape. The non-inverting electrode was placed on the vertex (Cz), inverting electrode on the test ear mastoid, and the ground electrode on the low forehead (Fpz). The absolute electrode impedance of each electrode was less than 5000 ohms, and the inter-electrode impedance was less than 2000 ohms. The ABR was elicited monaurally from both ears using click stimuli at 80 dBnHL. The clicks were delivered to the test ear of participants at a rate of 11.1 stimuli/sec, using ER-3A insert earphones. The ongoing EEG was recorded differentially from the scalp. The EEG was amplified 100,000 times and filtered using a bandpass filter of 100 to 3000 Hz. In each recording, a total of 2000 artifact free sweeps were obtained, and when the amplitude of the EEG was greater than 50 μV, such sweeps were rejected from averaging. Finally, all the sweeps were averaged to obtain the averaged waveform. The duration of the analysis window was 17 msec with a pre-stimulus duration of -5 msec. Two ABR recordings were obtained from each ear to check the reproducibility of the response.

Data and Statistical Analysis: Two experienced audiologists analysed the waveforms recorded from all participants to identify peaks of the ABR. The latency and peak amplitude of peaks I, III, and V of the ABR and interpeak latency of I-III, III-V, and I-V were measured for both ears. The latency was measured in milliseconds (msec), and the amplitude was measured in microvolt (μv).

Table 1: Mean and standard deviation (in parenthesis) for latency and inter-peak latency of the ABR.

	Peak latency (msec)						Inter-peak latency (msec)					
Peak	I		III		V		I-III		III-V		I-V	
Ear	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Group 1	1.5 (0.1)	1.7 (0.1)	3.6 (0.1)	3.7 (0.1)	5.6 (0.1)	5.7 (0.1)	2.0 (0.1)	2.1 (0.1)	2.0 (0.1)	2.0 (0.1)	4.1 (0.1)	4.0 (0.1)
Group 2	1.6 (0.1)	1.6 (0.2)	3.6 (0.1)	3.7 (0.1)	5.6 (0.1)	5.7 (0.1)	2.1 (0.1)	2.1 (0.1)	2.0 (0.2)	2.0 (0.1)	4.1 (0.1)	4.0 (0.1)
p-value	0.266	0.493	0.342	0.874	0.336	0.242	0.711	0.315	0.752	0.131	0.916	1.0

Table 2: Mean and standard deviation (in parenthesis) for peak amplitude of the ABR.

	Peak amplitude (μV)					
Peak	I		III		V	
Ear	Right	Left	Right	Left	Right	Left
Group 1	0.7 (0.4)	0.4 (0.3)	0.7 (0.5)	0.5 (0.2)	0.5 (0.4)	0.6 (0.2)
Group 2	0.4 (0.2)	0.4 (0.2)	0.6 (0.5)	0.7 (0.3)	1.0 (1.1)	0.7 (0.3)
p-value	0.140	1.0	0.674	0.372	0.37	0.645

Statistical analysis was carried out using SPSS software version 16. Initially, descriptive analysis was performed to calculate the mean and standard deviation for latency and amplitude of peaks of the ABR. After descriptive analysis, the Shapiro-Wilk test was administered. It showed that the latency and amplitude data of peaks of the ABR were not normally distributed. Thus, the Mann-Whitney U test was used to investigate whether the mean latency and amplitude of peaks are significantly different between groups.

RESULTS

Table 1 shows the mean and standard deviation for the latency of peaks I, III, and V and inter-peak latency I-III, III-V, and I-V of the ABR for both groups. Table 2 shows the mean and standard deviation for the peak amplitude of peaks I, III, and V of the ABR for both groups. The mean latency of peaks I, III, and V and mean I-III, III-V, and I-V inter-peak latencies for both ears were similar in both groups. In contrast, the mean amplitude of peaks I and V of the ABR in the right ear differed between groups. The amplitude of peak I of the ABR was larger in group I, while the amplitude of peak V was larger in group II. The Mann-Whitney U test was performed to investigate whether the mean latency and amplitude are significantly different between groups. Results showed no significant difference for the latency and peak amplitude of peaks I, III, and V and inter-peak latencies I-III, III-V, and I-V of the ABR.

DISCUSSION

The present study showed no significant difference for the mean latency and amplitude of peaks of the ABR between children with beta-thalassemia major undergoing blood transfusion and chelating therapy and typically developing children. The results of the present study agree with the findings of earlier investigations[14, 16, 17]. Furher, Ambrosetti et al.[16] reported normal ABR in individuals with hearing sensitivity within normal limits. In addition, few studies have reported normal ABR in some individuals with thalassemia major undergoing long-term blood transfusion[13, 15]. The lack of abnormalities in the ABR found in the present study could be explained based on the hearing sensitivity of the participants. The abnormalities in the latency, amplitude, and morphology of the ABR are generally attributed to the degree, configuration, and type of hearing loss[18–20]. In the present study, since all participants had hearing sensitivity within normal limits, the latency and amplitude of peaks of the ABR were expected to be obtained at normal values.

In individuals with thalassemia major, abnormal findings of the ABR are attributed either to iron overload, DFO neurotoxicity, or both[15, 21]. Triantafyllou et al.[15] reported recovery in the latency and amplitude of peaks of the ABR in individuals with thalassemia major after adjusting the administration of DFO, and the ABR was reported to be normal. These findings suggest a possible effect of chelating agents on the ABR. Among the chelating agents, the DFO is reported to have ototoxic effects on the cochlea, causing hearing loss. The ototoxic effects are documented even when the DFO was administered at doses below 50 mg/kg/day, which is accepted to be safe. In contrast, chelating agents such as deferiprone and deferasirox are reported not to cause ototoxicity[3]. Yadav et al.[21] investigated the effect of DFO and deferiprone on the ABR, and results showed plonged latency for peaks of the ABR among individuals who received DFO. Participants in the present study had received either deferiprone or deferasirox as chelating agents, which might not have caused otoxicity or neurotoxicity. Thus, normal ABR among individuals with thalassemia major in the present study could also be explained based on the chelating agents used by participants.

The limitation of the present study is its small sample size. A similar study should be carried out on a large number of individuals before generalising the results of the present study. However, one study has reported normal ABR in all individuals with thalassemia major who had hearing

sensitivity within normal limits[16]. Thus, the findings of the present study are consistent with earlier investigations.

CONCLUSION

The findings of the present study show no abnormalities in the latency and peak amplitude of the ABR among children with thalassemia major with hearing sensitivity within normal limits.

REFERENCES

1. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5(1):1-5.
2. Keikhaei B, Farmani-Anooshe N, Bahadoram M, Mahmoudian-Sani MR, Alikhani K, Helalinasab A. An overview of complications associated with deferoxamine therapy in thalassemia. J Nephropharmacol. 2020 ;10(1):e05-.
3. Derin S, Azık FM, Topal Y, Topal H, Karakuş V, Çetinkaya PU, et al. The incidence of ototoxicity in patients using iron chelators. The J Int Adv Otol. 2017;13(1):136.
4. Khan MA, Khan MA, Seedat AM, Khan M, Khuwaja SF, Kumar R, et al. Sensorineural hearing loss and its relationship with duration of chelation among major β-thalassemia patients. Cureus. 2019;22;11(8).
5. Faramarzi A, Karimi M, Heydari S-T, Shishegar M, Kaviani M. Frequency of sensory neural hearing loss in major Beta-thalassemias in southern iran. Iran J Pediatr. 2010;20:308–12.
6. Osma U, Kurtoglu E, Eyigor H, Yilmaz MD, Aygener N. Sensorineural hearing loss in β-thalassemia patients treated with iron chelation. Ear, Nose Throat J. 2015;94(12):481-5.
7. Bhardwaj V, Verma R, Chopra H, Sobti P. Chelation-induced ototoxicity in thalassemic patients: Role of distortion-product otoacoustic emissions and various management parameters. Indian J Otol. 2016;22(3):193.
8. Alzaree FA, Shehata MA, Atti MA, Elzaree GA, El-Kassas GM. New Advances in Evaluation of Hearing in a Sample of Egyptian Children with β-Thalassemia Major. Open Access Maced J Med Sci. 2019;7(9):1494.
9. Khalaf Q, Bargas O. Otorhinological Manifestation in Patients with Thalassemia Major. Egypt. J. Ear Nose Throat Allied Sci. 2020;21(3):111-5.
10. Manara R, Ponticorvo S, Perrotta S, Barillari MR, Costa G, Brotto D, et al. Auditory cortex hypoperfusion: A metabolic hallmark in Beta Thalassemia. Orphanet J Rare Dis. 2021;16(1):1-1.
11. Tartaglione I, Carfora R, Brotto D, Barillari MR, Costa G, Perrotta S, et al. Hearing Loss in Beta-Thalassemia: Systematic Review. J Clin Med. 2021;11(1):102.
12. Delehaye E, Capobianco S, Bertetto IB, Meloni F. Distortion-product otoacoustic emission: Early detection in deferoxamine induced ototoxicity. Auris Nasus Larynx. 2008;35(2):198-202.
13. Chao YH, Wu KH, Lin CY, Tsai MH, Peng CT, Wu HP, et al. Audiologic and vestibular assessment in patients with β-thalassemia major receiving long-term transfusion therapy. Pediatr Blood Cancer. 2013;60(12):1963-6.
14. Amabile G, Stefano E, Bianco I, Aliquo MC, Giunti P, Pierelli F, et al. Electrophysiological (EEG, BAEP, VEP) study in patients with beta-thalassemia major. Acta Neurol Belg. 1987;87(4):181-90.
15. Triantafyllou N, Fisfis M, Sideris G, Triantafyllou D, Rombos A, Vrettou H, et al. Neurophysiological and neuro-otological study of homozygous beta-thalassemia under long-term desferrioxamine (DFO) treatment. Acta Neurol Scand. 1991;83:306–8.
16. Ambrosetti U, Dondè E, Piatti G, Cappellini MD. Audiological evaluation in adult beta-thalassemia major patients under regular chelation treatment. Pharmacol Res. 2000;42(5):485-7.
17. Economou M, Zafeiriou DI, Kontopoulos E, Gompakis N, Koussi A, Perifanis V, et al. Neurophysiologic and intellectual evaluation of beta-thalassemia patients. Brain Dev. 2006;28(1):14-8.
18. Watson DR. The effects of cochlear hearing loss, age and sex on the auditory brainstem response. Audiol. 1996;35(5):246-58.
19. Ferguson MO, Cook RD, Hall JW, Grose JH, Pillsbury HC. Chronic conductive hearing loss in adults: effects on the auditory brainstem response and masking-level difference. Arch Otolaryngol–Head & Neck Surg. 1998;124(6):678-85.
20. Narne VK, Prabhu P, Chandan HS, Deepthi M. Audiological profiling of 198 individuals with auditory neuropathy spectrum disorder. Hearing, Balance and Communication. 2014;12(3):112-20.
21. Yadav M, Yadav J, Tiwari AD, Abrol P, Sood S. Effect of iron chelating agents desferrioxamine, deferiprone and their combination on brainstem auditory evoked potential (BAEP). JK-Practitioner. 2012;17(4):29-34.