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ORIGINAL ARTICLE

Evaluation of hearing loss in patients with Graves' disease

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Abstract Hearing loss has commonly been reported in association with thyroid disorders and during treatment with propylthiouracil. The relationship between hyperthyroidism and the auditory system has not been previously investigated. The aim of this cross-sectional, case–control study was to investigate hearing loss in patients with Graves' disease (GD). The study population consisted of patients with newly diagnosed GD and healthy controls. Pure tone audiometry at frequencies of 250, 500, 1000, 2000, 4000 and 8000 Hz, along with immittance measures including tympanometry and acoustic reflex tests, were performed in all participants. Twenty-two GD patients and 22 healthy controls consented to inclusion in the study. The differences between groups with regards to age and gender distribution were statistically insignificant ($P = 0.567$ and $P = 0.757$, respectively). The hearing thresholds of right and left ears were also similar in both groups ($P > 0.05$). When single-ear evaluations were taken into account (total of 44 ears for both groups), hearing thresholds in the GD group were significantly higher than healthy controls at all frequencies ($P < 0.05$). Following testing at the designated frequencies, the only significant effect of thyrotoxicosis was observed with frequencies of 4000 and 8000 Hz. The odds ratio for having hearing loss at a frequency of 8000 HZ associated with GD was 14.97 (95% confidence interval 4.03–55.64). In patients with GD, right and left pure tone audiometric findings at a frequency of 8000 Hz correlated positively with FT3, FT4 and negatively with TSH. Our results are highly suggestive of a decrease in hearing ability in patients with GD, particularly at high frequencies. Further studies are needed to help elucidate the mechanisms behind hearing loss which develops in association with GD.

Keywords Thyrotoxicosis · Graves' disease · Hearing loss · Pure tone audiometry

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Introduction

Thyroid hormones are essential for the development of hearing [1]. They act through the thyroid hormone receptor-β to initiate myelinogenesis of the cochlea and vestibulocochlear nerve (cranial nerve VIII) [2]. Brucker-Davis et al. [3] have postulated that the critical period of thyroid-sensitive cochlear development in humans occurs between the close of the first trimester of intrauterine life and the first month after birth. On the other hand, hypothyroidism,

caused by exposure to thyroid-disrupting chemicals, has also been implicated as a possible cause of hearing loss with cochlear and/or auditory nerve dysfunction [4–6]. A decrease in the abundance of outer hair cells in the upper middle turn (responsible for detection of lower frequency sounds), as well as the apical turn of the cochlea has also been reported in association with hypothyroidism [7]. In a follow-up study, it was reported that postnatal administration of thyroid hormone resulted in partial reversal of low frequency hearing loss [8].

Hearing loss is commonly associated with thyroid disorders in humans, including congenital hypothyroidism, iodine deficiency, and resistance to thyroid hormone [3, 9–11]. Several cases of drug-related hearing loss have been reported in patients with Graves' disease (GD) on propylthiouracil treatment [12–15]. However, to date, the relationship between hyperthyroidism and the auditory system has not been fully elucidated. The aim of the present study was to compare the hearing ability in patients with Graves' hyperthyroidism and healthy controls using audiometric tests, and to investigate the effects of hyperthyroidism on hearing.

Materials and methods

Study design and patient selection

This study was undertaken as a joint venture by the Otorhinolaryngology Departments of two hospitals (Kecioren Training and Research Hospital and Diskapi Yildirim Beyazit Training and Research Hospital), and the Department of Endocrinology and Metabolic Disorders at Ankara Numune Teaching and Research Hospital, with the approval of the local ethics committee. Patients newly diagnosed with Graves's disease between June 2009 and September 2009 were approached for inclusion in the study. The diagnosis of GD was based on the clinical signs of hyperthyroidism combined with suppressed serum thyroid-stimulating hormone (TSH) and positive thyrotropin receptor antibodies (TRAb). Consenting patients were screened for eligibility, and those fulfilling all criteria were included in the study. The control group consisted of age and gender-matched healthy individuals. Potential participants with a history of a connective tissue disorder, hypertension, a coagulation disorder, atherosclerotic disease, a history of smoking, ongoing infection and inflammation, malignancy, chronic renal failure, diabetes mellitus, impaired fasting glucose, impaired glucose tolerance (fasting glucose $\geq$100 mg/dl and OGTT second hour glucose $\geq$140 mg/dl) and on any medication were excluded. Detailed information was obtained about possible etiological factors leading to hearing loss, such as ototoxic drugs, exposure to noise, ear surgery, perforated tympanic membrane, Ménière's disease, cranial trauma, metabolic diseases, and systemic diseases.

Otologic evaluation

All the participants (GD patients and healthy controls) were subjected to careful otologic examination to identify any abnormalities that may influence the results of audiometric testing. Individuals with any of the following findings were excluded from the study: (1) otoscopic evidence of a perforated tympanic membrane or other middle-ear pathology; (2) a flat tympanogram or absence of acoustic reflexes at 1 kHz with contralateral stimulation; or (3) an air–bone gap of 5 dB at any frequency.

Audiometric evaluation

Audiometric evaluation was preceded by otoscopy, tympanography and an evaluation of middle-ear function by immittance and acoustic reflex testing, using a GSI Tympstar Version 2 Middle Ear Analyzer (Grason-Stadler, Inc, Milford, NH). Only participants with normal peak compliance, peak pressure, gradient, ear canal volume, and acoustic reflexes obtained by immittance measures (as defined by the American Speech Language and Hearing Association) were included in the study.

Subjects deemed suitable for further testing were subjected to a complete audiologic evaluation, including pure tone air and bone conduction audiometry as well as speech audiometry. Pure tone audiometry was performed at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz using a Clinical Audiometer Orbiter 922, V.2 (Madsen Electronics, Minnetonka, Minnesota, USA) in a sound-proof cabin. Pure tone averages (PTA) were calculated for three groups: PTA1 (250 Hz), PTA2 (500, 1000, and 2000 Hz) and PTA3 (4000 and 8000 Hz).

Laboratory assay

Venous blood samples were obtained for all patients from the antecubital region between 8.00 and 9.00 a.m. after an 8–12 h overnight fast. Serum levels of TSH, free triiodothyronine (FT_3) and free thyroxine (FT_4) levels were measured using the chemiluminescence microparticle immunoassay (CMIA) method on an Abbott Architect 2000 Analyzer (Abbott Diagnostics, IL, USA), whereas TRAb titers were determined by radioreceptor assay (Radim, Italy). According to the reference values of the local laboratory at our hospital, a TR-Ab level of <9 U/l indicated a negative result, while a level >14 U/l was indicative of a positive result. Values that fell between 9 and 14 U/l were considered borderline.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). Normality of distribution for continuous variables was tested using the Shapiro–Wilk test. Comparison of the mean age of GD patients and healthy controls was made using Student's *t* test. The Mann–Whitney U test was used for comparisons of thyroid function tests and pure tone thresholds. Intra-group comparisons were evaluated by the Wilcoxon signed rank test. Comparisons between groups for the frequencies of 250, 500, 1000, 2000, and 4000 Hz were performed using Fisher's exact test, while Pearson's Chi-square test was used for the frequency of 8000 Hz. Values for odds ratio were calculated using logistic regression analysis. Degrees of association between continuous variables were analyzed by Spearman's correlation test. A P value <0.05 was considered indicative of statistical significance.

Results

Following initial screening, and subsequent otologic and audiometric evaluation, 22 patients with GD and 22 healthy controls were included in the final analysis. The differences between groups with regards to age and gender distribution were statistically insignificant ($P = 0.567$ and $P = 0.757$, respectively). Patients with GD has significantly higher serum levels of FT3 and FT4 levels, as well as lower serum TSH levels compared with their healthy counterparts ($P < 0.001$, for all) (Table 1). Comparisons of right ear and left ear pure tone thresholds of patients with GD and healthy controls did not reveal a statistically significant difference (Table 2).

Table 1 Demographic and laboratory features of the study population

Variables	GD ($n = 22$)	Control ($n = 22$)	P value
Age (years)	36.0 ± 11.1	37.6 ± 8.0	0.567[a]
Female/male	13/9	14/8	0.757[b]
FT3 (pg/ml)	4.7 ± 1.4	2.6 ± 0.4	<0.001[c]
FT4 (ng/dl)	2.0 ± 0.7	1.2 ± 0.6	<0.001[c]
TSH (μIU/ml)	0.02 ± 0.01	1.9 ± 1.0	<0.001[c]
TR-Ab (IU/l)	16.8 ± 4.0	Negative	NA

TSH Thyroid-stimulating hormone, *FT3* Free triiodothyronine, *FT4* Free thyroxine, *TR-Ab* Anti-TSH receptor antibodies, *NA* not available

[a] Student's *t* test

[b] Pearson Chi-square test

[c] Mann–Whitney U test

When comparisons were made taking into consideration single-ear evaluations (total of 44 ears from both groups), hearing thresholds of the GD group were found to be significantly higher than those of healthy controls at all frequencies ($P < 0.05$) (Table 3).

Although the presence of hyperthyroidism did not seem to affect hearing at frequencies of 250, 500, 1000, and 2000 Hz, significant hearing loss was observed at frequencies of 4000 and 8000 Hz. GD was associated with an odds ratio of 14.97 (95% confidence interval 4.03–55.64) for the development of hearing loss at a frequency of 8000 Hz.

The PTA thresholds of patients with GD were significantly higher than those observed in healthy controls, regardless of PTA group ($P < 0.05$ for all). The difference was most prominent at higher frequencies (Fig. 1).

In patients with GD, right and left pure tone audiometric findings at a frequency of 8000 Hz were found to correlate positively with FT3 and FT4, and to correlate negatively with TSH. While a statistically significant correlation was noted between audiometric findings and TR-Ab at a frequency of 4000 Hz, no correlation was found between PTA values and TR-Ab values (Table 4).

Discussion

In our study, we managed to demonstrate the presence of sensorineural hearing loss more frequently in patients with GD compared to healthy controls. We also observed a significant correlation between PTA values and thyroid hormone levels.

Although few case reports on the occurrence of sudden hearing impairment in patients with hyperthyroidism treated with propylthiouracil may be encountered in the literature [12], the issue of hearing loss directly related to hyperthyroidism has not been previously explored. Our study results suggest the metabolic effects of thyroid hormones and thyrotoxicosis may play a role in the development of hearing loss. It has previously been demonstrated that sympathetic over-activity due to up-regulated adrenergic receptors in some tissues may accentuate the clinical findings of hyperthyroidism [16]. The inner ear has abundant sympathetic innervation [17]. Meniere's disease may serve as an interesting model to help explain the relationship between the autonomic nervous system and hearing [18]. Emotional stress may trigger episodes of inner ear dysfunction. Under stressful conditions, normal ambient noises may seem to be unbearably loud. It is widely believed that cochlear vasoconstriction, which is likely to be under perivascular sympathetic control, may occur as a result of acoustic exposure. Sympathetic input to the cochlea can be either from the stellate ganglion and

Table 2 Comparison of right ear and left ear pure tone thresholds of patients with Graves' disease and healthy controls

Frequency (Hz)	GD group			Control group		
	Right ear	Left ear	*P* value*	Right ear	Left ear	*P* value*
250	10.0 (5.0–25.0)	15.0 (5.0–30.0)	0.109	7.5 (0–15.0)	10.0 (0–20.0)	0.034
500	10.0 (5.0–30.0)	10.0 (5.0–40.0)	0.088	5.0 (0–20.0)	5.0 (0–20.0)	0.655
1000	10.0 (0–30.0)	10.0 (0–35.0)	0.135	10.0 (0–15.0)	10.0 (0–15.0)	0.776
2000	7.5 (0–25.0)	7.5 (0–25.0)	0.791	5.0 (0–20.0)	5.0 (0–20.0)	0.380
4000	5.0 (0–35.0)	12.5 (0–35.0)	0.020	5.0 (0–20.0)	5.0 (0–20)	0.380
8000	20.0 (5.0–55.0)	27.5 (5.0–65.0)	0.024	10.0 (5.0–25.0)	10.0 (0–30.0)	0.149

* Wilcoxon Sign Rank test

Table 3 Comparison of pure tone thresholds in right and left ears within groups

Test	GD ($n = 22$)				Control ($n = 22$)				*P* value*
	Min.	Max.	Mean	SD (dB)	Min.	Max.	Mean	SD (dB)	
250 Hz	5	30	12.7	5.4	0	20	9.2	4.3	0.002[a]
500 Hz	5	40	10.8	6.9	0	20	6.5	4.1	0.001[a]
1000 Hz	0	35	11.6	7.9	0	15	8.1	4.1	0.056[a]
2000 Hz	0	25	10.3	7.3	0	20	6.3	4.5	0.004[a]
4000 Hz	0	35	12.8	10.1	0	20	6.8	5.3	0.004[a]
8000 Hz	5	65	25.8	15.4	0	30	12.0	6.7	<0.001[a]
SDS	80	100	96.6	5.1	92	100	98.1	2.5	0.555
PTA 1	5	30	12.7	5.4	0	20	9.2	4.3	0.002[b]
PTA 2	3	28	10.9	6.3	0	18	6.9	3.6	<0.001[b]
PTA 3	5	47.5	19.3	11.7	2.5	25	9.4	4.5	<0.001[b]

SD standard deviation, *PTA* pure tone average, *SDS* speech discrimination score, *Hz* hertz, *dB* decibel

* Mann–Whitney U test

[a] According to Bonferroni correction $p < 0.0083$ for the results were considered statistically significant

[b] According to Bonferroni correction $p < 0.0017$ for the results were considered statistically significant

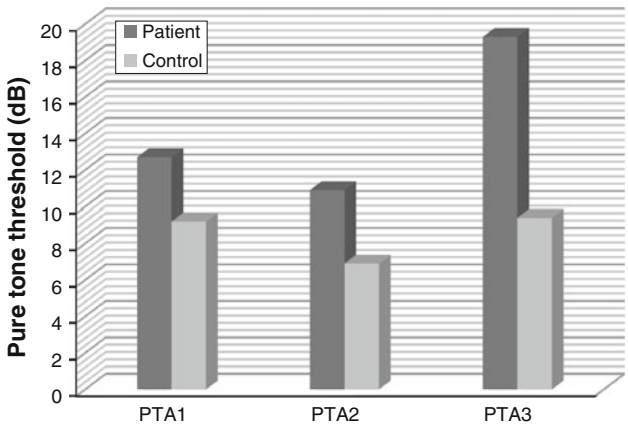

Fig. 1 Comparison of pure tone averages of patients with GD and healthy controls

associated with blood vessels or from the superior cervical ganglion, mostly independent of blood vessels [18]. The blood vessel-independent sympathetic system utilizes norepinephrine and previous immunohistochemical studies have localized this system outside the organ of Corti in close association with afferents and efferents at the level of the habenula [19].

Graves' disease is an autoimmune disorder, and the basic underlying pathology is the production of antibodies against TSH receptors. This not only results in gland hyperplasia due to the thyrotropic effects of TSH, but also promotes the formation of monoiodotyrosine and diiodotyrosine, and the release of T3 and T4. Certain major histocompatibility complex (MHC) susceptibility genes have been linked with GD in some populations [20–23]. All of the patients included in our study were TR-Ab positive. Although we could not demonstrate a direct correlation between TR-Ab levels and hearing thresholds, antibody positivity in our patient group suggests that autoimmunity may play a role in the pathogenesis of hearing impairment in GD.

Sensorineural hearing loss has been reported in association with many autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune

Table 4 Results of correlation analysis between pure tone thresholds and thyroid parameters

Test	FT3		FT4		TSH		TR-Ab	
	rho	*P* value	rho	*P* value	rho	*P* value	rho	*P* value
250 Hz	0.282	0.008	0.206	0.054	−0.232	0.030	0.169	0.272
500 Hz	0.332	0.002	0.261	0.014	−0.249	0.019	0.157	0.308
1000 Hz	0.176	0.102	0.081	0.455	−0.160	0.136	0.085	0.583
2000 Hz	0.083	0.441	0.023	0.834	−0.235	0.027	0.016	0.623
4000 Hz	0.202	0.059	0.156	0.146	−0.303	0.004	0.163	0.160
8000 Hz	0.327	0.002	0.271	0.011	−0.447	<0.001	0.168	0.276
PTA2	0.222	0.037	0.136	0.207	−0.244	0.022	0.099	0.524
PTA3	0.307	0.004	0.250	0.019	−0.431	<0.001	0.268	0.079

TSH thyroid-stimulating hormone, *FT3* free triiodothyronine, *FT4* free thyroxine, *TR-Ab* TSH receptor antibody

sensorineural hearing loss, relapsing polychondritis, disseminated vasculitis, polymyalgia rheumatica, and ankylosing spondylitis [24]. Several mechanisms have been implicated in the development of hearing loss. Autoimmune diseases can lead to vasculitis, resulting in a variety of secondary degenerative changes. The most widely documented effects of autoimmune diseases resulting in sensorineural hearing loss are mediated by a vascular mechanism [25]. Several studies have demonstrated the capability of the inner ear to respond to an antigen challenge by producing its own antibodies [26–28]. Harris et al. [29] have shown a parallel rise of antibody titres over a 3-week period in guinea pigs immunized by antigen presentation either through the inner ear or via the peritoneal route. These findings indicate that the inner ear is an effective route of antigen processing, which can result in the acquisition of systemic humoral immunity as well as cellular immunity. Although we could not ascertain a correlation between TRAb and hearing thresholds, the statistically significant difference in hearing thresholds observed in TRAb-positive patients and TRAb-negative control group is highly suggestive of a possible role of autoimmunity in the pathogenesis of hearing impairment. In other words, lack of correlation between serum TRAb levels and the extent of increase in hearing thresholds does not necessarily rule out the presence of an association between the two.

To the best of our knowledge, the relationship between thyrotoxicosis and hearing impairment has not been previously studied. Despite certain limitations of our study, our results might serve as preliminary findings for designing future controlled studies on larger populations. One of the limitations of our study is in its design as a cross-sectional study evaluating relationship between thyroid hormones, thyroid autoimmunity and hearing. A repeat of audiometric tests after achieving a euthyroid state in patients with GD would have perhaps helped in better understanding the effects of thyroid hormones on hearing. Furthermore, only patients who were positive for TRAb were selected for this study. A subgroup analysis comparing TRAb-positive and TRAb-negative GD patients could be helpful in ascertaining the effects of autoantibodies on hearing loss, and may even help to distinguish whether hearing impairment noted in Graves' hyperthyroidism is caused by autoimmunity or excessive thyroid hormone levels.

Conclusion

Our findings suggest that hearing loss of patients with GD was sensorineural and that their hearing level decreased mostly at high frequencies, although pure tone thresholds of both groups differed at all frequencies. Further studies are needed to fully comprehend the immunopathogenic mechanisms behind sensorineural hearing loss, the priority being in vitro pathophysiological and molecular animal studies [18].

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