Is the Degree of Discomfort Caused by Tinnitus in Normal-Hearing Individuals Correlated with Psychiatric Disorders?
Ronaldo Campos Granjeiro, Helga Moura Kehrle, Taciana Sarmento Cardoso de Oliveira, André Luiz Lopes Sampaio and Carlos Augusto Costa Pires de Oliveira

Otolaryngology -- Head and Neck Surgery 2013 148: 658 originally published online 11 January 2013
DOI: 10.1177/0194599812473554

The online version of this article can be found at:
http://oto.sagepub.com/content/148/4/658

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>> Version of Record - Mar 27, 2013
OnlineFirst Version of Record - Jan 11, 2013

What is This?
Abstract

Objective. To evaluate the annoyance of tinnitus in normal-hearing patients and to correlate it with outer hair cell function and with anxiety and depression disorders.

Study design. Case-control study.

Setting. Tertiary care medical center.

Subjects and Methods. Sixty-eight patients with tinnitus (study group) and a control group consisting of 46 subjects without tinnitus were studied. The subjects ranged in age from 20 to 45 years and had a hearing threshold of up to 25 dB in the frequency range of 500 to 8000 Hz. The subjects were submitted to otoacoustic emission (OAE) tests. Tinnitus annoyance was evaluated using the Tinnitus Handicap Inventory, and anxiety and depression were measured using the Beck Anxiety and Depression Inventories.

Results. In the study group, 67% of the transient-evoked OAE tests were altered, with the observation of significant differences for all frequencies tested. In addition, 65.2% of the distortion product–evoked OAE tests were altered at 3000, 6000, and 8000 Hz, and this difference was significant when compared with control. Anxiety (44.1%) and depression (33.3%) were significantly more frequent among patients with tinnitus. Tinnitus annoyance was not correlated with the OAE results or tinnitus duration but showed a correlation with the presence of anxiety and depression. In the study group, no difference in tinnitus annoyance, anxiety, or depression was observed between patients with normal and altered OAE tests.

Conclusion. This study showed altered OAE in patients with tinnitus and normal hearing. It also demonstrated a positive correlation between the annoyance of tinnitus and anxiety and depression in normal-hearing patients.

Keywords

Tinnitus, normal-hearing, annoyance, anxiety, depression, outer hair cell function.
The theories of tinnitus generation are not completely clear, but cochlear (outer hair cells) dysfunction has been suggested to produce tinnitus in some situations. A reduction in the otoacoustic emission (OAE) amplitude was observed in patients with tinnitus and normal hearing at high frequencies (3000, 4000, 5000, and 8000 Hz), a finding supporting the role of cochlear dysfunction in the generation of tinnitus. The aim of the present study was to evaluate the annoyance of tinnitus in normal-hearing patients and to correlate it with OHC dysfunction and with anxiety and depression disorders.

Patients and Methods

The study was conducted between November 2008 and November 2010 at Hospital de Base, Federal District, Brazil. Approval was obtained from the hospital’s ethics committee (Permit No. 334/08). The sample was selected by convenience sampling. Sixty-eight subjects (31 men and 37 women) with subjective tinnitus and normal hearing were enrolled in the study group (SG). The control group (CG) consisted of 46 subjects (13 men and 33 women) without tinnitus and with normal hearing. The mean age was 36.8 and 31.7 years in SG and CG, respectively. A total of 112 ears with tinnitus (men, n = 50; women, n = 62) were analyzed in SG and 92 (men, n = 26; women, n = 66) in CG.

Criteria for inclusion in the study were age ranging from 20 to 45 years, good general health, and normal hearing. The last criterion was defined as otolaryngological and laboratory tests within normal limits, auditory thresholds of 0 to 25 dB in the frequency range from 250 to 8000 Hz, static emittance between 0.2 and 1.3, and presence of ipsilateral and contralateral acoustic reflexes. Exclusion criteria were drug treatment for tinnitus during the past 6 months; duration of tinnitus of less than 6 months; history of acoustic trauma, vascular disease, metabolic and middle ear diseases, ear surgery, vestibular disorders, head trauma, and neurological diseases; recent intake of ototoxic drugs (salicylates, nonsteroidal anti-inflammatory drugs, aminoglycosides, diuretics); and chemotherapy/radiotherapy.

The OAE tests were conducted in a soundproof room by the same examiner using the AUDX Plus Bio-Logic device (AUDX Plus Bio-Logic Systems Corp, Mundelein, Illinois). A broadband continuous click at 80 dB sound pressure level (SPL) was used for transient-evoked otoacoustic emission (TEOAE) recording. Distortion product–evoked otoacoustic emission (DPOAE) was evaluated by evoking 2 tones at a lower (F1) and higher frequency (F2), with the F2/F1 ratio = 1.22 (65 dB SPL for F1 and 55 dB SPL for F2). The following TEOAE parameters were analyzed: (1) signal-to-noise (S/N) ratio ≥6 dB for at least 3 of the 4 frequencies tested (1500, 2000, 3000, and 4000 Hz) and (2) reproducibility of the responses ≥70% at 3 of the 4 frequencies tested. The following DPOAE parameters were analyzed for all frequencies tested: (1) S/N ratio ≥8 dB at frequencies from 1000 to 8000 Hz and (2) amplitude of the signal within the 90th percentile of the normal distribution for the frequencies tested. Otoacoustic emission test analysis was done considering the results in ears, not patients, because the answers were independent between ears of the same individual.

The Tinnitus Handicap Inventory (THI) was used to evaluate the discomfort caused by tinnitus based on the score proposed by Newman et al: very mild disability (0-16), mild disability (18-36), moderate disability (38-56), and severe disability (58-100). The Beck Depression and Anxiety Inventories were used for the evaluation of depression and anxiety. The study group was divided into 2 subgroups, with and without annoyance of tinnitus, to determine the correlation of THI scores with depression and anxiety.

Statistical analysis was performed using the SPSS 18.0 for Windows program (SPSS, Inc, an IBM Company, Chicago, Illinois). A P value < .05 was considered significant. The OAE test results were pooled since there was no significant difference between the right and left sides (P > .05). Means were compared between groups using the Student t test. The odds ratio was calculated with the 95% confidence interval to measure the association between the variables. The χ² test was used to verify the existence of associations between normal and altered OAE tests in both SG and CG and to compare the proportions of individuals by sex, level of anxiety, and depression. Fisher exact test was used in cases in which the number of individuals in the category was small. The association between the degree of discomfort and the presence of anxiety and depression was evaluated using the χ² or Fisher exact test. Spearman’s coefficient was applied to determine the correlation of tinnitus annoyance with anxiety and depression.

Results

The mean (SD) duration of tinnitus in SG was 5.95 (6.7) years. Bilateral tinnitus was observed in 60.3% of the subjects, 20.6% had tinnitus in the left ear, 14.7% had it in the right ear, and 4.4% had it in the head. No significant difference in sex distribution was observed between SG (n = 68) and CG (n = 46) (P = .062).

The TEOAE test results are shown in Table 1. The TEOAE test was altered in 67.0% (75 ears) of the subjects in SG vs 19.6% (18 ears) in CG. This difference was statistically significant (P < .0001). Comparison of the 2 groups according to frequency showed a significant difference at all frequencies tested. The mean S/N ratio was significantly lower in SG when compared with CG in all frequencies.

An altered DPOAE test was observed in 73 of 112 ears (65.2%) in SG vs 46 of 92 (50%) in CG. This difference was statistically significant (P < .029) (Table 1). Analysis of normal and altered DPOAE according to frequency showed a significant difference at 3000 Hz (P = .042), 6000 Hz (P = .016), and 8000 Hz (P = .006). The mean S/N ratio of DPOAEs differed significantly between SG and CG at 1500 Hz (P = .016), 3000 Hz (P = .002), 4000 Hz (P = .004), and 8000 Hz (P = .011).

According to the THI, annoyance of tinnitus in SG was very mild or mild in 63.2% of the subjects, moderate in 25.0%, and severe in 11.8%. The tinnitus annoyance was higher among women (P = .014).
Thirty (44.1%) subjects in SG presented anxiety vs 8 (17.4%) in CG. This difference was statistically significant (P < .004). Depression was observed in 23 (33.8%) subjects in SG vs 6 (13.0%) in CG, with the difference being significant (P < .016) (Table 2).

In SG, 45 (66.2%) of the 68 patients had no depression, and tinnitus annoyance assessed by the THI was very mild and mild in 37.7% (n = 17) and 40.0% (n = 18), respectively. Among the 23 subjects in SG with depression, 43.5% (n = 10) had moderate tinnitus annoyance and 21.7% had severe annoyance. A significant association was observed between the presence and absence of depression and tinnitus annoyance (P < .001)—that is, tinnitus annoyance was more severe in subjects with depression (Table 3).

Thirty-eight (55.9%) patients in SG presented no anxiety. Of these, 14 (36.8%) had very mild discomfort, 19 (50.1%) had mild discomfort, 4 (10.5%) had moderate discomfort, and 1 (2.6%) had severe discomfort. Among the 30 (44.1%) subjects in SG with anxiety, 13 (43.4%) had moderate annoyance, 7 (23.3%) had severe annoyance, and 10 (23.3%) had very mild or mild discomfort. This difference was statistically significant (P < .0001), with a trend of higher THI scores in patients with anxiety (Table 3).

In a correlation between the THI and categories of depression and anxiety, using the Spearman correlation test, patients with depression had milder tinnitus symptom than those with anxiety who had a moderate THI score and those with anxiety and depression who had severe annoyance. This difference was statistically significant (P = .001) (Table 4). Patients without anxiety and depression had very mild or mild discomfort. Thus, a significant correlation exists between anxiety and depression and THI scores, with high anxiety and depression scores tending to be correlated with higher scores for tinnitus annoyance. However, no cause-effect relationship could be established between these parameters.

### Table 1. Results of the TEOAE and DPOAE Tests in the Study Group and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Study Group (n = 112 Ears), %</th>
<th>Control Group (n = 92 Ears), %</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEOAE test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered</td>
<td>67.0</td>
<td>19.6</td>
<td>8.333</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Normal</td>
<td>33.0</td>
<td>80.4</td>
<td>1.872</td>
<td>&lt;.029</td>
</tr>
<tr>
<td><strong>DPOAE test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered</td>
<td>65.2</td>
<td>50.0</td>
<td>1.872</td>
<td>&lt;.029</td>
</tr>
<tr>
<td>Normal</td>
<td>34.8</td>
<td>50.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** DPOAE, distortion product–evoked otoacoustic emission; TEOAE, transient-evoked otoacoustic emission.

### Table 2. Results of the Beck Depression and Anxiety Inventories in the Study Group and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Study Group (n = 68), %</th>
<th>Control Group (n = 46), %</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>33.8</td>
<td>13.0</td>
<td>3.407</td>
<td>&lt;.016</td>
</tr>
<tr>
<td>Normal</td>
<td>66.2</td>
<td>87.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>44.1</td>
<td>17.4</td>
<td>3.750</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Normal</td>
<td>55.9</td>
<td>82.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Level of Tinnitus Annoyance According to the Presence or Absence of Anxiety and Depression in Patients of the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Very Mild, %</th>
<th>Mild, %</th>
<th>Moderate, %</th>
<th>Severe, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n = 23)</td>
<td>0</td>
<td>34.8</td>
<td>43.5</td>
<td>21.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absent (n = 45)</td>
<td>37.7</td>
<td>40.0</td>
<td>15.6</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n = 30)</td>
<td>10.0</td>
<td>23.3</td>
<td>43.4</td>
<td>23.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absent (n = 38)</td>
<td>36.8</td>
<td>50.1</td>
<td>10.5</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Total (n = 68)</td>
<td>25.0</td>
<td>38.2</td>
<td>25.0</td>
<td>11.8</td>
<td></td>
</tr>
</tbody>
</table>
No significant association was observed between tinnitus annoyance and unilateral or bilateral tinnitus \( (P = .547) \) or between tinnitus annoyance and normal or altered OAE (TEOAE, \( P = .799 \); DPOAE, \( P > .700 \)). There was also no significant association with tinnitus duration \( (P = .134) \) when durations of less than 5 years, 5 to 10 years, and more than 10 years were analyzed.

A normal or altered TEOAE test was not correlated with anxiety \( (P = .424) \) or depression \( (P = .991) \). There was also no correlation between a normal or altered DPOAE test and anxiety \( (P = .538) \) or depression \( (P = .348) \) by the \( \chi^2 \) test. Six patients in SG had normal TEOAE and DPOAE results. Comparison of SG patients with normal and altered OAE results showed no influence on the level of annoyance \( (P = .527) \) and presence or absence of anxiety \( (P = .244) \) or depression \( (P = .380) \).

Thirty-two \( (47.1\%) \) patients in SG had no anxiety or depression. Comparison of normal and altered TEOAE and DPOAE tests between SG patients without depression or anxiety and those with anxiety and depression revealed no statistically significant difference \( (\text{TEOAE}, \ P = .418; \text{DPOAE}, \ P = .805) \). Tinnitus in SG patients without anxiety and depression was very mild in 43.8\% \( (n = 14) \), mild in 46.9\% \( (n = 15) \), moderate in 6.3\% \( (n = 2) \), and severe in 1.0\% \( (n = 1) \). The level of annoyance was higher in the group with depression and/or anxiety \( (\text{moderate and severe in } 47.1\% \text{ and } 19.4\%, \text{respectively}) \). This finding indicates a significant difference between patients without anxiety and depression and those with anxiety and depression \( (P = .0001) \).

**Discussion**

Annoyance of tinnitus has been associated with anxiety and depression in patients with hearing loss\(^4\) but not with psychoacoustic measurements or hearing thresholds.\(^1,17\) In the present study, 67.0\% of the TEOAE results and 65.2\% of the DPOAE results were altered in patients with tinnitus and normal hearing. The high percentage of altered TEOAE and DPOAE results in these patients suggests the involvement of cochlear dysfunction in the generation of tinnitus.\(^9,10\) especially at higher frequencies \( (6000 \text{ and } 8000 \text{ Hz}) \). This dysfunction may be a trigger of tinnitus in patients with normal hearing.\(^1\)

The percentage of normal TEOAE results was 80.4\% in control subjects without tinnitus. A similar percentage of normal tests \( (83.9\%) \) has been reported by Granjeiro et al.\(^9\) The finding of 50\% normal DPOAE tests in CG agrees with Probst and Hauser,\(^12\) who reported that only in 50\% of normal ears are DPOAEs present in all frequencies from 1000 to 6000 Hz. A significant difference in DPOAE results was observed between SG and CG at frequencies of 3000, 6000, and 8000 Hz. Studying patients with tinnitus and normal hearing, Paglialonga et al.\(^10\) found lower mean TEOAE and DPOAE amplitudes, particularly at high frequencies, when compared with patients without tinnitus.

In SG, 63.2\% of the subjects had very mild and mild tinnitus, 25.0\% had moderate tinnitus, and 11.8\% had severe tinnitus. In the study by Araújo et al.,\(^18\) who evaluated patients with tinnitus due to various causes, 81\% had mild discomfort, 18\% had moderate discomfort, and only 1\% had severe discomfort. The level of annoyance was similar in SG and patients with tinnitus of various etiologies, suggesting that tinnitus annoyance is not related to etiology or hearing threshold.

The annoyance caused by tinnitus was not correlated with OHC function evaluated by the TEOAE \( (P > .799) \) or DPOAE \( (P > .700) \) test. No correlation was reported in a similar study conducted by Pagliaalonga et al.\(^10\) This observation supports the suggestion that annoyance of tinnitus is not related to the causes of the condition but rather to cognitive factors,\(^1,19\) perception, and interpretation of tinnitus.\(^19\)

In SG, 44.1\% of the patients had anxiety and 33.8\% had depression. This proportion was 17.4\% and 13.0\% in CG. The high frequency of anxiety and depression in SG is similar to that reported for patients with hearing loss,\(^4,20\) suggesting that, irrespective of auditory function, tinnitus is associated with a higher percentage of anxiety and depression when compared with the general population.\(^4\) The frequency of anxiety and depression disorders was 2.5 times higher in SG compared with CG.

This study demonstrated a significant correlation between annoyance of tinnitus and anxiety \( (\text{Spearman’s coefficient} = 0.520, \ P < .0001) \) and depression \( (\text{Spearman’s coefficient} = 0.506, \ P < .0001) \) scores, but their causes cannot be directly inferred. These findings suggest that the severity of tinnitus is associated with the severity of anxiety and depression disorders, in agreement with the study by Zöger et al.\(^21\) These data highlight the need to include tools for the identification of anxiety and depression disorders in the diagnostic process and treatment of tinnitus.\(^22\)

The response of the limbic system to tinnitus may have a subcortical origin. The reticular nucleus of the brainstem and
surrounding structures, such as the LC and raphe nucleus, have been suggested to be involved in the generation of subcortical limbic and autonomic responses. Hyperactivity of the DCN may contribute to anxiety responses to tinnitus. The hyperactivity in the DCN, by lesions of the OHC, is the hypothesis of a possible link of cochlear dysfunction, cochlear nucleus, and LC. This association was not verified in the present study when comparing the SG patients with normal and altered OAE with the presence or absence of anxiety and depression. Serotonergic neurons in the dorsal raphe nucleus project to the DCN, especially in its spindle and molecular cell layers. The common association between tinnitus and depression may thus reflect disturbances of the serotonergic system in the dorsal raphe nucleus. The lack of association between the OAE results and anxiety and depression in SG suggests that these variables are independent. In the presence of cochlear lesions, cortical plastic changes contribute to the sensation and perception of tinnitus, as well as to its maintenance in the absence of a peripheral stimulus. Cochlear dysfunction can induce changes in the central nervous system (tonotopic map) that are caused by deafferentation even in patients with a normal hearing threshold, generating and perpetuating tinnitus.

The finding of approximately 30% normal OAE test results in tinnitus patients and of 23.9% altered results in patients without tinnitus suggests that multiple mechanisms are responsible for tinnitus generation and that there is no single cause of this condition. On the other hand, OHC dysfunction is neither necessary nor sufficient for the generation and perpetuation of tinnitus in some patients.

Several regions of the brain play a role in the auditory processing and cognitive aspects of tinnitus. This supports the hypothesis that a central mechanism is involved in the processing of peripheral auditory signals. Emotion, memory, and attention are therefore active in the perception of tinnitus. According to the neurophysiological model of tinnitus, the auditory pathways are not passive transmitters of the auditory signal but interact with various subsystems in the nervous system. The annoyance of tinnitus is the result of the integration of a neural network that involves the limbic system, auditory memory, habituation in the hypothalamus and emotional centers, and sensory processing and attention. The origin of tinnitus is multifactorial, and the interpretation of annoyance does not appear to depend on its cause but is rather associated with cognitive functions, with its perception and exacerbation in situations of anxiety and depression. This might involve genetic factors in the limbic and autonomic nervous systems that are connected to the auditory pathways to give rise to a common central pathway.

In conclusion, altered TEOAE and DPOAE results in patients with tinnitus and normal hearing suggest the involvement of cochlear dysfunction in the generation of tinnitus. In the present study, tinnitus annoyance was correlated with anxiety and depression disorders in patients with tinnitus and normal hearing. No correlation was observed between OHC dysfunction evaluated by OAE tests and annoyance of tinnitus, anxiety, or depression.

Author Contributions
Ronaldo Campos Granjeiro, collected data, analyzed data, wrote article and revised article; Helga Moura Kehrle, collected data, designed study; Taciana Sarmento Cardoso de Oliveira, analyzed data, revised article; Andre Luiz Lopes Sampaio, collected data, designed study; Carlos Augusto Costa Pires de Oliveira, analyzed data, revised article.

Disclosures
Competing interests: None.
Sponsorships: None.
Funding source: None.

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