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"MONITORING OF HEARING BY DISTORTION PRODUCT OTO-ACOUSTIC EMISSION IN CHILDREN WITH DRUG-RESISTANT TUBERCULOSIS –IN VIVO STUDY"

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KEYWORDS :

Introduction:

The treatment of drug-resistant (DR)-tuberculosis (TB) necessitates the use of second-line injectable anti-TB drugs which are associated with hearing loss. Hearing loss affects communication and the development of language and social skills in children. The World Health Organization (WHO) estimates that there are 650,000 cases globally of multidrug-resistant (MDR) tuberculosis (TB) (*Mycobacterium tuberculosis* resistant to rifampicin and isoniazid).

A small proportion of these cases are diagnosed and appropriately treated but with the imminent roll-out of newer molecular diagnostic tools, a much larger proportion is likely to be treated. The treatment of drug-resistant (DR)-TB requires the use of second-line anti-TB medications many of which are associated with significant adverse events. The injectable drugs, aminoglycosides and polypeptides are associated with a risk to renal function, hearing and the vestibular system. Nephrotoxicity is generally reversible but damage to the auditory and vestibular systems is usually permanent.

The monitoring of hearing loss is important for two reasons. First, if detected early it may be possible to alter the regimen to stop or reduce the dose of the responsible drug, preventing progression of hearing loss to the point where it would impact on communication. Secondly, if significant hearing loss has developed and is detected, interventions can be implemented to assist in communication. These include hearing aids, cochlear implants or other hearing impaired tools, teaching and training. Despite the increasing literature on DR-TB over the last 20 yrs, few studies have investigated hearing loss in patients undergoing treatment.

Physiology of Hearing:

Sounds, in the form of vibrations, impact on the pinna of the ear and are transmitted down the auditory channel to the tympanic membrane. The vibrations are transmitted through the auditory ossicles (the malleus, incus and stapes) onto the hair cells of the basilar membrane within the organ of corti, situated within the cochlea. Signals are transmitted by the cochlear nerve to the brainstem and from there to the cortex where they are interpreted into meaningful sounds. Blockages within the channel, such as wax or discharge can impede this process. Perforations of the tympanic membrane or effusions behind it (otitis media with effusion) and acute or chronic otitis media, can also affect transmission. Both chronic otitis media and tympanic perforations are common in many of those on treatment for DR-TB, hearing evaluation must take this into consideration.

The injectable anti-TB drugs selectively destroy the basal hair cells of the basilar membrane, which are required for high-frequency hearing. This occurs by reacting with transition metal ions to produce reactive oxygen species which in turn damage the cells through an oxidative process. Hearing loss in those treated with aminoglycosides and polypeptides usually starts with high-frequency loss first, with later progression to the frequencies more associated with speech communication. Damage is usually permanent. These drugs can also destroy the hair cells of the vestibule.

Methods:

2.1 Subjects

The subjects were children undergoing treatment for tuberculosis at Govt. Medical College Hospital Raigarh Chhattisgarh as part of a frontline protocol. Initially, fifteen children were scheduled for DPOAE monitoring tests, but these tests could not be completed in three children due to scheduling issues. Two additional children did not receive DPOAE monitoring tests because of known active cases of otitis media. The final sample was comprised of 10 children (five females, five males) taking tuberculosis treatment. The age (rounded to the nearest month) of the children at the onset of treatment ranged from 62 to 75 months. Prior to enrollment in the study, the parents/legal guardians of the children signed informed consent forms. The demographic details of the children are shown in Table 1.

Subject	Age of Onset of Treatment	Gender	Number of Antibiotic Courses	Ototoxic change in DPOAE
S01	62 months	Female	2	No
S02	70 months	Male	3	Yes
S03	75 months	Female	4	No
S04	65 months	Female	3	Yes
S05	68 months	Male	2	No
S06	81 months	Female	3	No
S07	62 months	Male	3	Yes
S08	70 months	Female	4	No
S09	63 months	Male	2	Yes
S10	66 months	Male	4	No

Table 1: Demograohic details of subjects

2.2 Drug Dosage Schedule

All subjects were under medication and medicines administered were Inj. Kanamycin – 750 mg IM-OD (aminoglycoside), Tab. Levofloxacin – 750 mg OD (fluoroquinolone antibiotics), Tab. Ethionamide – 1000 mg OD (antibacterial agent), Tab. Pyrazinamide – 1500 mg OD (anti-tuberculosis agent) and Tab. Ethambutol – 1200 mg OD (antibacterial agent). The individual was on these drugs for last 10 month.

2.3 Ototoxicity Monitoring

Audiological tests were conducted at Govt. Medical College and Hospital Raigarh Chhattisgarh. After otoscopic examination by otolaryngologist the Distortion product oto-acoustic emission test administered using Otodynamic instrument. DPOAE tests in children 62 months of age at the onset of treatment were conducted in a surgical suite. The older child was tested in a double-walled sound-treated booth. All of the children completed the monitoring protocol during a baseline evaluation and an interim evaluation. For nine of the 10 children, the baseline evaluation took place prior to tuberculosis treatment. In the remaining child, the baseline evaluation was conducted one week after the child received one course of antibiotics. The interim evaluation in all children was conducted following the course of tuberculosis.

During the baseline and interim evaluations, eight children were sedated during testing. One child was tested during natural sleep, and the remaining child (the oldest) was tested after completing pure-tone audiometry. In this child, hearing thresholds were obtained at the baseline and interim tests using a standard clinical procedure with a diagnostic audiometer. Middle-ear function was assessed in both ears of each child using tympanometers capable of obtaining

measurements with 226- or 1000-Hz probe tones. Tympanometry results suggested normal middle-ear function bilaterally in the children at the time of the baseline and interim evaluations. This was indicated by the presence of single-peaked 226- and/or 1000-Hz tympanograms with a maximum admittance near 0 deca Pascals. Measurements of DPOAEs were obtained from both right and left ears of each child with an otoacoustic emission analyzer (Otodynamics, ILO 296) interfaced with a laptop computer. The ILO probe was calibrated using the 1-cc cavity provided by the manufacturer prior to each baseline and interim test. The primary-tone stimuli for 2*f*1-*f*2 DPOAE measurements were generated by the ILO v6 software program at targeted sound pressure levels (SPL) of 65 dB SPL (*L*1) and 55 dB SPL (*L*22 level was lowered to 45 dB SPL at the baseline and interim tests due to a technical error. The primary tones were stepped across an *f*2 frequency range of 793–7996 Hz at a fixed *f*2: *f*1 ratio of 1.22 and with a resolution of 3 points/octave. In order to assess the adequacy of the probe fit in the ear canal for the purposes of meeting targeted primary-tone levels, a checkfit procedure preceded actual measurements of DPOAEs. This procedure measures the ear-canal sound pressure at a distance from the tympanic membrane. It is recognized that in adults, setting of the primary-tone level may be influenced by standing waves, particularly at higher frequencies. The checkfit procedure utilized in this study was limited in accounting for the influence of standing waves. When the checkfit procedure was completed, distortion-product grams (DP-grams) were obtained by plotting the levels (in dB SPL) of the 2*f*1-*f*2 DPOAEs as a function of *f*2 frequency.

Estimates of the noise floor were made by determining the mean level of five frequency bins above and below the 2*f*1-*f*2 DPOAE frequency bin. No automated stopping rules were utilized, due to time constraints in many of the children who were under sedation at the time of the test. Instead, the tests were manually terminated once the DPOAE levels were determined to be stabilized through visual inspection of the DP-gram. In order to be counted as a valid response, the level of the DPOAE was required to exceed the mean level of the noise floor + 2 standard deviations by ≥ 6 dB at each *f*2 frequency. A minimum signal-to-noise ratio (SNR) of 6 dB is recommended when DPOAEs are used to monitor cochlear status over time.

2.4 Data Analysis

The data were analyzed using the Statistical Analysis Software (SAS) version 9.2. A significance level of 0.05 was adopted for all statistical tests, while multiple tests were adjusted using the Bonferroni correction. The DPOAE levels were averaged across right and left ears at each *f*2 frequency in children exhibiting valid DPOAEs in both ears, resulting in mean DPOAE levels. Wilcoxon signed-rank tests showed there was no significant difference in DPOAE levels between right and left ears. Therefore, the DPOAE levels were collapsed across ears in order to avoid increasing type I error due to lack of independence between ears according to the recommendation of Coren and Hakstian. Wilcoxon signed-rank tests were conducted on mean DPOAE levels measured at the baseline and interim evaluations in order to determine if any significant differences were registered between these conditions. Since DPOAE levels can be altered due to changes in the level of primary-tone stimulation alone, it is important to recognize if primary-tone levels in dB SPL were similar at the baseline and interim evaluations. Mean primary-tone levels (*L*1 & *L*2) estimated in the ear canal at the baseline and interim evaluations were also evaluated with Wilcoxon signed-rank tests. Another factor that may influence DPOAE levels is the noise floor. In order to determine the similarity of noise floor levels (in dB SPL) at the baseline and interim evaluations, Wilcoxon signed-rank tests were conducted on mean noise floor levels. In addition to mean data, potential ototoxic changes on an individual basis were examined by applying a criterion used in current practice at Govt. Medical College & Hospital Raigarh. In comparing between baseline and interim tests, the criterion for ototoxic change was defined as a ≥ 6 dB decrease in DPOAE level at two or more adjacent *f*2 frequencies in a given ear where decreases in DPOAE levels were calculated by subtracting the interim DPOAE levels from the baseline DPOAE levels for each *f*2 frequency. Currently, there is no universal agreement on the criterion for ototoxic change using OAE tests.

Sockalingam et al. calculated minimal changes in DPOAE level that exceeded the limits of test-retest reliability at individual *f*2 frequencies in children aged 5–12 years. Based on their data, the average minimal change exceeding the limits of normal variation at four *f*2 frequencies between 2530–7029 Hz was 6.47 dB. This is reasonably close to the minimal value for ototoxic change selected in this investigation. The number of ears and children with both ears for which baseline DPOAEs met or exceeded the SNR criterion at each individual *f*2 frequency are listed in Table 2. As can be seen, the SNR criterion was met in limited numbers of children at the *f*2 frequencies of 793 Hz–2515 Hz. However, the criterion was met in the majority (>75%) of children at the *f*2 frequencies of 3174 Hz, 4004 Hz, 5042 Hz, 6348 Hz, and 7996 Hz. Wilcoxon signed-rank tests were conducted on mean DPOAE levels measured at the baseline and interim conditions at the 5 highest *f*2 frequencies (3174–7996 Hz). The Bonferroni correction was applied to adjust the level of significance for the number of tests conducted (0.05/5= 0.01).

3. Results:

The first aim of this study was to examine if mean DPOAE levels acquired before and after several courses of tuberculosis multi drug antibiotic treatment were significantly different. The mean ± standard error of DPOAE levels at the baseline and interim evaluations are plotted as a function of *f*2 frequency in Figure 1.

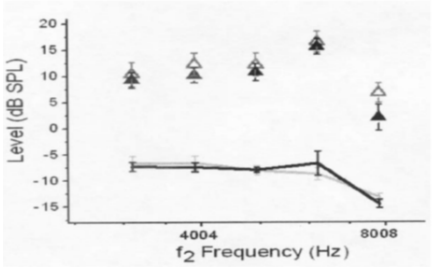

Figure: Mean DPOAE and noise levels as a function of f2 frequuency.

At the *f*2 frequency of 7996 Hz, DPOAE levels were reduced at the interim test compared to the baseline test. This observation was confirmed through statistical testing, as the results of the Wilcoxon signed-rank tests revealed that mean DPOAE levels at the baseline and interim evaluations were significantly different only at the *f*2 frequency of 7996 Hz (p=0.004) for 9 children with valid responses in both ears.

Wilcoxon signed-rank tests were also conducted separately on mean *L*1 and *L*2 primary-tone levels at corresponding *f*2 frequencies from 3174–7996 Hz evaluated at the baseline and interim tests. There were no significant differences between *L*1 levels at the baseline and interim tests or between *L*2 levels at the baseline and interim tests. The mean noise floor levels at *f*2 frequencies from 3174–7996 Hz were not significantly different at the baseline and interim tests.

Frequency-f2(Hz)	793	1001	1257	1587	2002	2515	3174	4004	5042	6348	7996
Ears	3/20	3/20	3/20	11/20	14/20	15/20	17/20	18/20	19/20	16/20	18/20
Children	1/10	1/10	1/10	5/10	8/10	6/10	8/10	8/10	9/10	8/10	9/10

Table 2: the number of ear and children meeting the + 6dB or greater SNR criterion.

The second aim of the study was to examine if criterion reductions in DPOAE levels were observed in individual children. Figures 2 and 3 illustrate decreases in DPOAE level across f2 frequency for left and right ears in each child. DPOAE level decreases ≥ 6 dB at two or more adjacent f2 frequencies in at least one ear were observed in four children (6/20 ears).

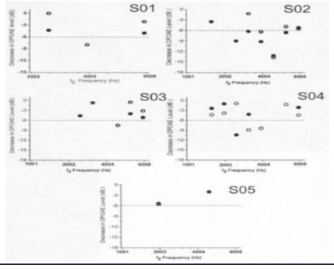

Figure 2: Plot of DPOAE level decreases as a function of f2 frequency. Criterion DPOAE level decreases were observed in both ears of S02, the right ear of S04, both ears of S07, and the left ear of S09. At f2 frequencies where criterion changes in DPOAE level were observed in these children, the lowest DPOAE SNR was 12.3 dB. This suggested that DPOAE SNRs were sufficiently high so that the minimum criterion decrease of 6 dB could easily be detected at the f2 frequencies where the changes were observed. Three out of the four children identified with criterion changes in DPOAE level received cumulative dosages of carboplatin above 1800 mg/m2 at the time of the interim test (see Table 1).

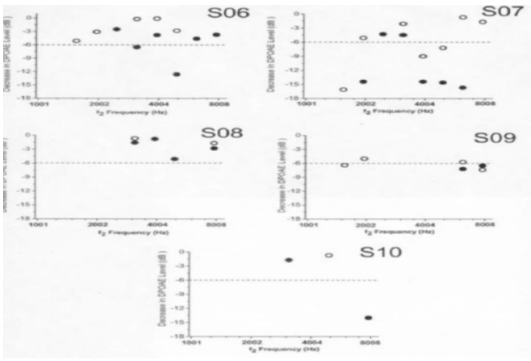

Figure 3: Plot of DPOAE level decreases as a function of f2 frequency. In one of these children (S07), behavioral hearing thresholds were obtained at the baseline and interim evaluations using a standard clinical procedure. These hearing thresholds are displayed in Table 3. As can be seen, hearing thresholds were at or better than 15 dB HL (dB re: normal hearing level) from 250–8000 Hz at the baseline test, and were at or better than 25 dB HL across the same frequency range at the interim test. On both occasions, the tympanograms from both ears of this subject were within normal limits. Figure 3 illustrates the decreases in DPOAE level seen in this subject. Decreases exceeding the 6 dB criterion were observed at adjacent f2 frequencies at or above 4004 Hz in both right and left ears. These findings suggest that reductions in DPOAE level have occurred prior to hearing loss being manifested on the audiogram in this child.

	Frequency in Hz							
Baseline	250	500	1000	2000	3000	4000	6000	8000
Right	10	10	15	15	5	10	10	5
Left	5	10	10	15	15	5	5	10
Interim	250	500	1000	2000	3000	4000	6000	8000
Right	20	25	20	15	20	25	25	20
Left	25	15	20	15	15	10	20	20

Table 3: Hearing threshold in Puretone audiometer test of S07 subject.

4. Discussion

The first aim of this pilot study was to examine if mean DPOAE levels obtained from the ears of children diagnosed with retinoblastoma during tests completed before and after several courses of tuberculosis antibiotic treatment were significantly different. The results of Wilcoxon signed-rank tests indicated that mean DPOAE levels were significantly reduced only at the highest frequency tested (f2=7996 Hz). The change in DPOAE level seen at this frequency is not likely due to variation in primary-tone stimulation or noise floor levels at the baseline and interim tests, as no significant differences in these factors were observed between measurement periods. Another explanation for the significant decrease in DPOAE level at this frequency is that exposure to kenamicin resulted in a change in OHC function. It is well known that compounds, such as ethianomine, initially affect OHC function in the basal turn of the cochlea. When ethianomine induces hearing loss, it is usually manifested first at frequencies higher than 4000 Hz. Since the children evaluated in this study received 3–4 courses of multi drug antibiotics, it is conceivable that initial changes in OHC function would be localized to higher f2 frequencies, resulting in a reduction of DPOAE levels. Further exploration of this hypothesis would be aided by examining DPOAEs acquired with primary tones higher than 8000 Hz. Although there is a considerable research effort aimed at evaluating high-frequency DPOAE tests, most of these studies have been conducted in adults with normal hearing thresholds at the conventional audiometric frequencies. Evaluation of high-frequency DPOAE tests in normal-hearing infants and young children and the creation of a normative database would facilitate the clinical application of this method, particularly in pediatric populations exposed to ototoxic agents.

The second aim of this study was to examine if criterion changes in DPOAE level would be observed in individual children while they were receiving multi drug antibiotics. Ototoxic changes in DPOAE levels were observed in four out of the 10 children monitored. There were two cases of unilateral retinoblastoma and two cases of bilateral retinoblastoma among these children. However, three of these children (S02, S04, S07) received cumulative antibiotic dosages above 1800 mg/m2 at the time of the interim test. Therefore, these higher dosages appeared to be related to children being identified with ototoxic changes in DPOAE levels. In the oldest child (S07), criterion reductions in DPOAE levels were observed in both ears, even though hearing thresholds remained within normal limits bilaterally at the time of the interim test.

The selection of the criterion defining ototoxic change for DPOAEs used in this study was arbitrary. Other investigators have recommended different criteria that define significant changes in DPOAE level. For example, Beattie et al. found that changes in DPOAE levels across measurement conditions needed to exceed 7 dB in the 1000–4000 Hz range in order to be considered statistically significant. Reavis et al. proposed that a DPOAE reduction of 4 dB or greater at adjacent f2 frequencies constituted an ototoxic change. However, both of these studies were conducted in adults, and the criterion selected for this study was more consistent with the limits exceeding normal variation in children identified by Sockalingam et al. In addition, the finding that three children receiving high cumulative dosages of carboplatin were identified as having ototoxic change in DPOAE levels was in agreement with previous research in animal models. Hofstetter et al. found OHC loss and large reductions in DPOAE levels in chinchillas were only observed for high doses of antibiotics.

5. Conclusion:

A large proportion of patients treated for DR-TB are developing hearing loss, a significant adverse event that can impair their quality of life. The effects on the development of children are profound. Additionally, WHO recently recommended extending the duration of injectable drug use from 6 to 8 months, as longer use of injectables has been found to be associated with more successful treatment outcomes.

Although the flippant expression “better deaf than dead” is frequently employed, it is rarely such a simple decision. Clinicians must carry out a risk assessment whereby the risk of hearing loss is weighed against the risk of treatment failure from stopping or not using an injectable drug. Patients need to be informed of the risks of treatment and the risks of not using injectables and permitted input into treatment decisions. New, alternative drugs are urgently needed.

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