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Audiological differences in healthy individuals with generalized joint hypermobility: a case-control study

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ABSTRACT

Objectives: Despite the prevalence of generalized joint hypermobility (GJH), the audiological functions of individuals with GJH have not been documented. This study aimed to investigate audiological findings in individuals with GJH.

Methods: This observational, cross-sectional, controlled study was conducted between May 2017 and August 2017. The mean age of all participants was 20.25 ± 0.75 years (range: 19-22 years). The generalized joint hypermobility consisted of individuals with a Beighton score of ≥ 5, while the controls with a Beighton score of ≤ 4. Pure-tone audiometry, immittance audiometry, and Transient Evoked Otoacoustic Emsission (TEOAE) testing were performed on subjects with generalized joint hypermobility (n = 25, mean age: 20.24 ± 0.72 years) and sex- and age-matched healthy controls ((n = 31, mean age: 20.26 ± 0.77 years).

Results: There were no significant differences in the mean hearing thresholds between the groups, although six (5.4%) ears in the GJH group had thresholds > 15 dB at one (five ears) or more frequencies. Significant differences were detected between the groups in the left ear for TEOAEs at 4 kHz and acoustic reflex thresholds.

Conclusions: Individuals with GJH have some audiological differences that may be a predictor of changes related to future hearing loss. Further studies that involve larger samples and include participants of different ages are needed in order to determine whether individuals with GJH are more prone to hearing loss.

Keywords: Audiometry, joint laxity, generalized joint hypermobility, hearing loss, otoacoustic emissions

Generalized joint hypermobility (GJH) is characterized by an exaggerated ability to move the joints beyond the normal range of motion as a result of increased connective tissue flexibility and/or capsular or ligamentous looseness [1, 2]. GJH is often hereditary and thought to be caused by genetic alterations related to collagen [3]. It may occur without complications as an asymptomatic condition or may be accompanied by musculoskeletal symptoms, such as muscle or joint pain. GJH is commonly encountered in many other disorders [4]. It may exist as a part of genetic disorders that affect connective tissue (e.g., Ehlers-Danlos syndrome (EDS), Marfan syndrome, osteogenesis imperfecta (OI) or other syndromes (e.g., Down syndrome, bony dysplasias, velocardiofacial syndrome) [5].

GJH is defined by a Beighton score ≥ 5/9 [4, 6]. In a healthy university population, the prevalence of GJH was 33.0% for females and 12.3% for males [7]. Individuals with GJH are prone not only to musculoskeletal complaints, but also to manifestations such as cardiovascular dysautonomia, gastrointestinal

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motility issues, psychological distress, and fatigue [8]. However, the susceptibility to damage and the effect on hearing function have not been investigated. Although a few studies have shown sensorineural hearing impairment affecting predominantly high frequencies as an association between collagen tissue disorders featuring hypermobility (e.g. EDS, Stickler syndrome, Down syndrome, and OI) and audiological dysfunction [9-14], the association has not been examined in nonsyndromic, asymptomatic healthy individuals with GJH.

GJH is the best-known clinical manifestation of inherited defects of the connective tissue [15]. It has recently been shown that gene expressions of the asymptomatic healthy individuals with GJH (higher TNXB and SLC39A13 and lower COL1A1, COL1A2, COL5A1, FKBP14, and DSE) differ from those of the healthy controls, suggesting that genetic difference should not be underestimated [16]. As in all parts of the body, connective tissue is found in the ear. Collagen is the main component of connective tissue. Various collagen types have been found in multiple structures of the ear, such as the tympanic membrane, interossicular joints in the middle ear, and the cochlea [17]. Because of the genetic and acquired features that define joint hypermobility, which is related to connective tissue disorders, questions about the relationship between ear involvement and joint hypermobility are not unexpected. The aim of current study was to describe the relationship between GJH and audiological functions compared with age- and sex-matched controls.

METHODS

Participant Selection

Participants aged between 19 and 22 years of age were selected from a total of 131 students in the Audiometry Department from Health Services Vocational College of University. Students were evaluated according to the Beighton score, and those with a score ≥ 5/9 were considered to have GJH [4, 6]. A total of 25 participants with GJH were enrolled in the study. From the same source, 31 age- and sex-matched healthy volunteers with a Beighton score ≤ 4/9 and no risk for hearing deficit were selected. The exclusion criteria for both groups were a history of ototoxic drug use or ear

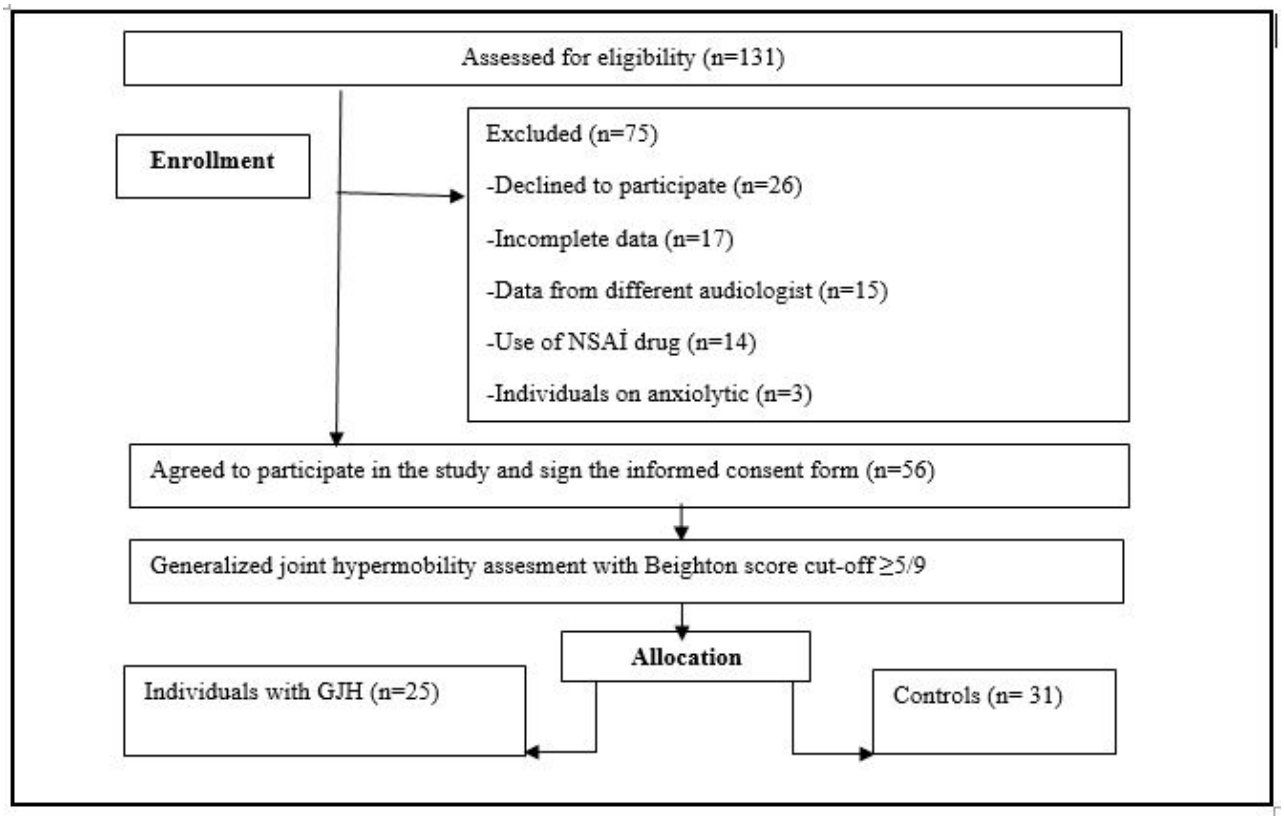

Fig. 1. The flowchart of the study.

surgery, congenital or acquired ear disease, and the presence of a known disease (Fig. 1). This observational and case control study was approved by the Ethics Committee of the University Medical Faculty (TUTF-BAEK-2017/146), and written informed consent was obtained from each student.

Clinical Evaluation

A total of 131 students from Health Services Vocational College of University underwent an initial clinical interview and musculoskeletal evaluation. All participants were evaluated and underwent examination by the second author. The Beighton score was determined by evaluating nine joints and the following items: I- Placement of hands flat on the floor without bending the knees, II- Hyperextension of the elbow to ≥ 10°, III- Hyperextension of the knee to ≥10°, IV- Opposition of the thumb to the volar aspect of the ipsilateral forearm, V- Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90° [2, 6]. During the physical examination, in order to exclude symptomatic GJH or Hypermobile Ehlers-Danlos syndrome, we investigated the presence of features used in the diagnosis of Hypermobile Ehlers-Danlos syndrome according to the 2017 International Classification of Ehlers-Danlos Syndrome [18]. Therefore, only participants with asymptomatic, nonsyndromic/isolated GJH were included in the study.

Evaluation of Hearing

Audiological measurements were performed in sound-isolated test rooms by a certified audiologist. The test procedure included otoscopy, impedance audiometry (tympanometry and acoustic reflexes), pure-tone audiometry, and transient evoked otoacoustic emission (TEOAE) tests.

Behavioral Audiometry

Air-conduction hearing thresholds were evaluated in both ears of the participants at 0.5-, 1-, 2-, 4-, and 8-kHz frequencies using Inter-acoustic Clinical Audiometer (AC-40, Denmark) and TDH-39 (Telephonics, USA) earphones. Bone conduction thresholds were measured if the air conduction thresholds were greater than 15 dB, using Radioear B-71 (Radioear, USA) bone vibrator.

Immittance Audiometry

Middle-ear function and acoustic reflexes were assessed using an AT235H impedance audiometer device (Interacoustics, Denmark). The tympanometry was performed with a 226 Hz probe tone. The measurement pressure range was set at + 200 daPa to -400 daPa. Type A tympanograms (peak pressure: between +100 daPa and -50 daPa) were accepted as normal. Contralateral acoustic reflex thresholds were measured at 1 kHz.

Otoacoustic Emission (OAE) Measurements

Transient Evoked Otoacoustic Emission (TEOAE) measurements were binaurally performed using the ILO 292 Echoport USB II and ILO V6 Clinical OAE software (Otodynamics, London), with non-linear click stimuli at 80 dB. TEOAEs were considered present if overall reproducibility was ≥ 70% and signal-to-noise ratio (SNR) was > 3 dB in at least three of the measured frequencies.

Statistical Analysis

Statistical evaluations were performed using IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). The normality of the distribution of the data was examined using the Kolmogorov-Smirnov (K-S) test. The TEOAE measurement results, which satisfy the conditions of normal distribution and variance equality, were compared using an independent samples t-test. Because data sets related to subjective audiometry and tympanometry measurements were not normally distributed and because no equality of variance was provided in the measurement of the acoustic reflex threshold (Levene test, $p < 0.05$), the Mann–Whitney U test was used in the comparisons of these measurements (K–S test, $p < 0.05$). In all comparisons between the groups, the data obtained from the left and right ears were compared separately. A p - value of < 0.05 was considered statistically significant.

RESULTS

The present study enrolled 56 participants: 37 (66.1%) females and 19 (33.9%) males. The GJH group consisted of 25 participants (17 females and 8 males), and the healthy control group consisted of 31 participants (20 females and 11 males). None of the participants met the criteria for Hypermobile Ehlers-Danlos syn-

drome. The mean age of all the participants was 20.25 ± 0.75 (range: 19-22) years; 20.24 ± 0.72 years; the mean age of the GJH group and control group were 20.24 ± 0.72 years and 20.26 ± 0.77 years, respectively. There was no difference between groups with respect to sex or age ($=\chi^2 0.36$, $p = 0.85$ and t-test, $p = 0.93$, respectively). The results of Beighton score evaluation are shown in Table 1. The median Beighton score of participants with GJH was 6 (min: 5, max: 8), and that of the controls was 2 (min: 0, max: 3). The mean body mass indexes of the GJH and control groups were 21.12 ± 2.28 and 21.84 ± 2.17 kg/m^2, respectively (t = 1.20, $p = 0.24$).

As table 2 shows, there were no significant differences in the mean hearing thresholds between the groups ($p > 0.05$). Six (5.4%) ears in the GJH group had thresholds above 15 dB at one or more frequencies (one at 0.5 kHz, four at 8 kHz, and one at all frequencies), whereas all subjects in the control group had hearing thresholds below 15 dB at all frequencies tested. One subject in the GJH group had a 55 dB threshold in the left ear at 8 kHz, despite normal values (≤ 15 dB HL) at the remaining frequencies. According to the pure tone average (PTA) across 0.5, 1, 2, and 4 kHz, another subject in the GJH group had unilateral minimal hearing loss (PTA for the left ear = 23 dB). None of the ears with elevated thresholds had air–bone gaps greater than 10 dB HL.

The mean reproducibility scores of the TEOAE measurements was as follows: right ear = 97.20 ± 2.93, left ear = 96.48 ± 5.35 in the GJH group, and right ear = 97.94 ± 1.31, left ear = 97.35 in the control

Table 1. Results of Beighton score evaluation

Beighton score items	GJH n (%)	Control n (%)	Total n (%)	OR (95% CI)	LR	LR *p* value
Placement of hands flat on the floor without bending the knees	7 (28.0)	2 (6.5)	9 (16.1)	0.177 (0.033-0.950)	4.896	**0.027**
Hyperextension of the right elbow to ≥10°	16 (64.0)	13 (41.9)	29 (51.8)	0.406 (0.137-1.202)	2.725	0.099
Hyperextension of the left elbow to ≥10°	14 (56.0)	12 (38.7)	26 (46.4)	0.496 (0.170-1.447)	1.669	0.196
Hyperextension of the right knee to ≥ 10°	11 (44.0)	6 (19.4)	17 (30.4)	0.305 (0.093-1.005)	3.994	**0.046**
Hyperextension of the left knee to ≥ 10°	9 (36.0)	6 (19.4)	15 (26.8)	0.427 (0.127-1.429)	1.952	0.162
Opposition of the right thumb to the volar aspect of the ipsilateral forearm	23 (92.0)	3 (9.7)	26 (46.4)	0.009 (0.001-0.061)	43.696	**< 0.001**
Opposition of the left thumb to the volar aspect of the ipsilateral forearm	21 (84.0)	2 (6.5)	23 (41.1)	0.013 (0.002-0.079)	39.022	**< 0.001**
Passive dorsiflexion of the right fifth metacarpophalangeal joint to ≥ 90°	17 (68.0)	5 (16.1)	22 (39.3)	0.090 (0.025-0.323)	16.306	**< 0.001**
Passive dorsiflexion of the left fifth metacarpophalangeal joint to ≥ 90°	21 (84.0)	9 (29.0)	30 (53.6)	0.078 (0.021-0.292)	18.012	**< 0.001**
Total	25 (100.0)	31 (100.0)	26 (100.0)			

GJH = generalized joint hypermobility

Table 2. **Results of pure-tone audiometry**

	Frequency (kHz)	Mean ± SD		Mean Ranks		*p* value
		GJH	Control	GJH	Control	
Left ear	0.5	7.00 ± 4.56	6.00 ± 2,38	29.00	28.10	0.79
	1	5.80 ± 3.12	5.19 ± 1.58	28.78	28.27	0.83
	2	6.00 ± 4.08	5.35 ± 1.80	28.30	28.66	0.89
	4	6.20 ± 4.15	5.19 ± 1.58	29.40	27.77	0.52
	8	7.20 ± 12.51	2.58 ± 4.44	31.96	25.71	0.11
Right ear	0.5	6.20 ± 3.61	5.48 ± 2.99	29.36	27.81	0.66
	1	5.40 ± 1.38	5.48 ± 2.37	28.16	28.77	0.83
	2	5.60 ± 2,20	5.16 ± 2.73	29.64	27.58	0.44
	4	5.00± 1.44	5.00 ± 1.83	28.50	28.50	1.00
	8	4.20 ± 5.89	3.06 ± 4.02	29.64	27.58	0.60

GJH = generalized joint hypermobility, SD = standard deviation

group ($p > 0.05$). The mean SNR values of TEOAEs by frequency are shown in Table 3 (after excluding one subject with a type B tympanogram). TEOAE amplitudes of the left ear at 4 kHz were significantly lower in the GJH group compared to the control group (t = 2.56, $p = 0.01$). In the immitancemetric measurements, no statistically significant difference was found between the groups with respect to the mean values of static compliance, which indicates the highest peak of the curve of the tympanogram. The mean values of static compliance in the GJH and control group, respectively, were as follows: for the left ear, M = 0.89 ± 0.61 and M = 0.71 ± 0.43; for the right ear, M = 0.89 ± 0.75 and M = 0.79 ± 0.43 ($p > 0.05$). All participants had bilateral type A tympanograms, with the exception of one subject in the GJH group, who had a type B curve (flat curve without peak) in the left ear. Acoustic reflex could not be obtained from the left ear of one

Table 3. **Mean signal to noise (SNR) values of TEOAEs by frequency and by ears in the groups**

Frequency (Hz)	Ear	GJH L ear (n =24) R ear (n = 25 (Mean ± SD)	Control (n = 31) (Mean ± SD)	T	*p value*
1000	Right	21.12 ± 6.63	21.25 ± 5.32	0.76	0.94
	Left	17.36 ± 8.61	17.96 ± 6.15	0.13	0.78
1400	Right	22.42 ± 6.25	23.49 ± 5.46	0.68	0.50
	Left	18.61 ± 8.37	21.05 ± 4.97	1.09	0.18
2000	Right	19.87 ± 4.88	20.76 ± 5.99	0.60	0.55
	Left	19.00 ± 5,95	18.19 ± 4.81	0.61	0.58
2800	Right	18.34 ± 5.41	20.19 ± 5.40	1.27	0.21
	Left	17.16 ± 5,41	19.79 ± 4.79	1.96	0.06
4000	Right	14.36 ± 5.17	17.02 ± 6.72	1.63	0.11
	Left	13.61 ± 6.60	17. 97 ± 6.01	2.56	**0.01***

GJH = generalized joint hypermobility, SD = standard deviation, L = left, R = right

Table 4. Acoustic reflex thresholds (dB) in the left and right ear for both groups

	Mean ± SD		Mean Ranks		*p value*
	GJH L ear (n =24) R ear (n = 25	Control (n = 31)	GJH	Control	
Left ear	96.46 ± 6.51	99.35 ± 3.59	24.08	32.03	0.018*
Right ear	95.40 ± 8.40	98.87 ± 5.43	25.78	30.69	0.12

GJH = generalized joint hypermobility, SD = standard deviation, L = left, R = right

subject with GJH. Therefore, when comparing the acoustic reflex thresholds (ARTs) for the left ear, the GJH group was taken as N = 24. As Table 4 shows, the ARTs for the left ears in the GJH group were significantly lower than in the control group ($p = 0.018$).

DISCUSSION

In this study, the mean hearing thresholds were statistically similar in the GJH and control groups. All subjects had normal hearing, with the exception of two subjects in the GJH group (one with slight unilateral hearing loss and the other with an elevated threshold of 55 dB at 8 kHz). However, significant differences were detected between the groups in the left ear for TEOAEs at 4 kHz and acoustic reflex thresholds.

Despite the lack of data about audiological features of individuals with nonsyndromic GJH, hearing loss is seen in patients who have genetic syndromes with joint hypermobility, including OI, EDS, and Stickler syndrome [13, 14, 19, 20]. Hearing loss in these disorders is thought to be related to structural changes in the middle and inner ear. However, the tympanometry results revealed that the middle ear system in the great majority of our study participants was normal. Only one subject in the GJH group had a type B curve, indicating little or no movement in the tympanic membrane. Although deep type A tympanograms were obtained from five subjects in the GJH group and from four subjects in the control group, there was no difference in the average compliance between groups. Static compliance represents the mobility of the middle ear, and a peak exceeding the upper compliance limit (> 1.6 cc) indicates an excessively flaccid middle ear system. This is a common finding in patients with Stickler syndrome [9, 19, 21]. Acke *et al*. [9] argued that the hypermobile middle ear system of Stickler patients may result from previous otitis media but that the collagen defect may also contribute. In the absence of hearing loss, as in this study's subjects, a deep type A tympanogram can be considered a result of minor tympanic membrane abnormalities, such as scar tissue and thin or single layer eardrum. The findings also showed that acoustic reflex thresholds (ARTs) were lower in the GJH group. Although acoustic reflex occurs at a lower sensation level in patients with cochlear pathology, it is broadly accepted that it varies from 70–80 to 100 dB HL in patients with normal hearing [22].

When comparing groups in terms of TEOAE measurement, SNR amplitudes in the left ear at 4 kHz were found to be lower in the GJH group than in the control group. In addition, pure-tone thresholds above 15 dB were observed only in the GJH group. These findings raise the question of whether individuals with GJH have an increased susceptibility to hearing loss. It is known that otoacoustic emissions are highly sensitive to cochlear pathology, and minimal amounts of cochlear damage that cannot be detected by behavioral pure-tone audiometry may cause measurable changes in OAE responses [23]. OAE testing permits early detection of cochlear dysfunction of genetic origin, as carriers of gene mutations who have normal behavioral hearing sensitivity may display subtle auditory abnormalities that can be observed in OAEs [24, 25]. Sensorineural hearing loss affecting mainly high frequencies has been detected in some patients with OI, EDS, and Stickler syndrome [13, 14, 18]. In a study of 141 children with EDS, Weir *et al*. [14] found that

the majority of patients had slight and mild hearing loss and that the type of hearing loss was equally divided between pure conductive and pure sensorineural deficits. Acke *et al*. [19] detected mild and predominantly high frequency (3-8 kHz) sensorineural hearing loss in Stickler patients. The same study, taking into account the normal pure-tone thresholds for several frequencies in most patients, found that OAEs were absent or had very low amplitudes, even in frequency bands with normal hearing. The pathogenesis of sensorineural hearing impairment associated with the above-mentioned disorders is not fully understood, but possible causes include hair cell loss, abnormalities of the tectorial membrane, and disruption of the stria vascularis [9, 13, 14, 21]. The functional integrity of outer hair cells is essential for the generation of OAEs. In addition, stria vascularis and spiral ligament, which are critical structures for the function of the cochlea, are thought to play an important role in the mechanisms of OAEs [26]. In this study, reduced TEOAE amplitudes at 4 kHz may be related to possible changes in these structures.

Limitations

This study has several limitations. First, the research conducted with a small sample characterized by a narrow age range. Second, there are no comparable studies, because previous research has focused only on syndromes associated with hypermobility. In addition, considering that acoustic reflex thresholds were found to be lower in the GJH group, it would have been useful to compare acoustic reflexes of the groups for all frequencies. Third, we didn't use the Auditory Brainstem Response (ABR) test. However, as we mentioned, some studies have detected a hearing loss in some patients with genetic syndromes with joint hypermobility. It is thought to be related to structural changes in the middle and inner ear. In the light of these studies indicating middle and inner ear pathologies, we aimed to investigate whether GJH patients have hearing loss and any audiological differences that could be specifically related to the middle and inner ear. For this reason, we thought that pure-tone audiometry, immittance audiometry, and OAE test could be enough to examine middle and inner ear function. Since OAE measures are sensitive indicators of cochlear function and thought to be an additional cross-check measure, we included the OAE test. In addition, the ABR test can provide additional information about the status of the auditory pathway, including the neural pathway. To our knowledge, this is the first report of audiological features of individuals with non-syndromic GJH. We believe that future studies could explore this issue further by investigating ABR differences in this population.

CONCLUSION

In conclusion, the findings of the current study showed that individuals with GJH have some audiological differences that may be a predictor of changes related to future hearing loss. Further studies that involve larger samples and include participants of different ages are needed in order to confirm the result and determine whether individuals with GJH are more prone to hearing loss.

Authors' Contribution

Study Conception: FT, MT; Study Design: FT, MT, ŞY; Supervision: FT, MT, ŞY; Funding: FT, MT, ŞY; Materials: FT, MT, ŞY; Data Collection and/or Processing: FT, MT, ŞY; Statistical Analysis and/or Data Interpretation: FT, MT, ŞY; Literature Review: FT, MT, ŞY; Manuscript Preparation: FT, MT, ŞY and Critical Review: FT, MT, ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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