

Glutaric Aciduria Type 1 ; Does it Effect of Hearing Function?

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Abstract

The main objective of this study was to observe the audiological findings of patients with Glutaric Aciduria Type 1 (GA-1), which is very difficult to evaluate and diagnose due to limited scientific literature.

We used an audiological test battery to evaluate the study group of 17 individuals with GA-1 diagnosis and the control group of 20 healthy individuals. Following the otoscopic examination, the audiological test battery consisting of pure-tone hearing threshold (PTA) test, immittancemeter, distortion product otoacoustic emissions (DPOAE), contralateral suppression of otoacoustic emissions, and auditory brainstem response (ABR) measurements were applied to all participants ($N=37$).

DPOAE amplitudes and the contralateral distortion product suppression values were significantly lower in the study group compared to control group ($p < 0,05$). In the study group, although they had a normal hearing level, there were morphologically different ABR waves than the control group, which was considered a remarkable finding. As well as I-V interpeak latency, the absolute latencies of I, III, and V waves ABR of the study group, were observed to be prolonged significantly compared to the control group ($p < 0,05$).

Our findings support that GA-1 disease of association with auditory damage. The use of otoacoustic emissions and ABR measurements in the audiological test battery would be useful tool in the early diagnosis and follow-up of hearing sensivity individuals with GA-1.

Introduction

Glutaric Aciduria Type 1 (GA-1) is an autosomal recessive congenital disorder caused by a defect in lysine, hydroxylysine, and tryptophan metabolism, as well as the insufficiency of the glutaryl-CoA dehydrogenase enzyme (essential for mitochondria) (Hoffmann & Zschocke, 1999). The worldwide prevalence of GA-1 is nearly one in 100,000 newborn screening (Lindner et al., 2004). Glutaryl-CoA dehydrogenase enzyme needs the mitochondrial matrix which assists to transform the lysine, hydroxylysine, and tryptophan proteins to acetoacetyl-CoA (Vester et al., 2015). The resulting accumulation of glutaric acid and 3-hydroxyglutaric acid, which can be detected in body fluids and tissues by using urine test mass spectrometry, creates acute basal ganglia injury, neuropsychologic impairment, and movement disorders (Hoffmann & Zschocke, 1999; Kölker et al., 2006). After the accumulation of hydroxyglutaric acid-3 and glutaric acid, it may lead to mitochondrial dysfunction via excitotoxicity changed neurotransmission and neuronal death (Kölker, Koeller, Okun, & Hoffmann, 2004). It is stated that with screening programs, diagnosis can be achieved before complications occur, which will prevent progressive neurological damage and deaths (Korman et al., 2007).

The cochlea, especially the stria vascularis, is an organ with high microvascular dependence. By increasing endothelial cell wall permeability and thus disrupting the electrolyte balance of the endolymph, signal transmission between hair cells is disrupted (Frisina, Mapes, Kim, Frisina, & Frisina, 2006). Mitochondrial excitotoxicity occurring due to glutamate increase and glutathione reduction plays a role in

the process of inner ear damage due to hypoxia (Lee, Shim, & Chung, 2013). Puel et al. (Liberman & Kujawa, 2017) reported the presence of glutamate receptor (GluR) antagonists in the inner hair cells of the cochlea exposed to excitotoxic effects, but not in the outer hair cells, and thus pointed out that intracochlear perfusion can be maintained through the glutamate antagonist.

In our study, possible effects on the hearing system due to cell-based damage caused by the enzyme deficiency in GA-1 were evaluated. It was aimed to increase the quality of life of patients with GA-1 by early diagnosis of hearing loss and early intervention, by evaluating their hearing functions.

Material And Methods

Study design and participants

The case-control study was conducted between February 2017 and April 2018 at Audiology, Balance and Speech Therapy Center of Hacettepe University.

Individuals who agreed to participate in our study were divided into two groups as study and control groups. Study group was created total of 17 individuals (7 males and 10 females) with GA-1 diagnosed on clinical, histopathologic, and genetic grounds at the Department of Pediatric Metabolism and a control group of 20 healthy individuals (8 males and 12 females). Exclusion criteria were the presence of otological disorders, ear infections, noise exposure, or the use of ototoxic medication. After the evaluations of pediatric metabolism and Ear Nose Throat (ENT), audiological tests were performed in a soundproof room in the audiology department. The study was approved by the Hacettepe University Medical School non-clinical studies ethics committee (Approval no: 17/16-18) on 31.01.2017 and the necessary permissions were obtained before initiating the study. and the 1964 Declaration of Helsinki's ethical principles on human experimentation were followed with its later amendments or comparable ethical standards.

Audiometry and immittancemetric measurements

Air conduction hearing thresholds were set at 250-8000 Hz octave frequencies (TDH-39P) and the bone conduction thresholds at 500-4000 Hz octave frequencies (Radioear B-71 vibrators), speech audiometry was performed on all participants according to American National Standards Institute (ANSI -2004) with Grason Staedler (Minnesota/USA) GSI-61 audiometer. Pure tone average (PTA) of 0.5, 1, 2, and 4 kHz thresholds were determined for each ear. The pure tone thresholds of the control group were 20 dB hearing level (HL) or greater at 250-8000 Hz octave frequencies. Tympanometry and acoustic reflex tests were performed using Interacoustic (Assens, Denmark) AZ26 impedancemeter with a 226 Hz probe tone. There was no middle ear dysfunction for any of the ears tested according to normal tympanometry values and patterns.

Distortion Product Otoacoustic Emissions

Distortion product otoacoustic emission (DPOAE) test was performed with all participants by Otometrics (Taastrup- Denmark) Capella DPOAE device using the General Diagnostic program in a sound-treated room. Firstly the DPOAE probe was placed to the external ear canal and measured at seven-octave frequencies (1, 1.5, 2, 3, 4, 6, and 8 kHz). Primary tones f1 (65 dB) and f2 (55 dB) were adapted at $f1/f2 = 1.22$ because the best distortion product signals procedure could be obtained with these proportion values (Fitzgerald & Prieve, 2001; Kemp, 2008).

Contralateral Suppression of Distortion Product Otoacoustic Emissions

In the contralateral suppression of the DPOAE test, the DPOAE probe was placed in the external ear canal, and 50 dB sensation level (SL) contralateral white noise (WN) was applied opposite ear at the same time. The contralateral WN stimulation was generated by the GSI 61 audiometer with 3A insert earphones. It was below the required intensity of contralateral stimulation to evoke the middle ear reflex in adults (Hall, 2000). The contralateral DPOAE suppression values were derived by the difference of DPOAE levels with contralateral noise with levels without noise, at the 1, 1.5, 2, 3, 4, 6, and 8 kHz octave frequencies (Tokgoz-Yilmaz, Kose, Turkyilmaz, & Atay, 2013).

Auditory Brainstem Response

Auditory Brainstem Response (ABR) measurements were recorded using the Vivasonic (Canada/USA) Integrity™ V500 device in the Faraday chamber. All participants were either in natural sleep or in calm conditions lying supine on the stretcher throughout the assessment. We analyzed the absolute latencies of waves I, III, V, and the interpeak latencies of intervals of I-III, III-V, and I-V. The click stimuli were checked using 2048 sweeps again. We used the normal pattern described by Hall in 1992 (J.W.Hall, 1992). The ABR tests were started using 3A insert earphones and 100 μ s (0.4 kHz) click stimulus at rarefaction polarity with signal filter pre-set for a band-pass was set to 0.1–3 kHz. The electrode skin impedance was less than 3 Ohms. The test click stimulus was given at the levels of 30 dB nHL, 50 dB nHL, 70 dB nHL and 90 dB nHL (normal hearing level). The stimulus was applied twice to make sure that the response was present and to obtain a reproducible tracing. All audiological tests were performed with the same audiology equipment in the same clinic.

Data and Statistical Analysis

Statistical package SPSS 20.0 version for Windows software was used to evaluate the findings statistically and analyzes were made at 95% confidence intervals for both groups. Kolmogorov-Smirnov ve Shapiro Wilks test were used according to whether there were differences between the groups in terms of quantitative variables, whether the variables showed normal distribution and whether the group variances were homogeneous. The paired t-test was used for the relation between the results for the contralateral suppression amplitudes, DPOAE, and ABR latencies. The independent samples t-test was used to analyze the difference between the study group and the control group's median values ($P < 0.05$).

Results

Demographical and clinical findings

The study involved a total of 17 patients were diagnosed with GA-1 and 20 healthy individuals between 2017 and 2018 years. The main clinical features of the patients are summarized in Table 1. GA-1 patients were created with the age ranged 6-27 years (mean; $15,1 \pm 9,2$). Of those, 7 (%42,2) were male (mean aged; $15,8 \pm 8,7$) and 10 (%58,8) were female (mean aged; $16,1 \pm 9,8$). On the other hand, the age at symptom onset ranged from 0.13 to 10 years (mean $2,69 \pm 6,63$), and the age at diagnosis ranged from 0,13 to 12,66 years (mean $4,54 \pm 6,62$). The consanguinity level was 82,32 % (n = 14), and there was no statistically difference between consanguinity and the onset of disease ($p = 0.279$). On the other hand, 14 (82,32%) missense, 3 (17,68 %) deletions variants type of mutation and 12 (70,58%) homozygous, 3(17,64%) heterozygous, 2 (11,76%) compound heterozygous mutation were detected among the patients. Unfortunately, case 17 died at age 19 but until her death, she would come to the clinical check-ups.

Audiometric findings

Pure tone hearing thresholds of the study group were higher (worse) than the control group's hearing levels and the difference was statistically significant ($p < 0.05$; Figure 1). Their mean and standard deviation (SD) thresholds at 0.25, 0.5, 1, 2, 4, 6 and 8 kHz were $15 \pm 3,13$; $15,37 \pm 3,50$; $16,62 \pm 3,84$; $17,12 \pm 5,19$; $18,12 \pm 5,18$; $21,87 \pm 6,31$ and $24,12 \pm 6,26$ dB HL. PTA results showed that a total of 23.53 % (n=4) of the individuals in the study group had normal hearing levels and 77.47 % (n=13) had mild sensorineural hearing loss. The hearing levels of the control group were within normal limits. Also, no difference was detected between left and right ears.

DPOAE amplitudes

There was no statistically significant difference between the left and right ear in DPOAE amplitudes ($p > 0,05$). DPOAE amplitudes of the study group were less than the control group in all octave frequencies (1, 1.5, 2, 3, 4, 6, and 8 kHz), and there was a statistically significant difference for 2 and 3 kHz on the right ear ($p = 0.027$, $p = 0.020$), while for 1, 2 and 3 kHz ($p = 0.034$, $p = 0.036$, $p = 0.041$) on the left ear ($p < 0.05$; Table 2).

Contralateral Suppression of DPOAE

We observed that the contralateral suppression values of the study group were below 1 dB which is considered as suppression amount (Prasher, Ryan, & Luxon, 1994; Yilmaz, Sennaroglu, Sennaroglu, & Köse, 2007). Contralateral suppression values of the study group were less than the control group for both ears at all frequencies ($p < 0,05$; Table 3).

Auditory Brainstem Response (ABR)

There is a significant difference observed in the ABR findings of the mean absolute latencies of wave I, III, V, and interpeak latencies of I–III and I–V when compared for statistical analysis in each group ($p < 0,05$).

ABR threshold results comparison of the GA-1 group: Absolute latencies of wave I, III and V were found to be significantly delayed at 30, 50, and 70 dB nHL in cases of GA-1 compared to the control group ($p < 0,05$). While wave I and III could not be obtained for the study group at the 30 dB nHL tone, the absolute latency of wave V was longer (8 ± 0.4 ms) in both ears compared to the control group ($p < 0,05$).

The absolute latency values of the wave I and III in the study group was shorter than the control group at 50 dB nHL tone (I= 2.4 ± 0.4 and III= 4.4 ± 0.5 ms , $p < 0,05$.) while there was not any significant difference in the absolute latency values between the groups for the wave V ($p > 0,05$).

The absolute latency values of the wave I and III in the study group was significantly shorter than the control group at 70 dB nHL tone (I= 1.8 ± 0.3 and III= 4.0 ± 0.3 ms , $p < 0,05$). There was not any significant difference in the absolute latency values between the groups for the wave V ($p > 0,05$).

While there was not a significant difference in the absolute latency values between the groups for wave I at 90 dB nHL tone ($p > 0,05$), the absolute latency values of the wave III and V in the study group was significantly longer than the control group for both ears (III= 4.1 ± 0.3 and V= 5.9 ± 0.3 ms, $p < 0,05$).

I-III, III-V, and I-V wave interpeak latency values of all the participants, regardless of their age and gender, at 90 dB nHL tone were presented in Figure 2. While I-III and I-V wave mean interpeak latency values of the study group were longer compared to the control group, III-V wave mean interpeak latency value was shorter ($p < 0,05$).

Discussion

The connection between brain cell mitochondria matrices and neurons and the glutaryl-CoA deficiency required in energy metabolism is defined as GA-I. It facilitates excitotoxicity by leading to an imbalance between excitatory and inhibitory neurotransmission in cellular metabolism, which cannot be adequately blooded and impaired (Coşkun, 2017). According to studies (Maddock & Buonocore, 2011; Rousseaux, 2008), increased acid deposits in the blood can be converted into glutamatergic or gamma-aminobutyric acid (GABA), causing a decrease in neurotransmitters and weakening of energy metabolism. Pathology of the basal ganglia and cerebellum after delayed myelination and progressive demyelination reveals a picture that supports common pathological mechanisms with organic acidemias and even characteristic mitochondrial diseases (Hoffmann & Kölker, 2016). In a study (Kokotas, Petersen, & Willems, 2007), it was noted that apoptotic cell metabolism has mitochondrial dysfunction, which can also cause hearing loss by damaging specific organs such as the cochlea. A 10-month-old girl admitted to a clinic in Korea was recorded as the first case of GA-1 with hearing loss (Park et al., 2010). In another study conducted on two babies with Canavan, from the organic acidemia group, post-mortem temporal bone structures were examined. The absence of inner-outer hair cells in cochlear structures was mentioned and it was revealed that excessive glutamate release in the cell caused cochlear damage due to the excitotoxic effect, however, the spiral ligament, tectorial membrane, and bacillary membrane were reported to have a normal appearance (Ishiyama, Lopez, Baloh, & Ishiyama, 2003).

We investigated the hearing thresholds of individuals with GA-1 and compared it with the control group, and there was a statistically significant difference between the study and the control group ($p < 0,05$). According to the present study, while % 77.47 (13 cases) of the individuals with had slight sensorineural hearing loss (SNHL), %23.53 (4 cases) of them were found to have normal hearing. Hearing levels were worse in our study group with a diagnosis of GA-1 than in the control group, suggesting that these people are at a significant risk of auditory damage.

Many studies of the auditory efferent pathway raise a lot of questions showing the need for detailed knowledge of it anatomically, physiologically, and clinically complex research (Lopez-Poveda, 2018). In our study, DPOAE amplitude, which is more directly related to the integrity of the cochlear outer hair cell, was well preserved in the control group but decreased significantly in the study group. There was a significant decrease in DPOAE amplitudes of the study group compared to the control group across all octave frequencies with the greatest change in the middle frequencies ($p < 0,05$). The finding of decreased DPOAE amplitudes at all frequencies in individuals with GA-1 supports the view that (Kotylo, 2002; Kölker et al., 2006) the cochlea is affected by metabolic problems.

Catabolism is suppressed with a diet rich in calories, poor in protein, and by providing L-carnitine and riboflavin in medical treatment, found useful in preventing acute encephalopathy crises, and possible complications (Monavari & Naughten, 2000). It is thought that in the long-term riboflavin and /or carnitine treatment in medical therapy, the level variability in the blood may cause an excitotoxic effect on the outer hair cells.

Our study group, consisting of individuals with GA-I, which is one of the rare metabolic diseases, was not numerically sufficient and balanced in terms of age and gender ($n = 17$), and the evaluation of DPOAE findings on age and gender differences were not sufficient/effective, therefore it should be evaluated with larger sample groups.

One of the techniques used to evaluate neural brain function is contralateral suppression measurement (Collet, Veuillet, Bene, & Morgon, 1992). In their study with the biotinidase enzyme deficiency from the organic acidemia group, Sivri et al. (Sivri et al., 2007) emphasized that it affects more central hearing than peripheral hearing. In this study using contralateral noise, we compared the DPOAE suppression data obtained from individuals diagnosed with GA-1 with the control group. In our study, it was thought that suppression, a physiological function, did not occur in the study group, since suppression values were below 1 dB in GA-1 individuals and this means that suppression was not present (Collet et al., 1992; Prasher et al., 1994). As a reason for this, it was concluded that efferent system dysfunction, which is responsible for the activation of external hair cells, may be shown.

ABR is the physiological response recorded to some extent dependent on the functional relationship between the inner hair cells and cochlea threshold sensitivity (Bramhall, Konrad-Martin, McMillan, & Griest, 2017). While DPOAE amplitude decrease was determined at all DPOAE frequencies in the study group, ABR analysis also showed greater changes in the interpeak delays.

Individuals with GA-1 were found to have a much higher level of ABR thresholds than their hearing level. It was observed that the ABR absolute latency findings obtained in individuals diagnosed with GA-1 were prolonged compared to the control group and that the wave morphology was highly impaired ($p < 0.05$). We think that the abnormal wave morphology and the finding of highly prolonged wave potentials obtained in the study group with near-normal hearing may be due to cellular enzyme deficiency. Besides, the inability to obtain the wave I at low-tone levels suggests the suspicion of hidden hearing loss due to damage to the cochlea and ribbon synapses peripherally. Given this situation, it was concluded that detailed audiological evaluations with bigger sample groups are necessary for GA-I patients.

The prolongations in I-III and I-V inter-wave latencies indicate the damage in the auditory pathways after the cochlear nucleus, and the absolute latency prolongation on wave I, which reflects the activity of the 8th cranial nerve, shows the possibility of cranial nerve disorder (Takahashi & Nakamura, 1976). In our study, I-III and I-V wave mean interpeak latency values of the study group at 90 dB nHL tone were longer compared to the control group, which is consistent with the literature. It has been stated that axonal degeneration in myelinated nerve cells leads to prolongation of interpeak latency, and since the bipolar cell bodies and axons of the 8th nerve are covered with myelin, it can be inferred that there is degeneration in the myelin layer of the 8th nerve (Chen, Hsu, & Chen, 1988). It has been shown that increased cholesterol acidosis in the cochlea exposed to metabolic stress may cause glucose accumulation, causing edema in the stria vascularis and outer hair cells and subsequent hearing loss (Komura et al., 1998). After all these metabolic effects, a decrease in hearing sensitivity and abnormal ABR wave responses were reported in the cochlea with vascular cellular effects (Oiticica & Bittar, 2010).

In line with the literature and the findings of our study, it was concluded that it would be guiding and useful to conduct hearing monitoring using the entire audiological battery together with the diagnosis and treatment of individuals with a clinical diagnosis of GA-1.

Conclusion

The obtained data in our study, the important audiological difference between individuals with GA-1 and healthy individuals, support the fact that the central auditory pathways of individuals with GA-1 are affected by metabolic episodes. The importance and necessity of audiological evaluation in terms of increasing social awareness about metabolic diseases, preventing complications secondary to this disease, and early intervention has been shown once again with this study.

Declarations

Funding: The authors declared that this study has received no financial support.

Conflict of Interest: The authors have no conflict of interest to declare. The authors alone are responsible for the content and writing of the paper.

Availability of data and material: The analyzed data sets generated during the study are

available from the corresponding author on reasonable request

Author Contributions:

Dilek ÖZGEDİK: Project development, Data Collection, Manuscript writing draft preparation, Analysis

Suna Tokgoz-YILMAZ: Conceptualization, Writing and draft preparation, Reviewing and Editing, Methodology.

Berrak Bilginer GÜRBÜZ: Data Collection, Analysis

H.Serap SİVRİ: Project development, Data Collection

Gonca SENNAROĞLU: Project development, Reviewing and Editing, Supervision

Ethics Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Medical School non-clinical studies Ethics Committee of the Hacettepe University (Approval no: 17/16-18) on 31.01.2017 and the necessary permissions were obtained before initiating the study.

Consent to participate: Written informed consent was obtained from the subjects who participated in this study.

Consent for publication: Consent for publication was obtained from the authors who participated in this study.

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Tables

Table 1. Demographic and clinical data of with GA-1 patients

No	sex	Age	Age of Onset	Age of diagnosis	Consanguinity	Type of mutation	Mutation state	Hearing status	Clinical outcome
1	F	22.41	7.25	7.25	Yes	missense	heterozygous	Normal hearing	Alive
2	M	25.5	1	10.33	Yes	missense	heterozygous	Mild Hearing Loss	Alive
3	F	18	0.58	3	No	missense	homozygous	Normal hearing	Alive
4	M	26	0.75	14	No	deletion	compound heterozygous	Mild Hearing Loss	Alive
5	M	18.58	4	4.08	Yes	missense	homozygous	Normal hearing	Alive
6	M	6	0.33	1.58	Yes	missense	homozygous	Mild Hearing Loss	Alive
7	F	12	0.13	0.13	Yes	missense	homozygous	Mild Hearing Loss	Alive
8	F	9.16	0.5	0.58	Yes	missense	homozygous	Mild Hearing Loss	Alive
9	M	11	0.5	0.83	Yes	missense	homozygous	Mild Hearing Loss	Alive
10	F	26	10	14	Yes	missense	heterozygous	Mild Hearing Loss	Alive
11	F	7	0.58	0.66	Yes	missense	compound heterozygous	Mild Hearing Loss	Alive
12	M	6.58	4.41	0.5	No	missense	homozygous	Mild Hearing Loss	Alive
13	M	15.41	0.5	0.5	Yes	missense	homozygous	Mild Hearing Loss	Alive
14	F	18	12	12.66	Yes	missense	homozygous	Mild Hearing Loss	Alive
15	F	8	2.08	2.16	Yes	missense	homozygous	Normal hearing	Alive
16	F	16	0.66	0.7	Yes	deletion	homozygous	Mild Hearing Loss	Alive
17	F	19	0.58	4.25	Yes	deletion	homozygous	Mild Hearing Loss	Died

F: Female, M: Male

Table 2 DPOAE amplitudes of the study and control groups for both ears

Frequency (Hz)	The study group				The control group				p*	
	mean ±SD	Medyan	Min	Max	mean± SD	Medyan	Min	Max		
Right	1000	8.9±10.6	11.5	-17	23	15.4±10.8	14	-11	36	0.061
	1500	11.2±8.8	12.5	-12	24	16.8±11.6	17.5	-13	35	0.091
	2000	12.3±9.8	12	-16	27	19± 8.6	18.5	-6	33	0.027*
	3000	12.7±10.3	14	-17	27	19.6±7.2	18.5	7	34	0.020*
	4000	12.8±11	15.5	-18	25	19.4± 12.2	21	-11	34	0.083
	6000	8.7±9.9	11	-18	22	13.5±10.5	16	-13	30	0.146
	8000	7.7± 8.9	9.5	-19	21	8.4± 10.7	11.5	-17	21	0.811
Left	1000	8.5±9.8	11.5	-16	19	15.1±9	15.5	-11	32	0.034*
	1500	10.9±8.6	12.5	-17	22	16.6± 9.6	17.5	-16	33	0.053
	2000	11.8±9.7	13	-20	26	18.7± 10.2	18.5	-12	34	0.036*
	3000	12.5±11.4	14	-18	27	19.2± 8.5	19	-5	33	0.041*
	4000	12.3± 10.8	16	-20	23	19± 11.2	20	-16	34	0.064
	6000	8.4± 11	13	-17	22	13.3± 12.3	15.5	-18	30	0.196
	8000	7.4± 10.3	10.5	-24	20	8.2± 9.7	10.5	-17	22	0.815

SD standart deviation * Significant differences (p<0,05)

Table 3 Contralateral suppression values of DPOAE of the study and control groups

Frequency (Hz)	The study group				The control group				P*	
	mean ±SD	Medyan	Min	Max	mean ±SD	Medyan	Min	Max		
Right	1000	0.73±0.74	0.6	0	2.4	1.44±0.78	1.4	0	3.3	0.007*
	1500	0.61±0.51	0.5	0	2.3	1.53±0.76	1.8	0	2.9	0.000*
	2000	0.66±0.48	0.7	0	1.6	1.77±1.09	1.6	0	4.3	0.000*
	3000	0.52±0.49	0.4	0	1.8	1.64±1.04	1.7	0	3.8	0.000*
	4000	0.44±0.47	0.3	0	1.6	1.21±0.61	1.2	0	2.8	0.000*
	6000	0.25±0.24	0.2	0	0.9	0.73±0.49	0.7	0	2.1	0.000*
	8000	0.18±0.2	0.1	0	0.7	0.61±0.4	0.6	0	1.4	0.000*
Left	1000	0.69±0.63	0.7	0	2	1.47±0.85	1.4	0	3.3	0.003*
	1500	0.63±0.52	0.6	0	2.1	1.55±0.79	1.5	0	3.2	0.000*
	2000	0.67±0.48	0.7	0	1.7	1.65±1.1	1.9	0	3.5	0.001*
	3000	0.54±0.54	0.4	0	1.9	1.53±0.8	1.4	0	3.1	0.000*
	4000	0.36±0.38	0.2	0	1.2	1.09±0.46	1.2	0	1.8	0.000*
	600	0.23±0.28	0.2	0	1.1	0.72± 0.47	0.7	0	1.7	0.000*
	8000	0.22±0.21	0.2	0	0.8	0.53± 0.4	0.5	0	1.1	0.004*

SD standart deviation * Significant differences (p<0,05)

Figures

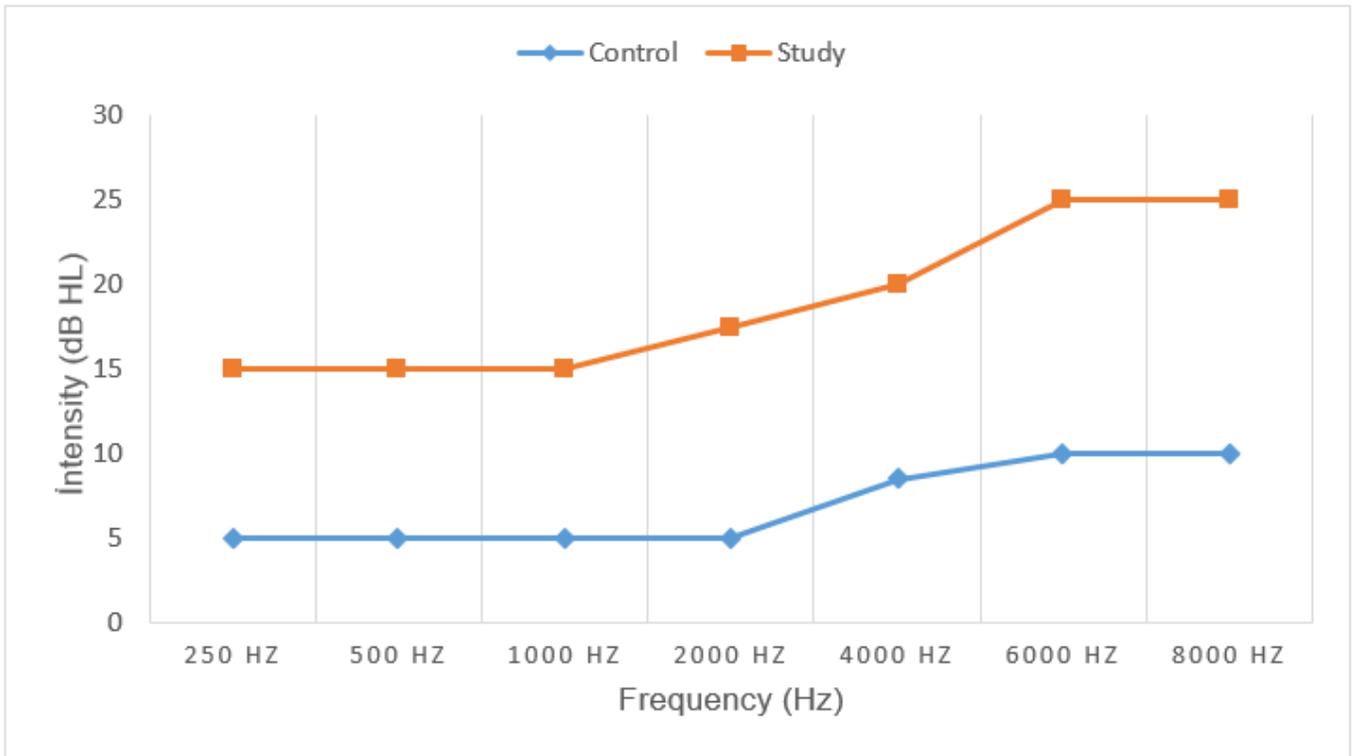


Figure 1

Pure tone hearing thresholds of the study group were higher (worse) than the control group's hearing levels and the difference was statistically significant ($p < 0.05$; Figure 1).

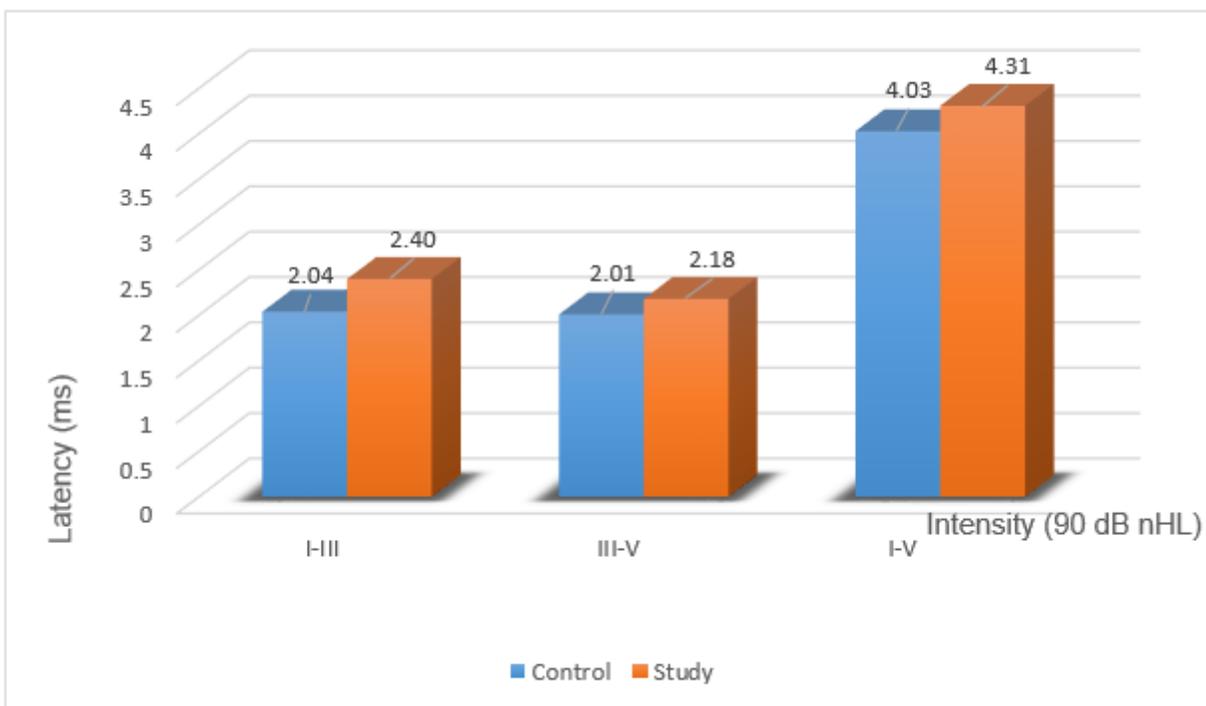


Figure 2

I-III, III-V, and I-V wave interpeak latency values of all the participants, regardless of their age and gender, at 90 dB nHL tone were presented in Figure 2. While I-III and I-V wave mean interpeak latency values of the study group were longer compared to the control group, III-V wave mean interpeak latency value was shorter ($p < 0,05$).