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Original Article

Middle Ear Transfer Function in Acromegaly Patients

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BACKGROUND: Acromegaly is a rare disorder in which growth hormone is secreted uncontrollably by the pituitary gland. Considering the risk of pathological effects of acromegaly on middle ear (ME) transfer function and hearing, we aimed to investigate the ME transfer functions of acromegaly patients who underwent transsphenoidal surgery using wide-band tympanometry (WBT) in this study.

METHODS: Pure tone audiometry (PTA), 226 Hz probe-tone acoustic immitancemetry, and WBT were performed on all participants. Twenty-eight patients with acromegaly and 29 healthy subjects were included in the current study.

RESULTS: The mean age of the acromegaly group (11 males, 17 females) was 49.25 ± 9.57 years, and that of the healthy controls (13 males, 16 females) was 45 ± 10.02 years. The PTA means of the acromegaly and healthy groups were between normal limits, but the mean of the acromegaly group (20.73 ± 10.95) was significantly worse than that of the healthy group (12.02 ± 6.67, $P = .000$). The WBT non-pressurized and pressurized absorbance values of the acromegaly and healthy groups did not show statistically significant differences. The equivalent ear canal volumes at 1000 Hz ($P = .041$) and the equivalent ear canal volume measured by averaging the WBT ($P = .023$) of the acromegaly group were larger than those of the healthy controls.

CONCLUSION: The investigation revealed that the equivalent ear canal volumes were statistically significantly higher in patients with acromegaly. However, this did not impact the ME transfer function.

KEYWORDS: Acromegaly, absorbance, hearing loss, wide-band tympanometry

INTRODUCTION

Acromegaly is a rare disorder in which growth hormone (GH) is secreted uncontrollably by the pituitary gland.[1] The main cause of acromegaly is excessive GH secretion due to pituitary adenoma.[2] Although the mortality rate is high, it can be reduced to normal levels if biochemical controls are adequate and the necessary interventions are performed in time. Females and males are equally affected. Patients are usually diagnosed between 30 and 50 years of age. The annual incidence is 3-6 per million.[3] It is known that the systemic findings in patients diagnosed with acromegaly are extensive and include large hands and feet, prominent frontal bones, sleep apnea, heart failure, cardiovascular problems, osteoarthritis, abnormal thyroid hormone changes, and glucose intolerance. Given that patients with acromegaly are typically diagnosed between 5 and 14 years after the onset of symptoms, it may take some time for the full range of associated symptoms to manifest. Patients with acromegaly have high levels of GH, insulin-like growth factor-1 (IGF-1), IGF-1 binding protein-3, and calcitriol. These factors affect connective tissue and bone cells.[1] Although it has been suggested that soft tissue enlargement and bone hypertrophy in acromegaly may cause ear problems, such an association has not been confirmed.[4] Surgery is the primary treatment for acromegaly. In cases where IGF-1 normalization is not achieved after surgical treatment, somatostatin receptor ligands are usually added to the treatment. This study evaluated acromegaly patients who underwent endoscopic transnasal transsphenoidal surgery.

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Wide-band tympanometry (WBT) allows the clinician to measure outer/middle ear (ME) transfer function and evaluate ME acoustic mechanics using wideband stimuli. This method is fast, simple, and non-invasive. The immittance measurements over a wide frequency range (226-8000 Hz) are based on the energy reflected and absorbed by the ME.[5] A click stimulus is used over a wide frequency range.[6] The WBT provides much more information about the ME and allows for a better assessment of ME pathology.[7] One of the parameters of tympanometry is resonance frequency (RF). Resonance frequency is the frequency at which the outer and ME systems operate most effectively and is the point at which the elements of mass and stiffness have the least effect on impedance. At this frequency, the system is only under the influence of friction.[7] In this study, considering the risk of pathological effects of acromegaly on ME transfer function and hearing, we aimed to investigate the ME transfer functions of acromegaly patients who underwent transsphenoidal surgery using WBT.

METHODS

Twenty-eight patients with acromegaly and 29 healthy volunteers were enrolled in this study. Ethical approval was obtained from Istanbul Medeniyet University, Süleyman Yalçın City Hospital Ethics Committee (Date: October 06, 2021, decision number: 2021/0408). Written informed consent was obtained from all participants. Acromegaly patients were diagnosed according to their blood IGF-1 levels by the Department of Endocrinology and Metabolism, Göztepe Prof. Dr. Süleyman Yalçın City Hospital. Prior to the audiological tests, all participants underwent an ear examination by an otolaryngologist using a microscope. All of the patients with acromegaly included in our study were in remission in the postoperative period, or somatostatin analog therapy was added in the postoperative period. Insulin-like growth factor-1 values of all patients were under control. Participants with any outer ear or ME pathology (any external auditory canal anomaly, any acute, chronic, or recurrent disease of the outer ear and ME) were excluded. After the otomicroscopic examination, 226 Hz probe-tone acoustic immittance was performed using the Interacoustics AT235h clinical tympanometer (Interacoustics, Assens, Denmark), and the participants with type A tympanograms were included. Pure-tone air conduction (AC) (between 250 and 8000 Hz) and bone conduction (BC) (between 500 and 4000 Hz) thresholds were obtained as dBHL (decibel hearing level) using the Interacoustics AC 40 two-channel clinical audiometer (Interacoustics, Assens, Denmark). The TDH-39 supra-aural headphone (Telephonics, Farmingdale, NY, USA) was used for AC thresholds. The Radio-ear B-71 bone vibrator was used for BC thresholds. Pure tone average (PTA) thresholds were calculated by taking the arithmetic mean of AC thresholds at 500, 1000, 2000, and 4000 Hz. Descriptions of normal hearing were made according to PTA values equal to or better than 25 dBHL.[8] The WBT (Interacoustics Titan Suite, Assens, Denmark) was used to evaluate the ME transfer functions of the participants. The click stimuli with a frequency range between 226 and 8000 Hz were introduced into the ear canal with a descending pressure sweep from 200 to −300 daPa pressure. The wideband absorbance values were measured at ambient pressure (unpressurized) and at peak pressure as components of wideband absorbance tympanogram (pressurized).

MAIN POINTS

- In view of the potential adverse effects of acromegaly on middle ear (ME) transfer function and hearing, the present study was designed to investigate the ME transfer functions of acromegaly patients.
- The unpressurized and pressurized absorbance values obtained from the wide-band tympanometry of the acromegaly and healthy groups did not demonstrate statistically significant differences.
- It was observed that the equivalent ear canal volumes at 1000 Hz and the average equivalent ear canal volume of the acromegaly group were larger in comparison with those of the healthy control group.
- However, this did not result in any impact on the ME transfer function.
- The effects of acromegaly on soft tissue can be considered to be more pronounced than its effects on bone tissue.

Absorbance values were obtained at 107 frequency points between 226 and 8000 Hz, and the values of 15 frequency points (250, 315, 400, 500, 630, 800, 1000, 1250, 1600, 2000, 2500, 3150, 4000, 5000, and 6000 Hz) were analyzed.[9] In addition, the values of equivalent ear canal volume (at 226 Hz, 1000 Hz, and averaged WBT), static admittance (at 226 Hz and 1000 Hz), tympanometric peak pressure (at 226 Hz, 1000 Hz, and averaged WBT), gradient (at 226 Hz, and 1000 Hz), and resonance frequencies of the right and left ears were recorded sequentially and separately. Participants were instructed not to swallow, speak, or yawn during acoustic immittance and WBT measurements.

Statistical Analysis

Normality of data distribution was analyzed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Nonparametric statistical methods were used according to the results of these analyses. The power analysis of the study was calculated using G*Power 3.1.9.4 (Program written by Franz Faul, Universitat Kiel, Kiel, Germany).[10] It was determined that the study had an effect size of 0.7, an α error value of 0.05, a critical t value of 1.68, and a power of 82% with 52.43 degrees of freedom. Descriptive analyses included means and standard deviations for continuous data and frequencies for categorical data. The WBT and hearing test scores of the right and left ears in the acromegaly and healthy groups were compared separately using the Wilcoxon signed-rank test. Because neither the acromegaly nor the healthy group showed a statistical difference between the right and left ear results ($P > .05$), the Mann–Whitney U test was used for the continuous data comparisons between groups as the number of ears. For categorical data, the comparisons of the number of participants was considered. Within groups, the significance of the differences between the results of WBT according to gender was analyzed using the Mann–Whitney U test. Spearman's correlation coefficients were also calculated to analyze the relationships between the WBT parameters and the mean hearing thresholds and age of the participants in each group separately. The frequencies of hearing loss (HL) were compared between groups using the chi-square test. SPSS 21.0 (SPSS Inc.; IBM, New York, USA) was used for statistical analyses, and a P-value less than .05 was considered significant for all tests.

RESULTS

The mean age of the acromegaly group (11 males, 17 females) was 49.25 ± 9.57 years and that of the healthy controls (13 males, 16 females) was 45 ± 10.02 years. These values were statistically similar ($P = .115$). All patients with acromegaly underwent transsphenoidal surgery. Postoperative follow-up was 8.92 ± 6.24 years. Twenty acromegaly patients continued to receive somatostatin receptor ligand therapy after surgery. The IGF-1 levels of all acromegaly patients were within the age- and sex-adjusted reference range. The mean PTA values of the acromegaly and healthy groups were between normal limits, but the mean value of the acromegaly group (20.73 ± 10.95) was significantly worse than that of the healthy group (12.02 ± 6.67, *P* = .000) (Table 1). In the acromegaly group, there were 5 patients with bilateral mild sensorineural HL (min: 35-max: 53 years old, mean: 45.4 ± 6.87, 4 females, 1 male), 1 patient with bilateral moderate sensorineural HL (36 years old, male), and 1 patient with unilateral moderate sensorineural HL (48 years old, female). In the healthy group, all subjects had normal hearing. In the acromegaly group, the HL was sensorineural and we did not obtain air-bone gaps. The frequency of HL in the acromegaly group was significantly higher than in the healthy group (*P* = .01) (Table 1). Neither the acromegaly group (*r* = 0.081, *P* = .555) nor the healthy group (*r* = −0.168, *P* = .207) showed a significant relationship between age and PTA values.

The WBT unpressurized and pressurized absorbance values of the acromegaly and healthy groups did not show statistically significant differences (Table 2). The WBT parameters that showed a significant difference between the 2 groups were the equivalent ear canal volume at 1000 Hz (*P* = .041) and the equivalent ear canal volume measured by the averaged WBT (*P* = .023) (Table 3).

Differences in WBT results between males and females were also calculated separately in 2 groups. In the acromegaly group, ear canal volume values were higher in males. However, in the healthy control group, WBT absorbance values were higher in males (Table 4). On the other hand, there were positive weak correlations between 5000 Hz unpressurized and 5000 Hz pressurized absorbance values and age in the healthy group.

DISCUSSION

Acromegaly includes several otolaryngologic manifestations such as obstructive sleep apnea, thyroid and parathyroid hyperplasia, sinonasal symptoms consistent with neoplasia, hearing problems, and voice disorders.[11] In this study, we aimed to contribute to the literature by evaluating ME transfer function using WBT and assessing hearing status in patients diagnosed with acromegaly. There are few articles in the literature discussing the possible relationship between HL and acromegaly due to the systemic effects on soft and bone tissue changes and sensory function.[12] In addition, hypersecretion of GH and IGF-1 can lead to hypertrophy of soft and bone tissues, including the head and face.[13] Although some studies mention conductive HL due to structural changes in the ME bones, sensorineural HL is also reported in this group.[14]

Equivalent ear canal volume (VEA) is an important parameter that provides an idea of the external ear canal volume (EECV). In our study, VEA at 1000 Hz and averaged WBT were significantly higher in the acromegaly group. However, this difference was not found in the measurement at 226 Hz probe tone frequency. Shahnaz and Bork[15] reported that the EECV and ME volume may be larger in individuals with larger body sizes (e.g., Caucasians vs. Chinese). Due to the increase in volume, they found that the stiffness and resonant frequency in the ME in their study were lower than in the small ear volume group (hence higher absorbance at low frequencies). We did not find this in our study. This is probably because we did not measure the size of the head and facial structures of the acromegaly patients and healthy controls in our study, and we may not have been able to detect the existing difference.

In our study, 1000 Hz VEA was higher in males than in females in the acromegaly group, but no such difference was found in the control group. Shahnaz and Davies[16] reported that gender is an important factor in VEA, with males having significantly higher values than females. It can be assumed that acromegaly may have caused the overall growth of the temporal bone. On the other hand, statistical significance was observed between the acromegaly and control groups only for VEA at 1000 Hz. It is necessary to compare the results of VEA at 1000 Hz measured in different ME pathologies to determine whether this statistically significant difference is at a level that will affect clinical diagnosis. Roup et al[17] reported that age did not affect VEA in the 20-30 years group. However, Wiley et al[18] performed a study in healthy subjects aged 48-96 years and reported that VEA increased with age. In our study, the mean age of the acromegaly group was 49.25 ± 9.57 years and that of the control group was 45 ± 10.02 years, and there was no relationship between age and VEA in any group. This finding was thought to be related to the fact that the participants in our study were younger than those in Wiley. A weak positive correlation with age was found only for the 5000 Hz absorbance value in the control group.

In this study, the pressurized and unpressurized absorbances were also recorded. Absorbance is the amount of sound energy absorbed by the ME. Absorbance varies between 0 and 1. A value

Table 1. Demographics and Hearing Test Results and the Significance of the Difference Between Groups

Age (Gender)	Acromegaly Group n = 28 Participants	Healthy Group n = 29 Participants	*P*
	49.25 ± 9.57 (11 male/17 female)	45 ± 10.02 (13 male/16 female)	*.115
500-4000 Hz air-conduction hearing thresholds average (dBHL)	20.73 ± 10.95	12.02 ± 6.67	***.000**
Degrees of hearing loss (ears)			
Normal hearing	21	29	****.01**
Mild-degree hearing loss	5	–	
Moderate degree hearing loss	2	–	

*Mann–Whitney *U* test.
**Chi-square test.

Table 2. Non-Pressurized and Pressurized Absorbance Results of Wide-Band Tympanometry and the Significance of the Difference Between Groups

Wide-Band Tympanometry Parameters						
Frequency	Non-Pressurized Absorbance Results			Pressurized Absorbance Results		
	Acromegaly Group n = 56 (Ears)	Healthy Group n = 58 (Ears)	*P	Acromegaly Group n = 56 (Ears)	Healthy Group n = 58 (Ears)	*P
250 Hz	0.138 ± 0.07	0.119 ± 0.06	.305	0.149 ± 0.74	0.132 ± 0.54	.715
315 Hz	0.15 ± 0.09	0.128 ± 0.07	.392	0.164 ± 0.93	0.147 ± 0.06	.956
400 Hz	0.179 ± 0.11	0.149 ± 0.08	.376	0.197 ± 0.12	0.178 ± 0.08	.832
500 Hz	0.239 ± 0.14	0.213 ± 0.11	.648	0.262 ± 0.14	0.252 ± 0.11	.603
630 Hz	0.319 ± 0.17	0.3 ± 0.14	.954	0.352 ± 0.17	0.356 ± 0.14	.352
800 Hz	0.487 ± 0.19	0.465 ±0.17	.775	0.522 ± 0.19	0.53 ± 0.16	.382
1000 Hz	0.594 ± 0.18	0.541 ± 0.16	.235	0.626 ± 0.17	0.602 ± 0.15	.898
1250 Hz	0.67 ± 0.12	0.62 ± 0.13	.145	0.686 ± 0.11	0.647 ± 0.11	.227
1600 Hz	0.632 ± 0.11	0.603 ± 0.11	.659	0.631 ± 0.11	0.606 ± 0.11	.64
2000 Hz	0.6 ± 0.13	0.602 ± 0.14	.301	0.591 ± 0.12	0.587 ± 0.13	.578
2500 Hz	0.62 ± 0.15	0.635 ± 0.17	.266	0.613 ± 0.11	0.613 ± 0.18	.459
3150 Hz	0.638 ± 0.18	0.646 ± 0.18	.624	0.63 ± 0.18	0.622 ± 0.18	.91
4000 Hz	0.618 ± 0.17	0.61 ± 0.16	.765	0.614 ± 0.17	0.59 ± 0.16	.349
5000 Hz	0.436 ± 0.17	0.408 ± 0.16	.202	0.435 ± 0.16	0.399 ± 0.16	.158
6000 Hz	0.393 ± 0.16	0.392 ± 0.16	.939	0.392 ± 0.16	0.39 ± 0.16	.956

* Mann–Whitney *U* test.

closer to 0 indicates lower ME absorption and higher impedance, and a value closer to 1 indicates the opposite. It has been reported that in normal adults, the absorbance value reaches its highest value between 1000 and 4000 Hz.[19] In our study, the absorbance results of the acromegaly group and the control group were similar, and in both groups, the values between 1000 and 4000 Hz were higher than other frequencies. This finding shows that there is no compound impedance of the ME system and the impedance of the ear canal wall in the acromegaly group, which would negatively affect the absorbance function. We can associate this finding with the result that the mass effect is not dominant in the ME of acromegaly patients.

In our study, absorbance values that differed between genders were determined in both groups. Pressurized and non-pressurized absorbance values between 2000 and 6000 Hz showed some differences between genders in both groups. Absorbance values at 5000 and 6000 Hz were higher in females in the acromegaly group, a finding described in the literature in normal hearing subjects.[20] In the healthy group, absorbance was higher in males between 2000 and 3150 Hz. This finding has been related in the literature to the fact that the tympanic membrane is less stiff in adult males with normal hearing, resulting in less resistance to stimuli between 2 and 4 kHz. No significant gender difference was found in the literature for TPP 226 Hz,[20] but we found that ME pressure was closer to atmospheric pressure in females than in males.

Resonance frequency (RF) is the frequency at which the outer and ME systems work most effectively.[7] In other words, mass and stiffness

Table 3. Wide-Band Tympanometry Results and the Significance of the Difference Between Groups

Wide-Band Tympanometry Parameters	Acromegaly Group n = 56 (Ears)	Healthy Group n = 58 (Ears)	*P
Equivalent ear canal volume at 226 Hz	1.08 ± 0.24	1.01 ± 0.236	.1073
Equivalent ear canal volume at 1000 Hz	1.14 ± 0.24	1.05 ± 0.18	**.041**
Equivalent ear canal volume as measured by averaged wide-band tympanometry	1.15 ± 0.23	1.05 ± 0.18	**.023**
Static admittance at 226 Hz	0.865 ± 0.515	0.763 ± 0.35	.47
Static admittance at 1000 Hz	1.91 ± 1.13	1.94 ± 1.09	.796
Tympanometric peak pressure at 226 Hz	−6.12 ± 17.25	−14.46 ± 22.93	.089
Tympanometric peak pressure at 1000 Hz	21.78 ± 31.99	14.26 ± 27.16	.117
Tympanometric peak pressure as measured by averaged wide-band tympanometry	−4.07 ± 18.55	−12.31 ± 25.32	.214
Gradient at 226 Hz	76.25 ± 32.76	79.45 ± 29.49	.571
Gradient at 1000 Hz	84.16 ± 37.84	74.45 ± 22.82	.223
Resonance frequency	947.8 ± 298.88	838.81 ± 215.94	.067

* Mann–Whitney *U* test.

Table 4. The Significance of Differences Between the Findings of Wide-Band Tympanometry According to Genders

Wide-Band Tympanometry Parameters	Acromegaly Group n = 28 (Participants)		Healthy Group n = 29 (Participants)	
	***P**	**Genders**	***P**	**Genders**
Non-pressurized absorbance 2000 Hz right ear	.014	M > F	.035	M > F
Non-pressurized absorbance 2500 Hz right ear	–	–	.023	M > F
Non-pressurized absorbance 3150 Hz right ear	–	–	.005	M > F
Non-pressurized absorbance 5000 Hz right ear	.025	F > M	–	–
Non-pressurized absorbance 6000 Hz right ear	.025	F > M	–	–
Pressurized absorbance 2000 Hz right ear	–	–	.044	M > F
Pressurized absorbance 2500 Hz right ear	–	–	.032	M > F
Pressurized absorbance 3150 Hz right ear	–	–	.004	M > F
Pressurized absorbance 5000 Hz right ear	.029	F > M	–	–
Pressurized absorbance 6000 Hz right ear	.025	F > M		
Tympanometric peak pressure at 226 Hz right ear	.032	F > M	–	–
Equivalent ear canal volume at 1000 Hz right ear	.009	M > F	–	–
Equivalent ear canal volume at 1000 Hz left ear	.024	M > F	–	–

F, female; M, male.
*Mann–Whitney *U* test.

contribute equally to the admittance of the ME.[15] The ME transmits sounds at RF with minimal energy expenditure and more easily than sounds at other frequencies.[21] The RF of the ME system may be higher or lower than that of the normal ear in various pathologies. For example, the RF value is low in otitis media with effusion, while in otosclerosis, the resonant frequency increases above 800-1200 Hz as the stiffness of the ME system increases.[7,22] In the current study, when the 2 groups were compared, the RF value was higher in the acromegaly group than in the control group, but this difference was not statistically significant. With this finding, we cannot prove the dominance of stiffness or mass effect in the ME in patients with acromegaly.

Some previous studies have not found a significant association between acromegaly and otosclerosis.[23-25] Although ME ventilation problems, ossicular anomalies, and ossicular hypertrophy are found in acromegaly patients, the rates of conductive HL in these patients are similar to those in healthy individuals and have been reported to be lower than the rates of sensorineural HL.[14,24,26,27]

Participants with normal findings on otomicroscopy and 226 probe tone acoustic immittancemetry were included in our study. The presence of sensorineural HL was significantly higher in the acromegaly group than in the control group. It has been reported in the literature that cochlear vasculopathy may play a role in the development of sensorineural HL as a result of metabolic complications associated with acromegaly.[14,24,26,27] The findings of our study supported the literature. The effects of acromegaly on soft tissue can be considered to be more pronounced than its effects on bone tissue.

In a recently published study, Kaya Çelik et al[28] included 30 patients with acromegaly in their investigation and examined ME resonance frequencies and hearing levels. They compared the 30 acromegaly patients in remission with a control group of 38 healthy volunteers. In their study, ME RF was evaluated with multifrequency tympanometry, and it was determined that ME resonance increased in patients with acromegaly without conductive HL.

Our study has some limitations. First, only acromegaly cases with normal ME findings were included in our research. If acromegaly patients with abnormal ME findings had also been evaluated in this study, the otological and audiological profiles of these patients would have been revealed more clearly. Second, it would have contributed to the interpretation of the audiological findings if we had performed radiological imaging of the temporal region and taken the history of otological complaints such as tinnitus, fullness, and dizziness. Additionally, obtaining the medical history of the patients may help clarify the metabolic profile of the acromegaly patients. Third, there was a relatively small number of patients included in our study. It is anticipated that more definitive results will be obtained with larger sample sizes in further studies.

CONCLUSION

There are studies in the literature evaluating the relationship between acromegaly and HL, but no study was found that evaluated ME function using the WBT and compared it with healthy controls in this patient group. The rate of sensorineural HL was higher in patients with acromegaly than in the healthy group. On the other hand, there was no significant difference between the groups in the absorbance values measured under pressure and at ambient pressure. The equivalent ear canal volumes at 1000 Hz of the acromegaly group were larger than those of the healthy controls, but this difference was not valid for the RF. Analyses of correlations between audiologic and radiologic characteristics of patients with acromegaly are suggested for future studies.

Availability of Data and Materials: .Data and Materials are available in the hospital archieves.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul Medeniyet University, Göztepe Süleyman Yalçın City Hospital (approval no.: 2021/0408; date: October 6, 2021).

Informed Consent: Verbal informed consent was obtained from the patientst who agreed to take part in the study.

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