Transient evoked otoacoustic emissions and cochlear dysfunction

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Abstract Amplitude measurement and reproducibility of Transient-otoacoustic emissions (T-EOAE) depend on synchronicity and functional integrity of cochlear outer hair cells, thus, the main objective of this study was to determine the usefulness of amplitude measurement and reproducibility in five selective frequencies of T-EOAE in patients with Sensorineural hearing loss (SNHL). We studied 44 subjects with SNHL by means of T-EOAE and Brainstem auditory evoked potentials (BAEP), and compared the results with those of a six control-normal-hearing subject group. We observed significant differences in the reproducibility of T-EOAE and in amplitudes of 0.7, 1.5, 2.2, 3.0 and 3.7 kHz. In addition, we observed negative significant correlations between BAEP threshold and T-EOAE reproducibility and with all specific amplitude measurement frequency values. These results confirm the clinical usefulness of reproducibility and selective amplitude measurement of frequency of T-EOAE for SNHL identification.

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1. Introduction

Hearing loss is the most prevalent sensory deficit in humans.1 Frequency of hearing loss increases with age: 5% in adults < 45 years of age, and 60% in adults ≥ 70 years of age. The most common type of hearing loss in adults is sensorineural.2 The majority of researchers have used a classic audiometric test to search for Sensory-neural hearing loss (SNHL), but recently new techniques such as High-frequency audiometry and Threshold-equalizing-noise test, have been used for the early detection of SNHL.3,4 Other audiologists have used Otoacoustic emissions (OAE) to search for abnormal cochlear function.5,6 Recently, high-frequency OAE has been used to detect high-frequency SNHL.7 Some identified causes of SNHL are treatable, but basically SNHL requires a laboratory confirmation, in the majority of cases it is difficult to recognize the etiology if the patient’s medical history and physical examination show normal results. Thus, we need better studies with greater sensitivity to recognize subjects with SNHL as early as possible.8
Evoked OAE (EOAE) are low-intensity acoustic signals proceeding from the inner ear when this is stimulated with acoustic transient tones.\textsuperscript{9,10} The diagnostic usefulness of EOAE in audiology has proven the fact that only healthy cochlear systems are able to produce emissions, whereas nearly every cochlear hearing loss leads to a decrease or disappearance of EOAE.\textsuperscript{11,12} Since Kemp (1978) had first described Transient-EOAE (T-EOAE), the test has been used extensively in pediatric and adult populations for clinical and research applications.\textsuperscript{13,14} Among different types of EOAE; T-EOAE, and Distortion products of EOAE (DP-EOAE) have received particular attention, because they can be easily detected.\textsuperscript{14} EOAE can be modified by age and gender.\textsuperscript{15}

T-EOAE, can provide important information concerning the normal or abnormal condition of the Outer hair cells (OHC); for example, these are the main targets of high-level sound exposure\textsuperscript{16} or ototoxic drug treatment.\textsuperscript{17,19} Indeed, some researchers have suggested that T-EOAE may provide earlier evidences of cochlear damage than Brainstem auditory evoked potentials (BAEP).\textsuperscript{20} Their high test–retest reliability coupled with their accuracy and objectivity in assessing cochlear function permits their use in monitoring dynamic changes in cochlear responsiveness before these changes become functionally significant as a hearing loss. However, it should be stressed that the usefulness of testing with EOAE is limited to the evaluation of mild to moderate hearing losses.

BAEP to acoustic stimuli are used to estimate the neurophysiologic auditory sensitivity. They are generated on sequential levels of the auditory pathway in the brain stem. Clinical usefulness derives from their low intra- and inter-variability among subjects. Some BAEP studies found significant differences and are age and gender-dependent.\textsuperscript{21} Although, BAEP have been used in the screening of brainstem lesions in the auditory pathway, some researchers have found abnormal BAEP responses in cases of cerebral hearing loss.\textsuperscript{22}

Although there are several studies evaluating T-EOAE in patients with SNHL, today, we need more research to know the usefulness of reproducibility and selective amplitude frequencies at 0.7, 1.5, 2.2, 3.0 and 3.7 kHz of T-EOAE to identify SNHL, because EOAE amplitude depends on synchronicity and the functional integrity of the OHC. Thus, the main objective of this study was to determine the usefulness of reproducibility and the selective frequency of T-EOAE in patients with cochlear dysfunction. As secondary objective, due to a previously reported relationship between T-EOAE and BAEP in patients with SNHL, we searched for the force of correlations between variables of both tests in our group of patients.\textsuperscript{23}

2. Materials and methods

2.1. Subjects

We studied 50 subjects (16 males and 34 females) who presented sequentially for consultation at a tertiary-healthcare institution for hearing impairment in Mexico City during a period of one year by means of T-EOAE and BAEP studies.

Control subjects (\(n = 6\)) had to be healthy individuals without a cold at the time of evaluation or a negative history for ear surgeries. The eardrum must appear as a light-gray color or a shiny pearly-white; light should reflect off the eardrum surface in the otoscopic examination without visible pathology. Tympanometry results needed to fall within the following standard limits: middle ear pressure between \(-100\) and \(+50\) daPa, and compliance between 0.3 and 1.5 mL. All audiometric thresholds within the 250–8 kHz range were required to be \(\leq \) 25 dB HL (Hearing level). Retro-cochlear disorders were excluded by clinical history, Cranial tomography (CT) (when appropriate), and by BAEP evaluations to compare their results with those of the group of patients.

Patients (\(n = 44\)) were selected to cover a range of SNHL from mild to moderate severity due to several etiologies (e.g., congenital deafness, ototoxic drug use, Meniere’s disease, high-level noise exposure, presbycusis). Patient ages were between 44.06 \(\pm\) 9.82 years. Twenty-four patients had a bilateral SNHL, and twenty subjects had unilateral SNHL, all mainly in high frequencies. Retro-cochlear pathology was excluded by the same procedures utilized in control subjects.

Observations were carried out in accordance with Declaration of Helsinki guidelines. This study was approved by the Institute’s Research Committee with the number: NIR-112-2005, and informed consent was obtained from all subjects.

2.2. T-EOAE

T-EOAE were recorded in a soundproof room employing ILO88 equipment (Otodynamics, Ltd., UK). Stimuli were 80 \(\mu\)s non-linear, unfiltered rarefaction clicks provided by default protocol. Stimulus waveform intensity was expressed in decibel peak Sound pressure level (SPL) measured in the external ear canal at 80 dB SPL at 16 clicks/s of repetition rate. The probe (Otodynamics, Ltd., UK) was sealed in each of the external ear channels. T-EOAE were analyzed during the 20 ms following stimulation onset, averaging 260 responses in each recording session. Pass criteria were reproducibility >50% and signal–noise ratio >3 dB in four of five frequency bands (1, 1.5, 2.2, 3 and 4 kHz).

2.3. BAEP

Each subject was tested with BAEP using a Neuropack (Nihon–Koden, Japan) evoked potential recorder computer during physiological sleep. The test was performed in individuals within a sound proof room. Three standard electroencephalography (EEG) electrodes were attached to the scalp, the negative electrode on the ipsilateral mastoid, the positive on the vertex, and the neutral electrode on the contralateral mastoid. Inter-electrode impedance was always \(\leq 2\) K\(\Omega\). Electrical activity between the vertex and the mastoid ipsilateral to stimulation was amplified \(1 \times 10^3\) and averaged over a time base of 10 ms. Band pass filters were set between 100 and 3000 Hz. The stimulus consisted of 100 \(\mu\)s bipolar clicks administrated monaurally through TDH-49 earphones (Telephonics, USA) at a rate of 20/s. Former presentation intensity was 70 dB HL and decreased in 20 dB steps downward until the isoelectric line was reached; then, stimuli were increased in 10 dB steps to find the neurophysiological threshold. Contralateral ear masks with white noise at 30 dB below stimulus intensity were simultaneously administered to eliminate crossover responses, following suggestions of international standards.\textsuperscript{24} Stimuli average was 2024 clicks and this process was repeated at least once to ensure re-
response reproducibility; rejected criteria included trials containing EEG signals with amplitudes > 20 μV from baseline that were cut-out from the averaging process. Latencies of waves I, III and V were measured by a manual cursor placement at the left and right ear recordings separately, and I–III, III–V and I–V inter-wave intervals were calculated off-line.

### 2.4. Data analysis

We calculated data from T-EOAE and BAEP averaged from right and left response in control subjects (n = 6). For comparison purposes we used averages from both ears (n = 12 healthy ears). In subjects with bilateral SNHL, we used average data from both ears (24 patients = 48 ears with SNHL), while in subjects with unilateral SNHL (20 patients = 20 ears with SNHL) we utilized data only from damaged ear (n = 68 ears with SNHL). Quantitative variables included: reproducibility percentage; sound pressure level amplitude, and signal/noise ratio at 0.7, 1.5, 2.2, 3.0 and 3.7 kHz of T-EOAE, and BAEP thresholds; latencies of waves I, III, V; and latencies of intervals I–III, III–V, I–V of BAEP response. We calculated mean and Standard deviation (SD) of each variable and were compared by Student’s t test. Amplitude comparison of T-EOAE and BAEP responses in Controls and subjects with SNHL was carried-out by means of \(X^2\) analysis. Afterward, we performed Pearson’s correlation analyses between BEAP and T-EOAE parameters; alpha value a priori was set at ≤0.05.

### 2.5. Theory/calculation

Our work hypothesis was based on the premise that T-EOAE amplitudes of each selective frequency are proportional to the total number of residual active sites in the organ of Corti, i.e., to the total length of active basilar membrane. According to our data, it was shown that this type accounts for the effects disclosed by statistical analysis and fits the experimental data. It can be applied in the future for quantitative cochlear analyses predicting patient’s residual activity.

### 3. Results

#### 3.1. General data

Median of age in the control group was 40 years of age (range: 37–42), and in SNHL group was 46 years of age (range: 22–61). All CT in control and SNHL subjects revealed normal results. T-EOAE had a reproducibility in the control group of 91.83 ± 6.24% and in the SNHL group, 52.75 ± 30.68% (t = 6.60, p < 0.001).

#### 3.2. T-EOAE

T-EOAE response amplitudes and signal/noise ratio at 0.7, 1.5, 2.2, 3.0 and 3.7 kHz are presented in Table 1. All amplitudes showed significant differences among groups, with amplitudes two times greater when comparing the control with the SNHL group. Comparison of difference in amplitude between Controls and subjects with SNHL was statistically significant (\(X^2 = 44.95, p < 0.05\)).

#### 3.3. BAEP

Threshold average in BAEP response in the control group was 30.0 ± 0.0 dB, while the SNHL group yields an average BAEP

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Control (x, SD)</th>
<th>SNHL (x, SD)</th>
<th>t (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td>Amplitude</td>
<td>Signal/noise ratio</td>
<td>Signal/noise ratio</td>
</tr>
<tr>
<td>0.7</td>
<td>116.0 ± 13.26</td>
<td>58.56 ± 37.29</td>
<td>7.22 (&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>8.90 ± 8.14</td>
<td>7.60 ± 6.64</td>
<td>n.s.</td>
</tr>
<tr>
<td>1.5</td>
<td>125.33 ± 6.53</td>
<td>70.56 ± 43.46</td>
<td>7.51 (&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>13.70 ± 8.82</td>
<td>12.65 ± 6.38</td>
<td>n.s.</td>
</tr>
<tr>
<td>2.2</td>
<td>122.33 ± 7.73</td>
<td>57.53 ± 41.55</td>
<td>8.97 (&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>16.70 ± 8.01</td>
<td>15.50 ± 5.39</td>
<td>n.s.</td>
</tr>
<tr>
<td>3.0</td>
<td>117.16 ± 15.65</td>
<td>56.63 ± 42.16</td>
<td>6.59 (&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>16.42 ± 8.39</td>
<td>15.40 ± 8.46</td>
<td>n.s.</td>
</tr>
<tr>
<td>3.7</td>
<td>101.33 ± 36.62</td>
<td>49.31 ± 37.19</td>
<td>3.24 (0.015)</td>
</tr>
<tr>
<td></td>
<td>17.10 ± 6.18</td>
<td>15.70 ± 8.86</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = not significant.

<table>
<thead>
<tr>
<th>Group</th>
<th>Wave I (ms)</th>
<th>Wave III (ms)</th>
<th>Wave V (ms)</th>
<th>Interval I-III (ms)</th>
<th>Interval III-V (ms)</th>
<th>Interval I-V (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Right 1.49 ± 0.16 3.74 ± 0.21 5.52 ± 0.20 2.24 ± 0.12 1.82 ± 0.11</td>
<td>4.10 ± 0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left 1.43 ± 0.49 3.92 ± 0.28 5.48 ± 0.28 2.29 ± 0.18 1.89 ± 0.14</td>
<td>4.19 ± 0.19</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SNHL</td>
<td>Right 1.70 ± 0.23 3.89 ± 0.40 5.78 ± 0.48 2.18 ± 0.27 1.88 ± 0.34</td>
<td>4.10 ± 0.37</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Left 1.57 ± 0.21 3.78 ± 0.24 5.72 ± 0.27 2.21 ± 0.20 1.85 ± 0.15</td>
<td>4.06 ± 0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ms = milliseconds, n.s. = not significant.
threshold response of $49.71 \pm 19.47$ dB ($t = -5.98$, $p < 0.001$), audiometric syntheses (arithmetic mean of threshold at 500, 1000 and 2000 Hz frequencies) threshold average in SNHL group was $45.32 \pm 21.18$ dB HL. Because we obtained a better wave V morphology at 100 dB in BAEP studies in the SNHL group, we compared wave V between groups of study at this intensity. Data from latencies of the main waves and inter-wave intervals are presented in Table 2 and were also compared. No significant difference was observed in both measurements. Comparison of difference in BAEP amplitude between Controls and subjects with SNHL was statistically significant ($X^2 = 44.95$, $p < 0.05$).

3.4. Correlation analyses

Correlation analyses yielded negative significance values between BAEP threshold and T-EOAE reproducibility ($-0.576, < 0.001$) in all specific frequency values (see Table 3).

4. Discussion

4.1. Main findings

Significant differences in T-EOAE reproducibility and selective frequency analyses between control and SNHL groups were disclosed in this study. These results confirm the clinical usefulness of T-EOAE for SNHL identification and are in agreement with many research works in the same line. Frequency selectivity-analyses usefulness in T-EOAE contained in the default report was utilized, and to our knowledge this fact is reported here for the first time. On the other hand, BAEP threshold, T-EOAE reproducibility, and the amplitudes of all specific frequencies showed a significant correlation, suggesting that BAEP threshold determination aids in the same direction as T-EOAE in the search for SNHL and both studies are complementary.

4.2. Results explanation

Potential relationships between T-EOAE and tuning mechanisms that apparently involve only a small number of OHC, demand another investigation. Peripheral damage-related hearing loss is associated with cochlear OHC damage or loss and some retrograde degeneration of auditory nerve fibers. Surviving auditory nerve fibers in the impaired region present elevated and broadened frequency tuning, and thus the cochleo-topic representation of broad-band stimuli such as speech is distorted. In impaired cortical regions, increased tuning to frequencies near the edge of the hearing loss coupled with increased spontaneous and synchronous firing was also viewed.

The T-EOAE threshold is only sensitive to already important cochlear changes and this boundary does not afford a follow-up of early-stage cochlear dysfunction. Several researchers have used the method of amplitude analysis of the T-EOAE. Rahko et al. (1997), performed an analysis with the Matlab 4.2 system with a filter bank that provides graphically created 2D and 3D views of responses in the frequency, time and amplitude coordinates. The T-EOAE were normally modeled as the sum of many waveforms. Guo et al. (1999), found from the comprehensive analysis of spectrum, response amplitude and reproducibility, that these variables can be used as main sensitive parameters of T-EOAE to evaluate whether or not is a normal-hearing. Jedrzejczak et al. (2009), studied several functions to incorporate new T-EOAE waveform analysis; the matching pursuit functions of waveforms were described by five parameters, namely: frequency, latency, time span, amplitude, phase, and asymmetry. These results from other research groups support partially the use of amplitude analysis, that we conducted here in our study.

On the other hand, we found a great overlap between normal and impaired distributions of the signal/noise ratio. Comparison of signal/noise ratio in Controls and subjects with SNHL was not statistically significant. This fact suggests that signal/noise ratio measurements are not a significant variable to identify subjects with SNHL. However, other researchers found results in the contrary direction. Thus, we must be careful to ensure this statement firmly. More research is needed to answer this question.

BAEP threshold showed a good correlation with each selective T-EOAE frequency, although BAEP responses are obtained with a broad band stimuli, such as a click, several researches showed that the major energy of click is in the 2000–4000 Hz frequency region. This perhaps helps us to understand why there were better correlations between BAEP parameters and responses of T-EOAE at 1500, 2000 and 3000 Hz in subjects with SNHL, and complete the second objective of this paper. Regarding analysis between the two test parameters (BAEP and T-EOAE reproducibility percentage), it was interesting to see that the data were complementary. Higher the BAEP threshold, lower is the percentage of repeatability of T-EOAE. This result is in line with several observations from other researchers, such as those observed in neonates. Recently, the T-EOAE and BAEP relationship has been investigated. Brief tones of 1.0 and 8.0 kHz were used to produce BAEP, and the differences between the wave-V latencies for those two frequencies were used as a proxy for cochlear length. The proxy values for length were compared with various measures of OAE obtained from the same ears. Although, correlations were low, were significant, suggesting that cochlear length measured by this proxy at least, is related to the various group and individual differences that exist in OAE. Thus, T-EOAE and BAEP are robust tools for hearing examination of patients with SNHL.

Clinical implications are promising. Our data suggest that clinicians must be alert to T-EOAE reproducibility percentage when they studied subjects with mild to moderate SNHL, because the test yields comparable results to BAEP. We suggest that in future, research in T-EOAE focus on parameters
useful for early detection of SNHL,\(^\text{36}\) such as data presented here.

4.3. Limitations of the study

However, our study has some limitations, i.e. the low number of subjects studied and thus our data must be considered as a tendency and not as strong conclusions. In the other hand, the cross-sectional study design employed instead of a prospective follow-up limits the power of our results. In further studies we will use longitudinal observations with significant more observations in patients with SNHL.

5. Conclusions

In conclusion, our data support the usefulness of reproducibility of selective amplitude frequencies at 0.7, 1.5, 2.2, 3.0 and 3.7 kHz of T-EOAE to identify SNHL, and the help of BAEP parameters combined with T-EOAE in the evaluation of patients with SNHL. Further study will be necessary to examine closely in more patients these correlations and their clinical use in the patients with SNHL.

References


