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Article Type: Original Study

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EVALUATION OF HEARING LOSS IN PATIENTS WITH GRAVES’ HYPERTHYROIDISM

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Running title: Hearing Loss in Graves’ Disease

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ABSTRACT

Hearing loss is commonly associated with thyroid disorders, and during propilthiouracil treatment. However, the relationship between hyperthyroidism and auditory system has not been investigated. The aim of this cross-sectional, case–control study is to investigate hearing loss in patients with Graves’ disease (GD). Twenty-two patients with newly diagnosed GD and 22 healthy control subjects were included. Pure tone audiometry at 250, 500, 1000, 2000, 4000 and 8000 Hz and immittance measures, including tympanometry and acoustic reflex tests, were performed in the patients and controls. There were no statistically significant differences between the ages and genders of the patient and control groups (p=0.567 and p=0.757, respectively). No significant difference was observed between hearing threshold of right and left ears in GD and control groups (p>0.05). When only one ear was taken into account (44 ears), hearing thresholds of GD group were significantly higher than controls at all frequencies (p<0.05). Although no significant effect of thyrotoxicosis was observed on hearing loss at 250, 500, 1000 and 2000 frequencies, a significant effect was detected at 4000 and 8000 frequencies. In GD group, odds ratio for hearing loss at 8000 frequency was 14.97 (95% confidence interval 4.03-55.64) compared to controls. Right and left pure tone audiometric findings were positively correlated with FT3, FT4 and negatively correlated with TSH in GD at 8000 frequency. Our results revealed that hearing ability decreases, mostly at high frequencies, in patients with GD. Further studies are needed to explain the cause and mechanism of hearing loss in patients with GD.

Key words: Thyrotoxicosis, Graves’ disease, hearing loss, pure tone audiometry
INTRODUCTION

Thyroid hormone is essential for the development of hearing (1). Prior to the onset of hearing, thyroid hormones acting through thyroid hormone receptor-β influence hearing by initiating myelinogenesis of the cochlea and vestibulocochlear nerve (cranial nerve VIII) (2). Brucker-Davis et al. have estimated that the critical period of thyroid-sensitive cochlear development in humans occur between the close of the first trimester and the first month of life (3). Hypothyroidism caused by exposure to thyroid-disrupting chemicals may also lead to hearing loss with cochlear and/or auditory nerve dysfunction (4-6). It was due, in part, to 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 (7). In a subsequent experiment, postnatal administration of thyroid hormone partially blocked 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 during propilthiouracil treatment have been reported in patients with Graves' disease (GD) (12-15). However, the relationship between hyperthyroidism and auditory system has not been investigated. In the present study, our aim was to compare 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

Patients

Twenty-two patients with GD, and 22 healthy control subjects were included in the study. The diagnosis of GD was based on the clinical signs of hyperthyroidism combined with suppressed serum thyrotropin and positive thyrotropin receptor antibodies. Newly diagnosed patients, in whom no treatment was initiated, were included. Informed consent was obtained from all participants. 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. Participants were excluded from the study if they had any of the following: (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.

**Audiometry**

The initial hearing examination included otoscopy, tympanography and a complete audiologic evaluation, including pure tone air and bone conduction audiometry and speech audiometry. Pure tone audiometry was performed at the frequencies 250, 500, 1000, 2000, 4000 and 8000 Hz using a Clinical Audiometer Orbiter 922, V.2 (Madsen Electronics, Minnetonka, Minnesota, USA) in a sound-treated cabin. Three pure tone average (PTA) groups were calculated: PTA1 (250 Hz), PTA2 (500, 1000 and 2000 Hz) and PTA3 (4000 and 8000 Hz). Normal middle-ear function was defined by immittance and acoustic reflex results using a GSI Tympstar Version 2 Middle Ear Analyzer (Grason-Stadler, Inc, Milford, NH). The patients and controls who had 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.

**Laboratory Assay**

After an overnight fasting, blood samples were collected from all the study subjects for the determination of serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT$_3$), free thyroxine (FT$_4$), and anti-TSH receptor antibody (TR-Ab) levels. Serum TSH, FT$_3$ and FT$_4$ levels were evaluated using the Abbott Architect 2000 Analyzer (Abbott Diagnostics, IL, USA) and chemiluminescence microparticle immunoassay (CMIA) method. Patients with TSH level < 0.35 µIU/mL FT$_3$ level > 3.71 pg/mL and FT$_4$ level >1.48 ng/dL were accepted as hyperthyroidism. TR-Ab autoantibodies were measured using radioreceptor assay (Radim, Italy). The reference values in our laboratory indicated that TR-Ab < 9 U/L was normal whereas the borderline values of TR-Ab were between 9-14 U/L and positive values were > 14 U/L.

**Statistical analysis**

Statistical analysis was performed by statistical package for social sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). The normality of the distribution of continuous variables was tested by the Shapiro Wilk test. Mean ages of
the patients were compared using Student’s t test. Mann Whitney U test was used for the comparisons of the thyroid function tests and pure tone thresholds. Intra-group comparisons were evaluated by the Wilcoxon signed rank test. Degrees of association between continuous variables were analyzed by Spearman’s correlation test. A p value < 0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the ages and genders of the patient and control groups (p=0.567 and p=0.757, respectively). While FT3 and FT4 levels were significantly higher (p<0.001, p<0.001, respectively), TSH level was significantly lower (p<0.001) in the GD group compared to controls (Table 1).

No significant difference was observed between hearing threshold of right and left ears in GD and control groups (Table 2).

When only one ear was taken into account (44 ears), hearing thresholds of GD group were significantly higher than controls at all frequencies (p<0.05) (Table 3). Although no significant effect of thyrotoxicosis was observed on hearing loss at 250, 500, 1000 and 2000 frequencies, a significant effect was detected at 4000 and 8000 frequencies. In GD group, odds ratio for hearing loss at 8000 frequency was 14.97 (95% confidence interval 4.03-55.64) compared to controls.

The PTA thresholds of patients and controls were significantly different in all three PTA groups (p < 0.05). The differences were most prominent at higher frequencies (Figure 1).

Right and left pure tone audiometric findings were positively correlated with FT3, FT4 and negatively correlated with TSH in GD at 8000 frequency.

While a statistically significant correlation was noted between audiometric findings and TR-Ab at 4000 frequency, no correlation was found between PTA values and TR-Ab values (Table 4).
DISCUSSION

A sensorineural hearing loss was observed in patients with GD compared to healthy controls and PTA values were found to be correlated with thyroid hormone levels in the present study.

Despite few case reports regarding sudden hearing impairment due to the use of propilthiouracil during treatment of hyperthyroidism, hyperthyroidism-related hearing impairment has not previously been published (12). We suggest that hearing impairment in patients with Graves’ disease develops a result of the common effects of several different mechanisms. Since we have noted a correlation between thyroid hormone levels and hearing thresholds, we considered that the reason for increased hearing thresholds was due to the metabolic effects of high thyroid hormones and thyrotoxicosis. It is known that some of the clinical findings of hyperthyroidism result from sympathetic over-activity due to up-regulated adrenergic receptors in some tissues (16). The inner ear has abundant sympathetic innervation (17). Meniere’s disease episodes may serve as an interesting model for explaining the relationship between autonomic nervous system and hearing functions (18). Episodes of inner ear dysfunction can be associated with emotional stress. For example, in stress conditions normal ambient noises may seem to be unbearably loud. Stress has also been suspected to aggravate hearing disorders. Cochlear vasoconstriction which is likely to be under perivascular sympathetic control may occur during acoustic exposure. It is a well known fact that the sympathetic input to the cochlea can be either from the stellate ganglion and associated with blood vessels or from the superior cervical ganglion, mostly independent of blood vessels (18). The protection effects are related to the blood vessel-independent sympathetic innervations, rather than modification in vascular tone. The former sympathetic system is associated with norepinephrine and has been localized by immunohistochemistry outside the organ of Corti in close association with afferents and efferents at the level of the habenula (19).

The underlying pathogenesis of GD is the presence of antibodies against TSH receptor. This not only results in gland hyperplasia due to thyrotropic effects of TSH, but also promotes the formation of moniodotyrosine and diiodotyrosine, and the release of T3 and T4. Linkage evidence for a susceptibility gene for GD to the major histocompatibility complex (MHC) has also been found in some populations (20-23).
Graves’ disease is an autoimmune disorder. All of the patients included in the study were TR-Ab positive. Although we could not demonstrate a direct correlation between TR-Ab levels and hearing thresholds, antibody positivity in patients and antibody negativity in controls suggest that autoimmunity may play a role in the pathogenesis of hearing impairment in GD. Sensorineural hearing loss may occur in many autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune sensorineural hearing loss, relapsing polychondritis, disseminated vasculitis, polymyalgia rheumatica and ankylosing spondylitis (24). Autoimmunity may lead to hearing loss through a few mechanisms. Many of the 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 that the inner ear was the source of the antibody (26-28). According to these studies, the inner ear is capable of responding to antigen challenge. Harris et al. have shown a parallel rise of antibody titres over a three-week period in guinea pigs immunized by either inner-ear or peritoneal routes of antigen presentation (29). These studies 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. We suggested that there might be sensorineural hearing loss due to TR-Ab in patients with GD.

There have been no previous reports about the relationship between thyrotoxicosis and hearing impairment. Despite certain limitations of our study, our results might serve as preliminary findings for designing future controlled studies with large sample size. Whether hearing impairment noted in Graves’ hyperthyroidism is caused by autoimmunity or excessive thyroid hormone levels should be differentiated. At first, in vitro pathophysiological and molecular animal studies are required. It seems possible that hyperthyroidism may have some participation in the immunopathogenesis of sensorineural hearing loss (18). It is also possible to attribute some vascular participation to the physiopathology of sensorineural hearing loss.

**CONCLUSION**

Our findings suggest that hearing loss of patients with GD was sensorineural and that their hearing level decreased mostly at high frequencies, although the pure tone
thresholds of patient and controls differed at all frequencies. However, further studies are needed to explain the cause and mechanism of hearing loss in patients with GD.
REFERENCES


Legends

**Table 1.** Clinical and laboratory features of the groups

**Table 2.** Comparison of pure tone thresholds between right and left ears in the study groups

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

**Table 4.** Correlation between thyroid function tests, TSH receptor antibody and pure tone thresholds in right and left ears of all participants

**Figure 1.** Pure tone averages
**Table 1.** Clinical and laboratory features of the groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>GD (n=22)</th>
<th>Control (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>36.0±11.1</td>
<td>37.6±8.0</td>
<td>0.567&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female/Male</td>
<td>13/9</td>
<td>14/8</td>
<td>0.757&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>FT3, pg/ml</td>
<td>4.7±1.4</td>
<td>2.6±0.4</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>FT4, ng/dl</td>
<td>2.0±0.7</td>
<td>1.2±0.6</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>TSH, μIU/ml</td>
<td>0.02±0.01</td>
<td>1.9±1.0</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>TR-Ab, IU/L</td>
<td>16.8±4.0</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA= not analyzed

<sup>a</sup> Student’s t test, <sup>b</sup> Pearson Chi-square test, <sup>c</sup> Mann Whitney U test.

TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; TR-Ab: Anti-TSH receptor antibodies
**Table 2.** Comparison of pure tone thresholds between right and left ears in the study groups

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>GD Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>250</td>
<td>10.0 (5.0-25.0)</td>
<td>15.0 (5.0-30.0)</td>
</tr>
<tr>
<td>500</td>
<td>10.0 (5.0-30.0)</td>
<td>10.0 (5.0-40.0)</td>
</tr>
<tr>
<td>1000</td>
<td>10.0 (0-30.0)</td>
<td>10.0 (0-35.0)</td>
</tr>
<tr>
<td>2000</td>
<td>7.5 (0-25.0)</td>
<td>7.5 (0-25.0)</td>
</tr>
<tr>
<td>4000</td>
<td>5.0 (0-35.0)</td>
<td>12.5 (0-35.0)</td>
</tr>
<tr>
<td>8000</td>
<td>20.0 (5.0-55.0)</td>
<td>27.5 (5.0-65.0)</td>
</tr>
</tbody>
</table>

^* Wilcoxon Sign Rank test.
Table 3. Comparison of pure tone thresholds in right and left ears within groups

<table>
<thead>
<tr>
<th></th>
<th>GD Group</th>
<th>Control Group</th>
<th>p*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean</td>
</tr>
<tr>
<td>250 Hz</td>
<td>5</td>
<td>30</td>
<td>12.7</td>
</tr>
<tr>
<td>500 Hz</td>
<td>5</td>
<td>40</td>
<td>10.8</td>
</tr>
<tr>
<td>1000 Hz</td>
<td>0</td>
<td>35</td>
<td>11.6</td>
</tr>
<tr>
<td>2000 Hz</td>
<td>0</td>
<td>25</td>
<td>10.3</td>
</tr>
<tr>
<td>4000 Hz</td>
<td>0</td>
<td>35</td>
<td>12.8</td>
</tr>
<tr>
<td>8000 Hz</td>
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<td>65</td>
<td>25.8</td>
</tr>
<tr>
<td>SDS</td>
<td>80</td>
<td>100</td>
<td>96.6</td>
</tr>
<tr>
<td>PTA 1</td>
<td>5</td>
<td>30</td>
<td>12.7</td>
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<tr>
<td>PTA 2</td>
<td>3</td>
<td>28</td>
<td>10.9</td>
</tr>
<tr>
<td>PTA 3</td>
<td>5</td>
<td>47.5</td>
<td>19.3</td>
</tr>
</tbody>
</table>

N=44, SD: Standard deviation, PTA: Pure tone average, SDS: Speech discrimination score, Hz: Hertz, dB: Decibel
*Mann Whitney U test.
### Table 4. Correlation between thyroid function tests, TSH receptor antibody and pure tone thresholds in right and left ears of all participants

<table>
<thead>
<tr>
<th>Frequencies</th>
<th>FT3</th>
<th>FT4</th>
<th>TSH</th>
<th>TR-Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rho</td>
<td>p</td>
<td>rho</td>
<td>p</td>
</tr>
<tr>
<td>250</td>
<td>0.282</td>
<td>0.008</td>
<td>0.206</td>
<td>0.054</td>
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<tr>
<td>500</td>
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<td>0.002</td>
<td>0.261</td>
<td>0.014</td>
</tr>
<tr>
<td>1000</td>
<td>0.176</td>
<td>0.102</td>
<td>0.081</td>
<td>0.455</td>
</tr>
<tr>
<td>2000</td>
<td>0.083</td>
<td>0.441</td>
<td>0.023</td>
<td>0.834</td>
</tr>
<tr>
<td>4000</td>
<td>0.202</td>
<td>0.059</td>
<td>0.156</td>
<td>0.146</td>
</tr>
<tr>
<td>8000</td>
<td>0.327</td>
<td>0.002</td>
<td>0.271</td>
<td>0.011</td>
</tr>
<tr>
<td>PTA2</td>
<td>0.222</td>
<td>0.037</td>
<td>0.136</td>
<td>0.207</td>
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<tr>
<td>PTA3</td>
<td>0.307</td>
<td>0.004</td>
<td>0.250</td>
<td>0.019</td>
</tr>
</tbody>
</table>

TSH: thyroid-stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TR-Ab: TSH Receptor Antibody
Figure 1. Pure tone averages
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