Monitoring and Predicting Ototoxic Damage Using Distortion-Product Otoacoustic Emissions: Pediatric Case Study

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Abstract
Young children undergoing cisplatin chemotherapy are known to be at risk for progressive sensorineural hearing loss. Early detection of such hearing loss is important for providing management options. However, in ill and/or young children, behavioral audiometry may not be sufficiently precise to detect the early stages of hearing loss. This case illustrates that distortion-product otoacoustic emissions (DPOAEs) may be an appropriate cross-check measure to supplement and confirm pediatric behavioral data. Perhaps more importantly, this study suggests that DPOAEs may have the potential to predict the earliest stages of progressive hearing loss before such changes are seen in audiometric thresholds.

Key Words: Distortion-product otoacoustic emissions, ototoxicity, progressive hearing loss

Abbreviations: DPOAEs = distortion-product otoacoustic emissions, OAEs = otoacoustic emissions, OHC = outer hair cell, TEOAEs = transient evoked otoacoustic emissions

Sensorineural hearing loss has been reported in 50 percent (Brock et al., 1988) to 95 percent (Skinner et al., 1990) of children who are undergoing cisplatin chemotherapy. The losses tend to progress from 6000 and 8000 Hz to lower frequencies (Pasic and Dobie, 1991). However, behavioral audiometry in ill and/or young children may not be sufficiently precise to detect the initial stages of hearing loss, particularly at higher frequencies. An objective and accurate cross-check measure is needed for such monitoring. Otoacoustic emissions (OAEs) might be appropriate tools for this purpose because (a) cisplatin damages cochlear outer hair cells (OHCs) (Fleishman et al., 1975); (b) OAEs are sensitive to cochlear hearing loss associated with OHC damage (Long and Tubis, 1988; Brown et al., 1989; Brownell, 1990); and (c) OAEs appear to be sensitive to cisplatin ototoxicity in animals (McAlpine and Johnstone, 1990) and humans (Probst et al., 1993; Zorowka et al., 1993).

For monitoring purposes, distortion-product otoacoustic emissions (DPOAEs) would seem preferable to transient evoked otoacoustic emissions (TEOAEs) because DPOAEs provide better results at higher frequencies (Gorga et al., 1993), where cisplatin ototoxicity is first seen in children (Schell et al., 1989; Skinner et al., 1990; Pasic and Dobie, 1991).

The following case presentation illustrates the utility of DPOAEs for monitoring cisplatin ototoxicity in young children. Perhaps more importantly, this case demonstrates that DPOAEs may have some ability to "predict" the progression of hearing loss before the shift in pure-tone threshold occurs.

CASE REPORT

The subject of this report was diagnosed with medulloblastoma at 4½ years of age. Total resection of the tumor was achieved via posterior fossa approach. The patient was subsequently enrolled in a Pediatric Oncology Group.
Table 1 Medulloblastoma Treatment Protocol

<table>
<thead>
<tr>
<th>Dates</th>
<th>Treatment</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/20/95 to 11/7/95</td>
<td>Radiation (90 mg/mg2) and etoposide (300 mg/m2)</td>
<td>5320 cGy</td>
</tr>
<tr>
<td>12/12/95 to 2/2/96 (3 courses)</td>
<td>Cisplatin (90 mg/mg2) and etoposide (300 mg/m2)</td>
<td>270 mg/m²</td>
</tr>
<tr>
<td>2/22/96 to 9/20/96 (8 courses)</td>
<td>Cyclophosphamide (2000 mg/m2) and vincristine (1.5 mg/m2)</td>
<td>900 mg/m²</td>
</tr>
</tbody>
</table>

The ototoxicity of cisplatin (Schweitzer, 1993) and, to a lesser extent, vincristine (Mahajan, 1981; Lugassy, 1990) is well documented. Furthermore, prior cranial irradiation is known to potentiate cisplatin ototoxicity (Sexauer et al, 1985; Walker et al, 1989; Weatherly et al, 1991). Therefore, pre- and post-treatment audiologic monitoring was included in the treatment protocol.

METHOD

Audiometric evaluations included pure-tone air- and bone-conduction audiometry (using play techniques), an acoustic immittance battery, and DPOAEs (the cubic distortion product, $2f_1-f_2$). Due to patient fatigue, speech audiometry could not be completed until test 3. DPOAEs were collected with $f_1$ and $f_2$ levels of 65 and 50 dB SPL, respectively. The frequency ratio of the primaries ($f_2/f_1$) was 1.22. Ear canal calibration data were monitored to ensure that adequate stimulus energy was present at each frequency. Absent or reduced amplitude DPOAEs (less than 5 dB above the two standard deviation noise floor) were considered to be truly abnormal only if the ear canal sound pressure level of the primaries was within 5 dB of nominal levels. DPOAEs were accepted as normal if the primaries were no more than 10 dB below nominal levels and if $2f_1-f_2$ amplitude was 5 dB or more above the two standard deviation noise floor.

Figure 1 Baseline audiometric test results. Tympanograms and acoustic reflexes were within normal limits bilaterally. For this and for subsequent DPOAE plots at the bottom of Figures 2 and 3, DPOAE amplitude (circles connected by lines) is displayed as a function of frequency. The upper shaded area represents two standard deviations above the mean noise floor. DPOAE collection parameters are detailed in the Methods section.
Predictive Value of DPOAEs/Littman et al

TEST 2 (2-22-96)

RIGHT EAR

DB HL

250 500 1 kHz 2 kHz 4 kHz

Distortion Product-gram

LEFT EAR

DB HL

250 500 1 kHz 2 kHz 4 kHz

Distortion Product-gram

Figure 2 Test 2, following treatment radiation, cisplatin, and etoposide. Tympanograms and acoustic reflexes were within normal limits bilaterally. Bone-conduction thresholds were equivalent to air-conduction thresholds. DPOAE collection parameters are detailed in the Methods section.

RESULTS

Baseline audiometry, shown in Figure 1, reflects normal sensitivity and normal DPOAEs bilaterally. In the ear canal, the amplitude of f2 at 6000 Hz for the right ear was 6.8 dB below the nominal level of 50 dB SPL, possibly accounting for the somewhat diminished emission at that frequency. The amplitude of f2 could not be increased by refitting the probe, apparently due to idiosyncratic ear canal resonance characteristics. Nonetheless, the 6000-Hz emission is considered normal by our clinic's criteria because it exceeds the two standard deviation noise level by more than 5 dB. Acoustic immittance findings were normal for this evaluation and for all subsequent retests. The immittance data have been omitted from the figures to conserve space.

Audiometric results following completion of cisplatin and etoposide treatment are presented in Figure 2. A bilateral high-frequency sensorineural loss is apparent. DPOAEs were absent for the right ear at and above 1500 Hz and were absent or abnormal for the left ear at and above 2000 Hz. Note that DPOAEs were abnormal bilaterally at 2000 and 3000 Hz, despite audiometric thresholds of 10 and 15 dB HL for those frequencies in both ears. Bone-conduction thresholds were consistent with air-conduction thresholds but were omitted from the figures for the sake of clarity.

The results of test 3, following completion of cyclophosphamide and vincristine therapy, are presented in Figure 3. The high-frequency sensorineural loss had progressed in both ears. Note that the loss now included 2000 and 3000 Hz, despite audiometric thresholds of 10 and 15 dB HL for those frequencies in both ears. Bone-conduction thresholds were consistent with air-conduction thresholds but were omitted from the figures for the sake of clarity.

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The left ear emissions in Figure 3 remained abnormal for the higher frequencies, while lower frequency emission amplitude increased, relative to test 2. The left ear DPOAE at 2000 Hz appeared to have recovered partially and was now 2.2 dB above the noise floor (this emission might have been larger, but the noise floor at 2000 Hz was greater at test 2 than at the baseline). This subject’s most recent evaluation indicated that the hearing loss was stable, and the DPOAEs have shown no further recovery.

The relationship between DPOAEs and pure-tone thresholds at 2000 Hz is shown in Figure 4. This figure clearly indicates that the DPOAE amplitude dropped into the noise in test 2 before a significant threshold shift was observed at test 3. Figure 5 reflects a similar pattern at 3000 Hz, where DPOAE amplitude dropped into or near the noise floor while sensitivity remained normal during test 2. Sensitivity at 3000 Hz subsequently declined by 45 and 35 dB for the right and left ears, respectively, at test 3.

**DISCUSSION**

In this case study, DPOAEs were sensitive to the earliest stages of ototoxicity. DPOAEs were abnormal for frequencies at which sensorineural hearing loss exceeded 20 dB HL, consistent with group studies in which similar recording parameters were employed (Gorga et al, 1993; Sun et al, 1996). DPOAEs would therefore seem to be an appropriate cross-check measure for monitoring ototoxicity due to cisplatin and other agents. Furthermore, after a complete audiometric baseline has been established, it may be feasible to monitor periodically using DPOAEs alone. Additional audiometric data would then be obtained only when DPOAEs dropped below baseline levels. In this way, monitoring might be more rapid, less expensive, and less taxing for a patient who often is not feeling well.

Perhaps of greater interest, this case study suggests that DPOAEs may be more sensitive to incipient cochlear damage than behavioral thresholds. The striking pattern in Figures 4 and
Figure 4 The relationship between pure-tone thresholds at 2000 Hz and DPOAEs for $f_2 = 2000$ Hz. DPOAE amplitude is displayed in terms of signal-to-noise ratio (amplitude of the emission above the two standard deviation line of the noise floor). Note that the DPOAE dropped into the noise floor at test 2, while no significant change was seen in the pure-tone threshold for the right (a) and left (b) ear. The DPOAE for the left ear "recovered" somewhat at test 3 and is now 2.4 dB above the noise floor.

Figure 5 The relationship between pure-tone thresholds at 3000 Hz and DPOAEs for $f_2 = 3000$ Hz. DPOAE amplitude is displayed in terms of signal-to-noise ratio (amplitude of the emission above the two standard deviation line of the noise floor). Note that the DPOAE dropped into the noise floor at test 2, while no significant change was seen in the pure-tone threshold for the right ear (a). For the left ear (b), the DPOAE dropped to within 2.6 dB of the noise (a drop of 18.2 dB from baseline), with no significant change in pure-tone sensitivity.

5 is that DPOAE amplitudes fell into or near the noise floor before behavioral threshold changes were noted at corresponding frequencies. In this sense, the DPOAEs may be predictive, foretelling a substantial threshold shift for a given frequency prior to a measurable sensitivity loss. Because 11 months elapsed between monitoring sessions, we cannot speculate on how much time actually elapsed between the DPOAE drop and a pure-tone sensitivity shift.

Warning of impending hearing loss could be useful for the oncologist, who might have the option of adjusting the chemotherapy to a potentially less ototoxic regimen. Likewise, early indicators of threshold shift would be useful for planning audiologic management and counseling.

We speculate that the "predictive" drop in the DPOAE reflects the progression of hair cell damage. Thus, at the initial stage of toxicity, the chemotherapy agents may only damage one or two rows of OHCs, affecting DPOAEs but not threshold sensitivity. Subsequently, as the drugs damage the remaining OHCs in that $f_2$ frequency region, pure-tone sensitivity is reduced.

A limitation of this case study is that only two postbaseline measures were obtained. As a result, we do not have a clear picture of the time course of this phenomenon. We cannot determine the temporal interval by which the DPOAE drop precedes the sensitivity change. Similarly, we cannot comment on whether the DPOAE and pure-tone changes were gradual or precipitous.

The case described herein is not an isolated one. We now have similar data from 14 children (9 undergoing cisplatin chemotherapy and
5 with congenital cytomegalovirus infection), demonstrating the predictive ability of DPOAEs. It therefore seems that DPOAEs may have the potential to predict the earliest stages of progressive cochlear hearing loss.

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REFERENCES


