The Turkish Journal of Pediatrics 2022; 64: 658-670
https://doi.org/10.24953/turkjped.2022.142

Original Article

Assessment of auditory functions in patients with hepatic glycogen storage diseases

Merve Emecen Şanlı[1], Nuriye Yıldırım Gökay[2], Hakan Tutar[3], Bülent Gündüz[2], Ekin Özsaydı[1], Ayşe Kılıç[1], Aslı İnci[1], İlyas Okur[1], Fatih Ezgü[1], Leyla Tümer[1]

Departments of [1]Pediatric Inborn Errors of Metabolism and [3]Otorhinolaryngology, Gazi University Faculty of Medicine, Ankara; [2]Department of Audiology, Gazi University Faculty of Health Sciences, Ankara, Turkey.

ABSTRACT

Background. Hepatic glycogen storage diseases are a group of diseases manifesting mainly with hypoglycemia and hepatomegaly. The patients require frequent daytime and nocturnal feedings. Hypoglycemia may cause sensorineural hearing loss and nocturnal feeding is a risk factor for the development of gastroesophageal reflux that may cause chronic otitis media and hearing loss consequently. We aimed to determine the prevalence and characteristics of hearing loss in hepatic glycogen storage diseases.

Methods. A total of 24 patients with hepatic glycogen storage disease (15 glycogen storage disease type I and 9 non type I) and 24 age/sex matched healthy controls were enrolled in the study. Pure tone audiometer, immitansmetry, acoustic reflex measurement, otoacoustic emission test (OAE) and auditory brainstem response (ABR) tests were applied to all participants.

Results. Hearing loss was determined in 17/24 patients (12 glycogen storage disease type I and 5 non type I) with pure tone audiometer. Interpretation of all the findings revealed a total of 8 patients had conductive and 9 had mixed hearing loss. All parameters were significantly different than the control group.

Conclusions. This is the first study to comprehensively assess the auditory functions of patients with hepatic glycogen storage disease. Audiological findings determined a significantly increased prevalence of conductive/mixed type hearing loss in the patient group which is a new finding in the literature. Further studies with extended patient numbers are required to enlighten the underlying pathophysiology.

Key words: glycogen storage disease, hearing loss, auditory function, nocturnal feeding, hypoglycemia.

Glycogen is the storage form of glucose in mammalian cells, and it is mostly stored in muscle and liver. Glycogen is utilized as a glucose source to maintain blood glucose levels within the normal ranges between meals. In the muscle, glycogen provides glucose for glycolysis and ATP production and this energy is utilized during active contraction. Glycogen storage diseases (GSD) are a group of inherited metabolic diseases accompanied by abnormal glycogen storage or utilization resulting from variable genetic deficiency of enzymes in glycogen degradation or synthesis or mutations of regulatory proteins in glycogen metabolism. It is classified based on the enzyme deficiencies or affected tissues. Hypoglycemia and hepatomegaly are cardinal presenting manifestations in hepatic glycogenosis.[1,2]

Hepatic GSDs are type 0, I, III, VI and IX. In type I, either glucose 6- phosphatase (G6Pase) enzyme (type Ia) or glucose 6-phosphate (G6P) transporter (type Ib) is deficient, and hypoglycemia is earlier and more severe due to both gluconeogenesis and glycogenolysis impairment.[1,3] Glycogen synthase enzyme is deficient in type 0 resulting in impairment of glycogen synthesis and symptoms are seen after weaning and are less severe. Abnormal glycogen

✉ Merve Emecen Şanlı
merveemecan@gmail.com

Received 5th February 2022, revised 26th March 2022, 8th April 2022, accepted 19th April 2022.

accumulates in type III due to the debrancher enzyme deficiency. Glycogen phosphorylase and phosphorylase kinase enzymes are utilized in glycogenolysis, and deficiencies cause type VI and IX respectively.[1,4,5]

The severe forms of GSDs in childhood are associated with very short fasting intervals of less than 4 hours, overnight continuous gastric high-carbohydrate feedings; frequent daytime feedings with supplementing of uncooked cornstarch are quite a typical requirement of type I but can also be required in other types.[6]

Hypoglycemia may cause complications in the central nervous system involving vision loss, seizures, unconsciousness and auditory dysfunction. Hearing loss (HL) is seen in many kinds of metabolic disorders involving biotinidase deficiency, mitochondrial, peroxisomal and lysosomal diseases.[7-14] The primary defects of hearing loss in these diseases are lack of energy, disruption of inner ear cells due to substrate accumulation or vascular damage.[15,16] In the literature there are many reports indicating the association between hypoglycemia and auditory dysfunction. Hyperinsulinemia, hypocortisolemia, type II diabetes may cause hearing loss due to hypoglycemia.[17-19]

However, the data related to auditory functions in hepatic GSD is limited. Hearing loss was shown in many studies conducted with GSD type II (Pompe disease) patients; however, it is a lysosomal storage disease, and the pathophysiology is different. There is limited data suggesting that sensorineural hearing loss might be seen in type I patients. Melis et al.[20] and Aydemir et al.[21] evaluated the auditory functions of the type I patients with auditory brainstem response (ABR) only and found abnormalities. Since hepatic GSD are hypoglycemia associated and require overnight feeding that may cause gastroesophageal reflux (GER); an association between hepatic GSDs and HL could be hypothesized. In the present study we aimed to obtain a comprehensive assessment of auditory functions and determine the prevalence and characteristics of HL in hepatic GSD patients compared with healthy controls.

Material and Methods

Subjects

Patients with hepatic GSD and followed up in our clinic were evaluated. All patients were diagnosed with either presence of biallelic mutation in the concerning gene and/or low tissue enzyme activity. Those who had head trauma, otologic surgery, idiopathic urgent HL, acute acoustic trauma, exposed long term noise, frequent otitis media, familial HL, diabetes mellitus and exposure to ototoxic medicine were excluded. The study was conducted with hepatic GSD patients and age/sex matched healthy controls. Informed oral and written consent were obtained from all subjects and their parents before enrollment. The study was approved by Gazi University Ethical Comittee. (613/21.09.2020)

Hearing Assessments

Pure tone audiometer, immitansmetry, acoustic reflex measurement, otoacoustic emission test (OAE) and auditory brainstem response (ABR) tests were applied to all participants.

Pure-tone thresholds were analyzed for both air and bone conduction using TDH 39 supraaural headphones and GSI audiometry.[22] Degree of clinical hearing loss was classified according to the normative hearing data derived from WHO and based on a four-frequency pure-tone average (500, 1000, 2000 and 4000 Hz). Slight HL ranged between 16-24 dB; mild HL 25-39, moderate HL 40-69 dB, severe HL 70-95 dB, and profound HL >95 dB.[23]

To describe middle ear functions, immitansmetrical evaluation with middle ear pressures, static compliance and ear canal volume and ipsilateral reflex thresholds at 500, 1000, 2000 and 4000 Hz were measured.

Transient otoacoustic emission (TEOAE) test was applied to determine the cochlear functions using Interacoustics Eclipse 15 device and the responses in which a signal to noise ratio exceeding 3 dB in at least three of the five frequencies were recorded as "present" and other conditions as "absent". Present TEOAE shows that cochlear and middle ear functions are normal, and absence of TEOAE indicates cochlear and/or middle ear functions are abnormal.[24]

ABR was performed using Interacoustic Eclipse 15 device and ER-3A insert headphones to identify retrocochlear dysfunction. Click stimulus were presented in both ears and I, III, V wave latencies and amplitudes at 85 dB nHL were detected. In ABR test, I, III and V are the basic waves and can predict the type and degree of HL according to latency-amplitude values. Wave I originates from the distal region of the 8th cranial nerve, wave III from the cochlear nucleus and superior olivary complex, and wave V originates from the superior olivary complex and lateral lemniscus.[25] Prolonged I-III and I-V interpeak and interaural latencies and the absolute wave latencies show cochlear/ retrocochlear or conductive type pathology.

The origin of the hearing deficit was estimated by the combined interpretation of the ABR, otoacoustic emissions, and impedance audiometry.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with Kolmogorov-Smirnov test. Mann-Whitney U test were used for the comparison of quantitative data. Wilcoxon test was used for the repeated measurement analysis. The chi-square test was used for the comparison of qualitative data. ROC analysis was used to show the effect level. SPSS 27.0 was used for statistical analyses.

Results

Fifteen GSD type I and 9 non type I patients were included in the study. The age of patients ranged from 3 to 26 years (mean 8.8 ± 4.54). The mean age of the patient group was 11.08 ± 6.52 years. The female/male ratio was 12/12. The control group consisted of 24 healthy individuals (13 female and 12 male, mean age 10.88 ± 5.53 years, range 2–23 years).

No risk factors for hearing loss were identified by questionnaire and neither neurologic, nor intellectual complications were present in the patients. The results of age, gender distribution, pure tone audiometer, middle ear pressure, acoustic reflex threshold, click threshold, ABR I-III, III-V interpeak latencies, otoacoustic latencies are shown in Table I.

There was no significant difference between age and gender distribution amongst patient and control groups ($p > 0.05$). In the patient group, right, left and right-left mean values of pure tone audiometer, acoustic reflex threshold, click threshold, ABR I-V and III-V interpeak latencies, prolonged I-V interpeak latency rate and OAE rate were significantly higher and middle ear pressures were significantly lower than the control group ($p < 0.05$) (Table I).

The pure tone audiometer determined HL in a total of 17 (70.8%) patients which were slight in 9 (37%) and mild in 8 (33%) patients. HL was not described in 7 (29.1%) patients. Findings were significantly different than the control group ($p < 0.001$) (Table II, Fig. 1).

Immitansmetrical evaluation showed middle ear pressures were significantly decreased in the patient group (Table II). According to the Jegger classification, 14 (58.3%) patients (11 type I, 3 non type I) had Type C tympanogram, however all of the individuals in the control group had type A (24) (Fig. 2). Acoustic reflex couldn't be measured or measured at high decibels (approximately 100 dB) compatible with type C tympanogram, whereas acoustic

Table I. Summary of clinical features and audiologic results of patients.

Patient No/Disease type/Gender/ Age (y)/ metabolic control	Weight/ height percentiles	Right Ear					Left ear				
		Estimated Hearing Threshold	Tymp	OAE	I-V interpeak lantencies	III-V interpeak lantencies	Estimated Hearing Threshold	Tymp	OAE	I-V interpeak lantencies	III-V interpeak lantencies
1/type Ia/F/12/good	94/36	25	Abnormal	Absent	Normal	Normal	27	Abnormal	Absent	Normal	Normal
2/type Ia F/12/good	36/42	20	Abnormal	Absent	Normal	Normal	18	Abnormal	Absent	Normal	Normal
3/type Ia /F/8/good	98/84	32	Abnormal	Absent	Prolonged	Normal	30	Abnormal	Absent	Prolonged	Normal
4/type Ia /F/12/poor	18/<3	25	Abnormal	Absent	Normal	Normal	23	Abnormal	Absent	Normal	Normal
5/type Ia M/11/poor	<3/<3	27	Abnormal	Absent	Prolonged	Normal	25	Abnormal	Absent	Prolonged	Normal
6/type Ia /F/7/poor	5/<3	30	Abnormal	Absent	Prolonged	4.33	28	Abnormal	Absent	Prolonged	4.35
7/type Ia/F/4/poor	<3/7	33	Abnormal	Absent	Prolonged	Normal	28	Abnormal	Absent	Prolonged	Normal
8/type Ia /F/5/poor	99/56	23	Abnormal	Absent	Prolonged	Normal	20	Abnormal	Absent	Prolonged	Normal
9/type Ia F/9/poor	72/28	22	Abnormal	Absent	Prolonged	3.65	18	Abnormal	Absent	Prolonged	3.67
10/type Ia /M/7/poor	59/32	15	Normal	Present	Normal	Normal	13	Normal	Present	Normal	Normal
11/type VI/F/5	61/12	18	Normal	Present	Normal	Normal	13	Normal	Present	Normal	Normal
12/type Ib/M/4/good	88/6	25	Abnormal	Absent	Prolonged	Normal	21	Abnormal	Absent	Prolonged	Normal
13/type 0/M/6	75/25	15	Normal	Present	Normal	Normal	15	Normal	Present	Normal	Normal
14/type VI/M/7	53/8	12	Normal	Present	Normal	Normal	10	Normal	Present	Normal	Normal
15/type III/M/10	30/25	18	Abnormal	Absent	Prolonged	Normal	15	Abnormal	Absent	Prolonged	Normal
16/type III/F/3	91/7	25	Abnormal	Absent	Prolonged	Normal	22	Abnormal	Absent	Prolonged	Normal
17/type III/F/7	82/24	22	Abnormal	Absent	Normal	Normal	25	Abnormal	Absent	Normal	Normal
18/type Ia /F/22/poor	>18 year old	16	Normal	Present	Normal	Normal	14	Normal	Present	Normal	Normal
19/type VI/M/14	58/9	17	Normal	Present	Normal	Normal	17	Normal	Present	Normal	Normal
20/type III/M/16	44/<3	15	Normal	Present	Normal	Normal	14	Normal	Present	Normal	Normal
21/type I/M/16/poor	4/<3	21	Abnormal	Absent	Normal	Normal	25	Abnormal	Absent	Normal	Normal
22/type VI/M/24	>18 year old	13	Normal	Present	Normal	Normal	14	Normal	Present	Normal	Normal
23/type Ia /M/26/poor	>18 year old	10	Normal	Present	Normal	Normal	12	Normal	Present	Normal	Normal
24/type Ia /M/19/poor	>18 year old	15	Normal	Present	Normal	Normal	15	Normal	Present	Normal	Normal

Tym.: tympanometry, OAE: otoacustic emission

reflex thresholds were at normal ranges in controls (Fig. 3).

In the TEOAE test, no response was present in 11 type I and 4 non type I patients (58.3%) which was compatible with the immitansmetric findings (Table II). However, in the control group, TEOAE response was present in all the individuals (Fig. 4).

Table II. Audiologic findings of control and patient groups.

		Control Group		Patient Group		p
		Mean±sd/n-%	Median	Mean±sd/n-%	Median	
Age		10.9 ± 5.5	9.5	11.1 ± 6.5	9.5	0.877 [m]
Gender	Girl	13 54.2%		12 50.0%		0.773 [X²]
	Boy	11 45.8%		12 50.0%		
Pure Tone Audiometer						
Right Ear		7.8 ± 3.1	8.0	20.6 ± 6.3	20.5	0.000 [m]
Left Ear		8.5 ± 2.6	8.0	19.4 ± 6.4	18.0	0.000 [m]
R-L Mean		8.1 ± 2.4	8.8	20.0 ± 6.2	19.5	0.000 [m]
Middle Ear Pressure						
Right Ear		-6.2 ± 18.3	-7.5	-119.7 ± 81.6	-123.0	0.000 [m]
Left Ear		-5.2 ± 12.8	-4.5	-102.6 ± 64.3	-116.0	0.000 [m]
R-L Mean		-5.7 ± 10.5	-5.3	-111.2 ± 70.2	-120.3	0.000 [m]
Acustic Reflex Threshold						
Right Ear		85.0 ± 0.0	85.0	94.8 ± 8.5	95.0	0.000 [m]
Left Ear		85.0 ± 0.0	85.0	95.0 ± 6.4	95.0	0.000 [m]
R-L Mean		85.0 ± 0.0	85.0	94.6 ± 7.8	96.3	0.000 [m]
Click Threshold						
Right Ear		20.0 ± 0.0	20.0	29.4 ± 7.7	30.0	0.000 [m]
Left Ear		20.0 ± 0.0	20.0	29.6 ± 7.4	30.0	0.000 [m]
R-L Mean		20.0 ± 0.0	20.0	29.5 ± 7.3	28.8	0.000 [m]
ABR I-V Interpeak Latencies						
Right Ear		3.8 ± 0.4	3.8	5.2 ± 1.0	5.1	0.000 [m]
Left Ear		3.8 ± 0.4	3.8	5.1 ± 0.9	5.2	0.000 [m]
R-L Mean		3.8 ± 0.4	3.8	5.2 ± 0.9	5.2	0.000 [m]
ABR III-V Interpeak Latencies						
Right Ear		2.2 ± 0.1	2.2	3.2 ± 0.8	3.2	0.000 [m]
Left Ear		2.2 ± 0.1	2.2	3.1 ± 0.8	3.3	0.000 [m]
R-L Mean		2.2 ± 0.1	2.2	3.2 ± 0.8	3.3	0.000 [m]
Prolonged	Prolonged	0 0.0%		15 62.5%		0.000 [X²]
	Normal	24 100.0%		9 37.5%		
Otoacustic Emission (OAE)						
Right Otoacustic	(-)	0 0.0%		15 62.5%		0.000 [X²]
Emission(OAE)	(+)	24 100.0%		9 37.5%		
Left Otoacustic	(-)	0 0.0%		15 62.5%		0.000 [X²]
Emission(OAE)	(+)	24 100.0%		9 37.5%		
R or L Otoacustic	(-)	0 0.0%		15 62.5%		0.000 [X²]
Emission(OAE)	(+)	24 100.0%		9 37.5%		

[m] Mann-whitney u test [X²] Chi-square test

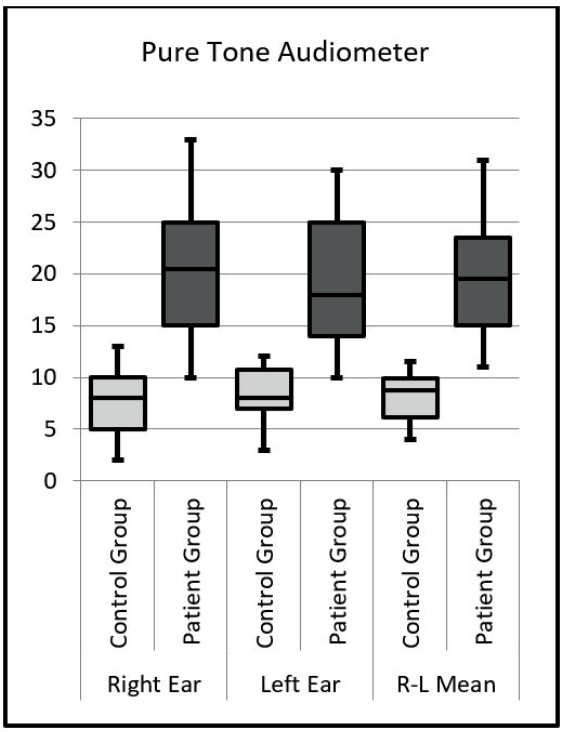

Fig. 1. Estimated hearing thresholds (dB) of patient and control group.

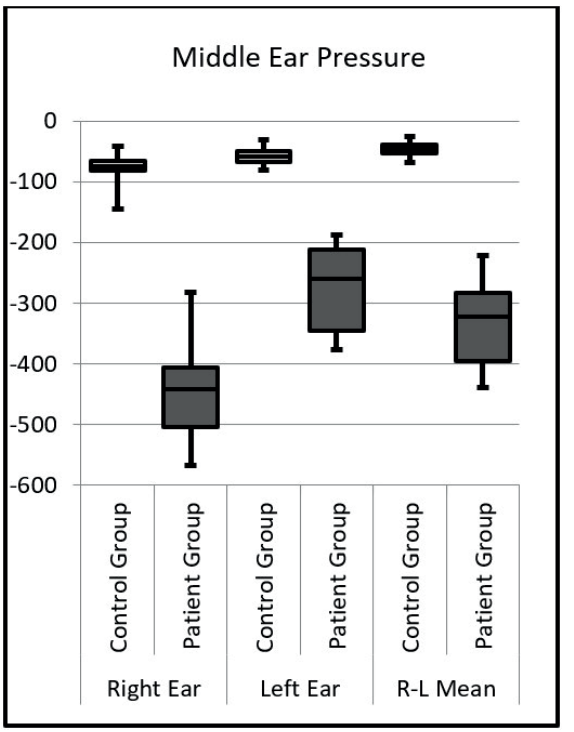

Fig. 2. Middle ear pressures of control and patient groups.

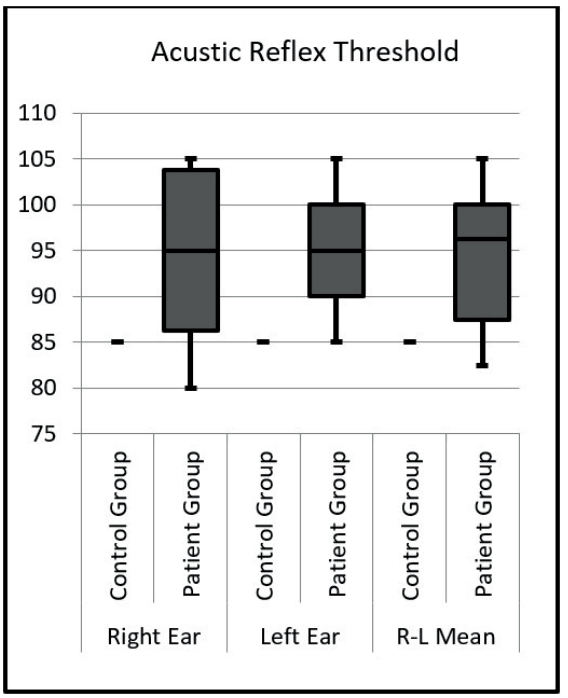

Fig. 3. Acustic reflex thresholds of control and patient groups.

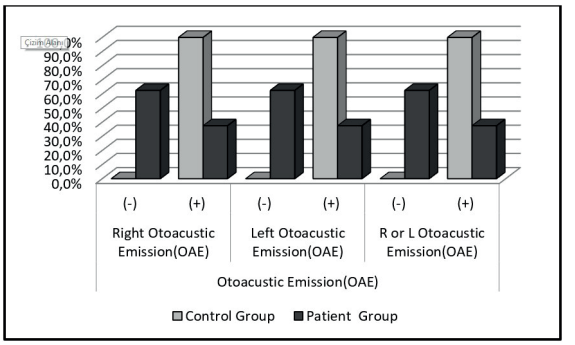

Fig. 4. Percentages of presence (+) and absence (-) of otoacustic emission in control and patient groups.

In click ABR test, thresholds of the patients were significantly higher ($p < 0.001$) (Table II, Fig. 5). Moreover, type I patients' thresholds were significantly higher than non-type I patients ($p = 0.031$). I-V and III-V interpeak latencies were significantly higher in the patient group ($p < 0.001$) (Fig. 6). However, no significant difference was detected between type I and non-type I patients. I-V interpeak latencies were

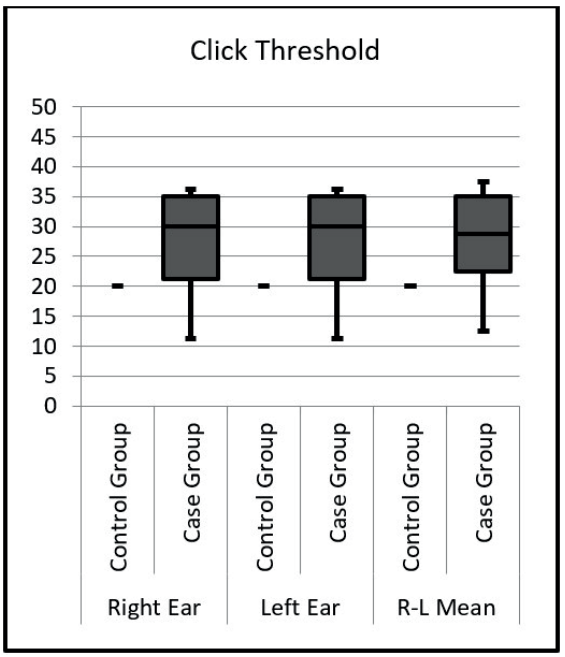

Fig. 5. Click thresholds of control and patient groups.

prolonged in 9 (37.5%) patients. Since, these patients also had type C tympanograms, they were diagnosed with mixed HL.

Interpretation of all the audiologic findings determined that 9 patients had a mixed type and 8 had conductive type hearing loss (Table I). Furthermore, all audiological findings showed a significant difference between GSD I patients and controls.

Type I patients were divided into two subgroups: those with good and poor metabolic control according to the criteria defined by European Study on Glycogen Storage Disease Type I.[21] Patients were assigned as good metabolic control if blood glucose was > 72 mg/dl, triglycerides < 531 mg/dl, uric acid < 6 mg/ dl, and lactate < 22.5 mg/dl. No correlation could be established between metabolic control and hearing assessment values in type I patients (Table II).

Because older patients are more likely to have fewer episodes of hypoglycemia and need less frequent nocturnal feeding, patients were also classified into two groups, those who were >12 and those who were <12-year-old. Comparing of two groups revealed that pure tone audiometer,

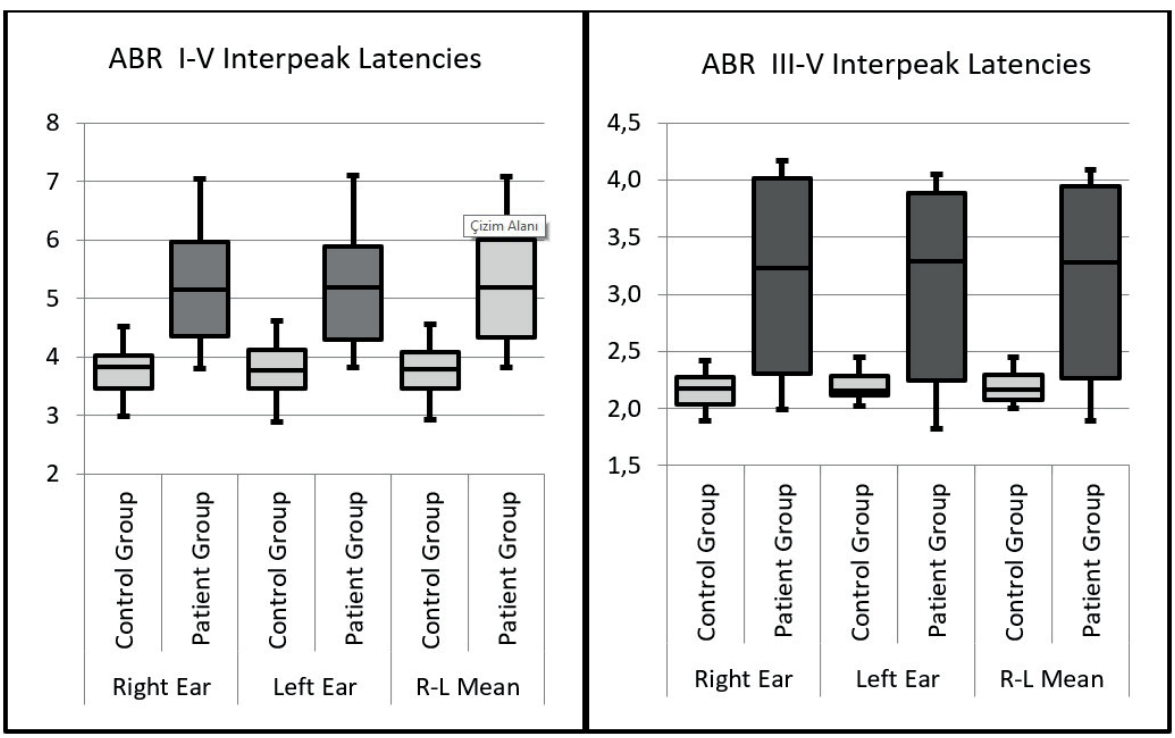

Fig. 6. ABR I-V and III-V interpeak latencies of control and patient groups.

middle ear pressure, acoustic reflex threshold, click threshold, ABR I-V and III-V interpeak latencies values were higher and hearing loss was more prevalent in patients < 12-year-old. In addition, otoacoustic emission responses were absent in 82.4% of patients <12 and 14.3% of >12-year-old.

Discussion

The results of the conducted study were consistent with the hypothesis. HL was detected in the individuals with GSD, particularly in type I. In GSD patients HL prevalence was significantly higher than in the controls. Slight/mild levels of conductive auditory thresholds in pure tone audiometer, type C tympanogram findings and prolonged I., III., V. interpeak latencies despite normal I-V interpeak latencies in ABR suggested conductive type HL in 8 patients.[26] In 9 patients, presence of prolonged III-V and I-V interpeak latencies suggest dysfunction of cochlear and retrocochlear structures that is consistent with mixed hearing loss. Conductive/mixed hearing loss suggests chronic middle ear dysfunction.[27] Infections, allergy, immunologic factors, and GER are the main causes of chronic otitis media.[28-30] Thus, we aimed to determine the etiologic factors of conductive/mixed hearing loss in the patients.

In GSD Ib patients, recurrent infections such as otitis, upper respiratory infections, gingivitis and mouth ulcers, abscesses and pneumonia are seen frequently due to neutropenia and neutrophil dysfunction.[31] However, these infections are much less frequent in GSD Ia. Nevertheless, we detected different reports in the literature relevant to recurrent otitis media, adenoid/tonsillar hypertrophy in GSD Ia patients. Bevan[32] reported a child diagnosed with GSD Ia who exhibited adenoid hypertrophy preventing nasogastric tube feeding and required a gastrostomy. In van Creveld et al.'s[33] report, a GSD Ia patient developed mouth thrush infection and recurrent otitis media which resolved with adenoidectomy. Bustamente et al.[34] reported a patient with GSD Ia who underwent adenoidectomy, tonsillectomy, and myringotomy tube placement due to recurrent suppurative otitis media and obstructive sleep apnea at 4 years of age. Farrington et al.[35] identified a GSD Ib patient with recurrent otitis media and oral thrush beginning at the age of 8 months explained with the possible result of partial obstruction introduced by the nasogastric tube. She had undergone bilateral myringotomy at age of 25 months followed by tonsillectomy and adenoidectomy at age of 51 months. In addition, recurrent otitis media in GSD III patients was shown in the studies of Assiri et al.[36] and Williams et al.[37]

Although adenoid or tonsillar hypertrophy and otitis are not common features of hepatic GSDs, the fact that they have been seen in many patients supports a predisposition to this condition in some way. This possible predisposition might be due to unknown factors affecting immune dysfunction. In addition, patients are fed with lactose, fructose and sucrose are restricted except for fruits, vegetables and small amounts of milk products which might cause consumption of insufficient essential nutrients, vitamins and minerals and could result in secondary immune dysfunction. There are some scarce data relevant to immune dysfunction in GSD Ia. Kim et al.[38] showed that impaired glucose homeostasis resulted in myeloid dysfunction in GSD Ia and Ib.

They demonstrated an elevated progenitor cell frequency in the bone marrow and spleen and increased serum levels of granulocyte colony stimulating factor and cytokine-induced neutrophil chemoattractant in mice with GSD Ia and Ib. These changes were more prominent in GSD Ib mice which was consistent with myeloid dysfunction. Weston et al.[39] also identified four patients with GSD Ia. They were homozygous for G188R mutation and presented with hypoglycemia, recurrent infections, and neutropenia. Bilateral ventilation tubes were placed in one patient because of recurrent otitis media. Neutrophil function analysis revealed neutrophil dysfunction like GSD Ib patients. They suggested that G6Pase might play a role

in the microsomal membrane transport of G6P, however because G6Pase gene is not highly expressed in human PMN, it is often difficult to interpret.

On the other hand, hepatic GSD patients are subjected to being fed during the night continuously or every 3-4 hours. During the feeding they are likely to be in a supine position which is a risk factor for gastroesophageal and extraesophageal reflux. The main side effect of this kind of nutrition is gastro-esophageal reflux disease (GERD), in 25-60% of cases.[40-42] Another possible mechanism for GERD may be an increase in antral volume during nutrition. Scott et al.[43] identified increased reflux episodes in children with cystic fibrosis who were under continuous nighttime nasogastric feeding due to poor nutrition status compared with their asymptomatic siblings. In a mouse model, it was shown that GERD causes the middle ear to be exposed to gastric enzymes which cause Eustachian tube dysfunction, impaired clearance of middle ear contents, and hearing impairment consequently.[44-47] Recent studies established the presence of gastric contents in the middle ear effusions of children with recurrent otitis media.[48,49]

Due to the angle and immaturity of the Eustachian tubes in children and the supine position in which infants are usually placed for prolonged periods, the possibility of reflux of stomach contents from the nasopharynx to the middle ear is considered especially in the pediatric age group.[44,50] When the stomach contents reach the middle ear, pepsin is present in active or inactive form depending on the pH of the environment. The pepsin/pepsinogen protein concentrations measured in middle ear effusions were 1000 times higher than the levels in serum.[51] Scott et al.[43] demonstrated that GER, when it becomes laryngopharyngeal reflux, could reach the middle ear, indicating a possible reflux passage through the Eustachian tube into the middle ear, could lead to otitis media. Crapko et al.[52] obtained middle ear effusion samples and analyzed pepsin presence in patients with otitis media with effusion and detected pepsin in 60% of patients confirming that extraesophageal reflux occurs in the middle ear in those children.

The patients with a history of frequent otitis media associated with any known causes were excluded in this study and because of this we have excluded 4 patients with known recurrent otitis media or ventilation tube placement or hearing loss. Therefore, the cause of conductive component of hearing loss might be associated with fluid collection in the middle ear as a result of adenoid and/or tonsil hypertrophy, otitis media due to the presence of possible immune dysfunction or GER due to nocturnal feeding, feeding in supine position and presence of more horizontal Eustachian tube in children.[16] The Eustachian tube reaches its physiologically normal position in older children. Prevalence of abnormal middle ear pressures and hearing loss were lower in patients >12-year-old who were on less frequent nocturnal feeding than type I patients <12-year-old. These findings also suggest that possible association. In addition, it might also be indirectly suggested with lacking correlation between metabolic control and hearing loss in type I patients.

Despite pure tone audiometer and particularly ABR values did not define pure sensorineural dysfunction in the patients, considering the interpeak latencies, cochlear and retrocochlear components of the HL might be suggested. In the study of Aydemir et al.[21] and Melis et al.[20], sensorineural hearing loss was detected in ABR in 20% and 15.7% of type I patients respectively. In these previous studies auditory functions were assessed with ABR only, however in the present study, it was comprehensively evaluated both in type I and non-type I patients. Moreover, in this study, tympanogram findings defined conductive hearing loss in the patients that elucidates a new complication of the disease group. Hypoglycemia might lead to sensorineural hearing loss as shown in patients with hyperinsulinism and diabetes. Previous studies on GSD I patients also suggest the association between hypoglycemia and sensorineural hearing loss, however conductive

hearing loss in hepatic GSD patients is a new finding.

Additionally, Iwanicka-Pronicka et al.[53] recently reported a study that is closest to the hypothesis of the present study. In this study ,10% of patients had bilateral sensorineural hearing loss that decreased towards high frequencies. Contrarily, in our current study, hearing loss was diagnosed in 17 patients with an accompanying conduction component in 9 patients. Especially considering the patients with mixed-type hearing loss in the current study, as Iwanicka-Pronicka et al.[53] suggested, pathophysiological changes related to the inner ear may also explain the sensorineural hearing loss. Accordingly, the specific mechanism of hearing impairment in GSD is unknown to date. The possible ototoxic effect of recurrent hypoglycemia, dyslipidemia or hypertension can also lead to inner ear damage. Therefore, the influence of the inner ears of patients with mixed hearing loss in our current study might be also explained by these theories. Unlike the current study, Iwanicka-Pronicka et al.[53] added molecular histopathological analysis, which enabled them to better explain the pathophysiological changes associated with cochlea and its components. The otoacoustic emission, ABR test findings and accordingly inner ear effect mechanisms are compatible with our current study findings. Additionally, our study included immitansmetric tests to further investigate the findings for conductive hearing loss. Thus, it brought a new perspective to the relevant literature and suggested that alertness should be given to pathologies originating from the outer ear/middle ear.[53]

To the best of our knowledge, this is the first study to comprehensively assess auditory functions in hepatic GSD patients by comparing type I and non-type I patients. Our study suggests that hearing loss might be seen in patients with hepatic GSDs, particularly in type I. Even in slight/mild HL, decreased academic performance, social and speech development might be seen. We suggest that in addition to the risk factors seen in the normal population such as recurrent otitis media, eustachian tube dysfunction and adenoid hypertrophy; the risk factors of hearing loss in GSD might be gastroesophageal reflux, immune deficiency and hypoglycemia. However, in terms of pathogenesis, further detailed studies in a larger number of patients are required to be enlightened.

Ethical approval

The study was approved by Gazi University Ethical Comittee (613/21.09.2020).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MEŞ, İO, FE, HT, LT; data collection: NYG, MEŞ, EÖ, AK, Aİ; analysis and interpretation of results: NYG, BG, HT, MEŞ, LT; draft manuscript preparation: MEŞ, HT, LT. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Chen YT, Kishnani PS, Koeberl D. Glycogen Storage Diseases. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA (eds). The Online Metabolic and Molecular Bases of Inherited Disease. McGraw Hill, 2019.
2. Burda P, Hochuli M. Hepatic glycogen storage disorders: what have we learned in recent years?. Curr Opin Clin Nutr Metab Care 2015; 18: 415-421. https://doi.org/10.1097/MCO.0000000000000181

3. Chou JY, Jun HS, Mansfield BC. Type I glycogen storage diseases: disorders of the glucose-6-phosphatase/glucose-6-phosphate transporter complexes. J Inherit Metab Dis 2015; 38: 511-519. https://doi.org/10.1007/s10545-014-9772-x

4. Preisler N, Pradel A, Husu E, et al. Exercise intolerance in Glycogen Storage Disease Type III: weakness or energy deficiency?. Mol Genet Metab 2013; 109: 14-20. https://doi.org/10.1016/j.ymgme.2013.02.008

5. Roscher A, Patel J, Hewson S, et al. The natural history of glycogen storage disease types VI and IX: Long-term outcome from the largest metabolic center in Canada. Mol Genet Metab 2014; 113: 171-176. https://doi.org/10.1016/j.ymgme.2014.09.005

6. Bhattacharya K. Investigation and management of the hepatic glycogen storage diseases. Transl Pediatr 2015; 4: 240-248.

7. Bener A, Al-Hamaq AOAA, Abdulhadi K, Salahaldin AH, Gansan L. Interaction between diabetes mellitus and hypertension on risk of hearing loss in highly endogamous population. Diabetes Metab Syndr 2017; 11 Suppl 1: S45-S51. https://doi.org/10.1016/j.dsx.2016.09.004

8. Canda E, Kalkan Uçar S, Çoker M. Biotinidase Deficiency: Prevalence, Impact And Management Strategies. Pediatric Health Med Ther 2020; 11: 127-133.

9. Gupta S, Eavey RD, Wang M, Curhan SG, Curhan GC. Type 2 diabetes and the risk of incident hearing loss. Diabetologia 2019; 62: 281-285. https://doi.org/10.1007/s00125-018-4766-0

10. Solmaz F, Unal F, Apuhan T. Celiac disease and sensorineural hearing loss in children. Acta Otolaryngol 2012; 132: 146-151. https://doi.org/10.3109/00016489.2011.635384

11. Gettelfinger JD, Dahl JP. Syndromic hearing loss: a brief review of common presentations and genetics. J Pediatr Genet 2018; 7: 1-8. https://doi.org/10.1055/s-0037-1617454

12. Bamiou DE, Campbell P, Liasis A, et al. Audiometric abnormalities in children with Gaucher disease type 3. Neuropediatrics 2001; 32: 136-141. https://doi.org/10.1055/s-2001-16611

13. Keilmann A, Hajioff D, Ramaswami U; FOS Investigators. Ear symptoms in children with Fabry disease: data from the Fabry Outcome Survey. J Inherit Metab Dis 2009; 32: 739. https://doi.org/10.1007/s10545-009-1290-x

14. Komura Y, Kaga K, Ogawa Y, Yamaguchi Y, Tsuzuku T, Suzuki JI. ABR and temporal bone pathology in Hurler's disease. Int J Pediatr Otorhinolaryngol 1998; 43: 179-188. https://doi.org/10.1016/s0165-5876(97)00176-6

15. Endo S, Mizuta K, Yamatodani T, et al. A case of improved hearing with cochlear implantation in Gaucher disease type 1. Auris Nasus Larynx 2018; 45: 603-607. https://doi.org/10.1016/j.anl.2017.05.013

16. Köping M, Shehata-Dieler W, Schneider D, et al. Characterization of vertigo and hearing loss in patients with Fabry disease. Orphanet J Rare Dis 2018; 13: 137. https://doi.org/10.1186/s13023-018-0882-7

17. Gosselin EJ, Yanick P Jr. Audiologic and metabolic findings in 90 patients with fluctuant hearing loss. J Am Audiol Soc 1976; 2: 15-18.

18. Kitabchi AE, Shea JJ. Diabetes mellitus in fluctuant hearing loss. Otolaryngol Clin North Am 1975; 8: 357-368. https://doi.org/10.1016/s0030-6665(20)32773-0

19. Doroszewska G, Kaźmierczak H. Hyperinsulinemia in vertigo, tinnitus and hearing loss. Otolaryngol Pol 2002; 56: 57-62.

20. Melis D, Parenti G, Della Casa R, et al. Brain damage in glycogen storage disease type I. J Pediatr 2004; 144: 637-642. https://doi.org/10.1016/j.jpeds.2004.02.033

21. Aydemir Y, Gürakan F, Saltık Temizel İN, et al. Evaluation of central nervous system in patients with glycogen storage disease type 1a. Turk J Pediatr 2016; 58: 12-18. https://doi.org/10.24953/turkjped.2016.01.002

22. Clark JG. Uses and abuses of hearing loss classification. ASHA 1981; 23: 493-500.

23. World Health Organization (WHO). International classification of impairments, disabilities and handicaps: a manual of classification related to the consequences of disease. Geneva: WHO, 1980.

24. Kemp DT, Ryan S, Bray P. A guide to the effective use of otoacoustic emissions. Ear Hear 1990; 11: 93-105. https://doi.org/10.1097/00003446-199004000-00004

25. Al-Qahtani A, Haidar H, Larem A, editors. Textbook of Clinical Otolaryngology. Springer International Publishing, 2021. https://doi.org/10.1007/978-3-030-54088-3

26. Isaacson JE, Vora NM. Differential diagnosis and treatment of hearing loss. Am Fam Physician 2003; 68: 1125-1132.

27. Cole EB, Flexer C. Children with hearing loss: developing listening and talking, birth to six. Plural Publishing, 2019.

28. Tisch M, Maier H, Sudhoff H. Balloon dilation of the Eustachian tube: clinical experience in the management of 126 children. Acta Otorhinolaryngol Ital 2017; 37: 509-512. https://doi.org/10.14639/0392-100X-1690

29. Tos M. Importance of eustachian tube function in middle ear surgery. Ear Nose Throat J 1998; 77: 744-747. https://doi.org/10.1177/014556139807700911

30. Abtahi SH, Kazerooni A, Brejis N, Abdeyazdan Z, Saneian H. Prevalence and characteristics of gastroesophageal reflux in children with otitis media in Isfahan, Iran. Adv Biomed Res 2016; 5: 81. https://doi.org/10.4103/2277-9175.182212

31. Dale DC, Bolyard AA, Marrero T, et al. Neutropenia in glycogen storage disease Ib: outcomes for patients treated with granulocyte colony-stimulating factor. Curr Opin Hematol 2019; 26: 16-21. https://doi.org/10.1097/MOH.0000000000000474

32. Bevan JC. Anaesthesia in Von Gierke's disease. Current approach to management. Anaesthesia 1980; 35: 699-702. https://doi.org/10.1111/j.1365-2044.1980.tb03884.x

33. Van Creveld S, Huijing F. Glycogen storage disease. Am J Med 1965; 38: 554-561. https://doi.org/10.1016/0002-9343(65)90133-6

34. Bustamante SE, Appachi E. Acute pancreatitis after anesthesia with propofol in a child with glycogen storage disease type IA. Paediatr Anaesth 2006; 16: 680-683. https://doi.org/10.1111/j.1460-9592.2005.01833.x

35. Farrington FH, Duncan LL, Roth KS. Looking a gift horse in the mouth: effects of cornstarch therapy and other implications of glycogen storage disease on oral hygiene and dentition. Pediatr Dent 1995; 17: 311-314.

36. Assiri YM, Iqbal MM, Almanie RA. Glycogen storage disease in pediatric population. Egyptian Journal of Hospital Medicine 2018; 70: 2067-2071. https://doi.org/10.12816/0045030

37. Williams HE, Kendig EM, Field JB. Leukocyte debranching enzyme in glycogen storage disease. J Clin Invest 1963; 42: 656-660. https://doi.org/10.1172/JCI104756

38. Kim SY, Chen L-Y, Yiu WH, Weinstein DA, Chou JY. Neutrophilia and elevated serum cytokines are implicated in glycogen storage disease type Ia. FEBS Lett 2007; 581: 3833-3838. https://doi.org/10.1016/j.febslet.2007.07.013

39. Weston BW, Lin JL, Muenzer J, et al. Glucose-6-phosphatase mutation G188R confers an atypical glycogen storage disease type 1b phenotype. Pediatr Res 2000; 48: 329-334. https://doi.org/10.1203/00006450-200009000-00011

40. Cameron BH, Blair GK, Murphy JJ 3rd, Fraser GC. Morbidity in neurologically impaired children after percutaneous endoscopic versus Stamm gastrostomy. Gastrointest Endosc 1995; 42: 41-44. https://doi.org/10.1016/s0016-5107(95)70241-5

41. Grunow JE, al-Hafidh A, Tunell WP. Gastroesophageal reflux following percutaneous endoscopic gastrostomy in children. J Pediatr Surg 1989; 24: 42-45. https://doi.org/10.1016/s0022-3468(89)80298-2

42. Berezin S, Schwarz SM, Halata MS, Newman LJ. Gastroesophageal reflux secondary to gastrostomy tube placement. Am J Dis Child 1986; 140: 699-701. https://doi.org/10.1001/archpedi.1986.02140210097034

43. Scott RB, O'Loughlin EV, Gall DG. Gastroesophageal reflux in patients with cystic fibrosis. J Pediatr 1985; 106: 223-227. https://doi.org/10.1016/s0022-3476(85)80291-2

44. Develioglu ON, Yilmaz M, Caglar E, Topak M, Kulekci M. Oto-toxic effect of gastric reflux. J Craniofac Surg 2013; 24: 640-644. https://doi.org/10.1097/SCS.0b013e31827c7dad

45. Heavner SB, Hardy SM, White DR, Prazma J, Pillsbury HC 3rd. Transient inflammation and dysfunction of the eustachian tube secondary to multiple exposures of simulated gastroesophageal refluxant. Ann Otol Rhinol Laryngol 2001; 110: 928-934. https://doi.org/10.1177/000348940111001007

46. White DR, Heavner SB, Hardy SM, Prazma J. Gastroesophageal reflux and eustachian tube dysfunction in an animal model. Laryngoscope 2002; 112: 955-961. https://doi.org/10.1097/00005537-200206000-00004

47. Yüksel F, Doğan M, Karataş D, Yüce S, Şentürk M, Külahli I. Gastroesophageal reflux disease in children with chronic otitis media with effusion. J Craniofac Surg 2013; 24: 380-383. https://doi.org/10.1097/SCS.0b013e31827feb08

48. McCoul ED, Goldstein NA, Koliskor B, Weedon J, Jackson A, Goldsmith AJ. A prospective study of the effect of gastroesophageal reflux disease treatment on children with otitis media. Arch Otolaryngol Head Neck Surg 2011; 137: 35-41. https://doi.org/10.1001/archoto.2010.222

49. Hodgen GD. Antiprogestins: the political chemistry of RU486. Fertil Steril 1991; 56: 394-395. https://doi.org/10.1016/s0015-0282(16)54528-2

50. Develoglu ON, Yalcin E, Bulut E, et al. Histopathologic changes in the middle ear mucosa after exposure to pepsin and unconjugated bile acid. J Craniofac Surg 2014; 25: e536-40. https://doi.org/10.1097/SCS.0000000000001041

51. Tasker A, Dettmar PW, Panetti M, Koufman JA, P Birchall J, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children?. Laryngoscope 2002; 112: 1930-1934. https://doi.org/10.1097/00005537-200211000-00004

52. Crapko M, Kerschner JE, Syring M, Johnston N. Role of extra-esophageal reflux in chronic otitis media with effusion. Laryngoscope 2007; 117: 1419-1423. https://doi.org/10.1097/MLG.0b013e318064f177

53. Iwanicka-Pronicka K, Trubicka J, Szymanska E, et al. Sensorineural hearing loss in GSD type I patients. A newly recognized symptomatic association of potential clinical significance and unclear pathomechanism. Int J Pediatr Otorhinolaryngol 2021; 151: 110970. https://doi.org/10.1016/j.ijporl.2021.110970