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Review

Monitoring Chemotherapy-induced Hearing Loss in Children

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INTRODUCTION

WHEN ADULTS with normal hearing are treated with ototoxic drugs, they notice hearing difficulties subjectively if damage involves the so-called speech frequencies (Figure 1). Early hearing loss normally occurs in the higher frequencies, which are very important in the discrimination of consonants. Thus, the first effects on hearing are loss of clarity of speech, described by adults as if the speaker is mumbling. The subject often compensates for this automatically by lip reading and continues to follow known vocabulary well, particularly when in context. The hearing disability becomes more evident as the loss extends downwards to involve the mid and, occasionally, the lower frequencies. Adults may also complain of tinnitus, a pointer to cochlea damage, and with some ototoxic agents balance problems may occur. However, young children do not normally complain of these symptoms, and the effects of a high frequency loss are not immediately apparent and are frequently underestimated by both parents and clinicians. Any hearing loss, including one confined to the high frequencies, is more disabling in young children, who are still developing language, than in an adult.

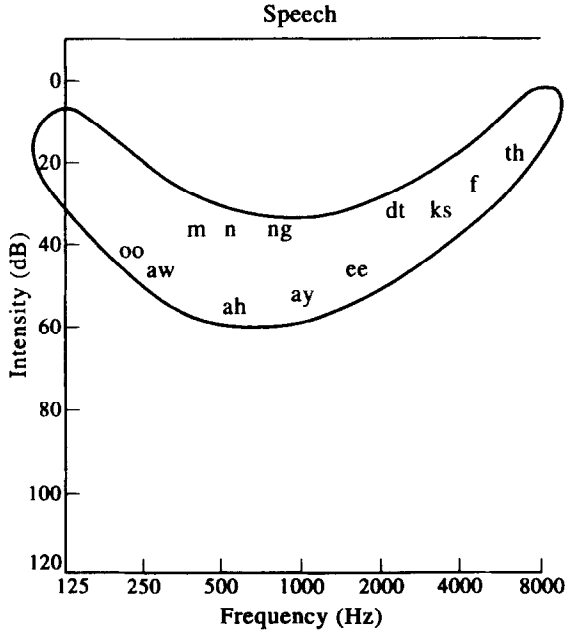

Figure 1. Spectrum of speech sounds for conversational voice at 1 metre.

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When considering appropriate methods of monitoring hearing status in children on chemotherapy, there are a number of different factors to consider: (a) the exact therapeutic regime used and its potential effect, (b) the age of the child and thus the type of tests that are feasible, (c) the effects of other ear disease on the hearing, and (d) the influence of monitoring on management.

TYPES OF OTOTOXIC DRUGS

A wide range of drugs have been reported to cause ototoxic damage in man. Cisplatin and its derivatives are the most ototoxic chemotherapeutic agents currently in use, and the hearing loss they produce appears to be irreversible. The main site of damage reported has been the outer hair cells of the cochlea, but animal and human studies have also reported damage to inner hair cells, type I cells in the spiral ganglion, the stria vascularis (with higher doses) and degeneration of the cochlea nerve [1–3]. Research continues into regeneration of hair cells, but damage sufficient to destroy the hair cells currently remains irreversible.

When considering the ototoxic effects of cisplatin, there is evidence that the extent of the damage is related not only to the total drug dosage, but also to the mode of delivery of the drug. Toxicity has been noted earlier and progresses faster following various high dose regimes [4] (Figure 2), although there is some evidence that ototoxicity may be reduced when mannitol is also given [5]. In addition, the ototoxic effects of cisplatin are reported to be greater when there has been previous cranial radiation [6] and also in those with low levels of red blood cells or serum proteins [7]. Carboplatin, thought originally to be less ototoxic than cisplatin, has also been shown to lead to significant ototoxicity [3], and regimes utilising both cisplatin and carboplatin have shown unexpectedly severe ototoxicity [8].

A number of other potentially ototoxic drugs may be used during treatment of a sick child, including some diuretics, antibiotics and even salicylates. With aminoglycoside anti-

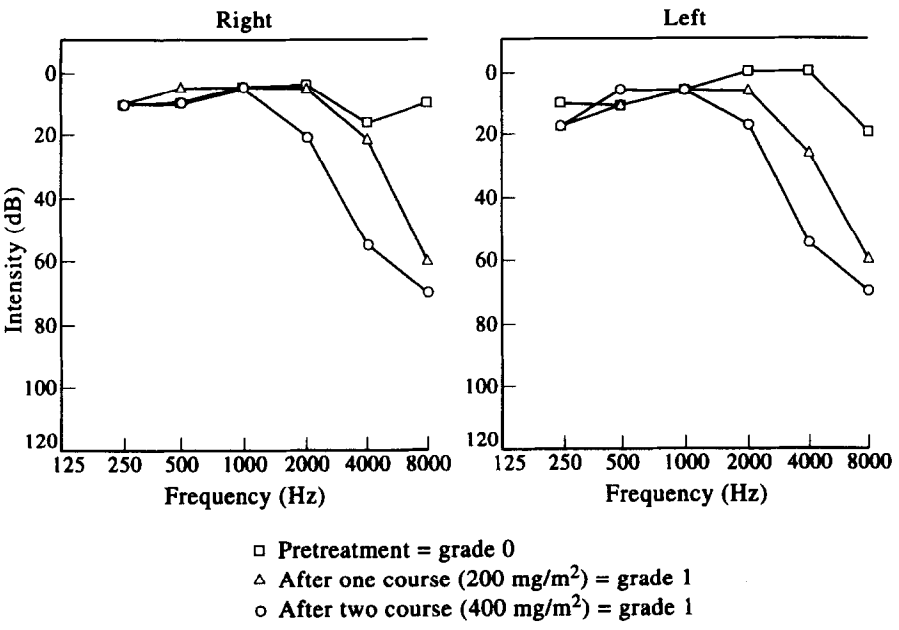

Figure 2. Example of progressive ototoxicity in a child on a high dose regime. Reprinted with permission of Wiley-Liss, Inc. from *Med Pediatr Oncol* 1991, 19, 295–300.

biotics, the hearing loss is irreversible, but with other drugs, for example loop diuretics, erythromycin, quinine and salicylates, the hearing loss is generally reversible, with the occasional report of a permanent problem [9]. However, ototoxic drugs have been shown, in both animal models and clinically in man, to potentiate each other [10]. These other ototoxic agents may cause or contribute to a greater than expected hearing problem in a cochlea which is also damaged by cisplatin and its derivatives [11,12]. Thus, when considering the frequency of monitoring the hearing in a child, the total therapeutic regime has to be considered.

METHODS OF ASSESSMENT

Pure tone audiometry

Assessment of ototoxicity is not difficult in older children and adults, who are able to co-operate with the regular monitoring by pure tone audiometry. Most children aged 3 years or over, and many under this age, are capable of carrying out at least a limited audiogram. However, children undergoing chemotherapy are often unwell and unable to cooperate with testing, even when developmentally old enough. In addition, many young children become very apprehensive about any form of intervention and may need several visits primarily to play in the department, before participating in any testing. Whenever possible, a pretreatment audiogram should be obtained, both for comparison and so that the child becomes aware of the non-threatening nature of hearing tests.

High frequency audiometry

As noted, cisplatin and its derivatives cause ototoxicity, which starts in the highest frequencies and extends apically (a similar pattern to aminoglycoside ototoxicity). High frequency (9–20 kHz) audiometry could identify early ototoxicity before the speech frequencies become affected. One study which tested these higher frequencies in adults, most of whom had a pre-existing hearing impairment, showed that 76% of ears in patients treated with cisplatin developed further hearing impairment. However, overall, only around 36% of ears developed a further loss in the conventional audiometric frequencies [13]. It was suggested that monitoring of only the five highest frequencies with hearing levels of 100 dB SPL or better, which would identify around 93% of affected ears, would be a quicker procedure than full audiometry. However, currently extended high frequency audiometers are not widely used. Testing time and co-operation need to be far greater, both initially and for monitoring, making the technique less suitable for routine use in younger children. In addition, children do not respond reliably to high frequency sound [3].

Most units will continue to restrict testing to the frequencies of 250 kHz to 8 kHz, the range of a conventional audiometer, to identify a clinically significant hearing loss. The recommended order of testing the different frequencies puts 8 kHz last. However, given a normal baseline hearing threshold, it is preferable to concentrate on the higher frequencies in young children with limited attention, to ensure that the most vulnerable frequencies are, in fact, tested (a similar philosophy to the limited five frequency testing described above). Assuming previously normal hearing, ototoxicity will usually manifest itself first as a drop in the hearing threshold at 8 kHz. This degree of ototoxicity alerts the clinician to the need for closer monitoring, but does not lead to significant disability in affected children (and adults).

Assessment for young children

Young children over 6 months of age can be monitored by tests carried out in a sound-field. For the younger children, these tests are based on distraction methods and include visual reinforcement audiometry (VRA). Results can be unreliable above 4 kHz because of calibration problems. Such tests can be difficult, with limited reliability in unco-operative children, but in skilled hands this usually gives an indication of deteriorating hearing. The child needs to be awake and relatively alert, but no physical intervention is involved in these techniques, and they should be unthreatening. From around 2 years of age, a skilled professional should be able to start to condition a child in a sound-field using play-audiometry. This requires

patience and co-operation, as do tests of speech discrimination, which can be introduced around this age [14].

The most difficult problem is that of monitoring hearing status in young and unco-operative children, and those too ill to carry out subjective testing. Knowledge of the site of ototoxic damage is important clinically as it will indicate the most appropriate way to assess the extent of damage to the auditory system. The two techniques used in such subjects are electric response audiometry (ERA) and tests based on oto-acoustic emissions (OAE).

Electric response audiometry

Of the range of tests available using ERA, only the auditory-evoked brain stem response (ABR) is relevant in this situation. This is because ERA techniques rely on a still subject to minimise any background electrical activity, which, despite averaging, will swamp the small evoked potential. All responses apart from the ABR and electrocochleography are abolished or very unreliable during sleep or anaesthesia, and the latter is an invasive medical technique requiring a general anaesthetic in children. ABR is routinely carried out using a click stimulus, but this has relatively poor frequency specificity, correlating best with the hearing at between 2 and 4 kHz. Frequency specific ABRs using a derived response technique are reported to be more sensitive [15]. High-frequency (8–14 kHz) tone bursts have also been reported to identify 93% of initial changes on behavioural audiometry in adults [16].

In practice, monitoring hearing levels by ABR in children is not practicable. Each test requires the child to be asleep or sedated, and older children may need general anaesthesia. The test time available during natural sleep or light sedation is short and often insufficient for a full range of frequency specific ABRs to be carried out. Thresholds obtained by ABR are usually within 20 dB of threshold, but are not sufficiently repeatable, particularly given the often difficult test conditions, to identify reliably minimal changes in hearing over time. However, the technique is useful in testing and confirming significant hearing impairment, if there is clinical concern during or after treatment.

Oto-acoustic emissions

The newest objective screening techniques use oto-acoustic emissions (OAE) which are thought to reflect outer hair cell activity. This would seem an appropriate test as cisplatin damage is reported to be mainly in the outer hair cells. Clearly, a test of hair cell function would not be of value if damage was known to occur solely at neural level. Two types of emissions are used clinically. The first are evoked (E) OAEs produced in response to a broad band sound. These are normally present when the hearing threshold is 25 dB or better, but give no information on hearing thresholds when absent. Earlier machines had limited frequency specificity, but more modern machines are reasonably frequency-specific up to 5 kHz [17] (Figure 3). The technique is much quicker than ABR in a co-operative, sleeping or sedated child, but is not easy in a moving or distressed child. EOAEs may also be absent or reduced in middle ear disease. EOAEs over 0.6–6 kHz have been shown to be reduced in amplitude in all patients after cisplatin therapy [18]. This was a non dose-dependent response, partially reversible after 2–9 weeks. However, only half the patients had a clinical hearing loss.

Unlike EOAEs, distortion product (DP) OAEs can be demonstrated when there is a mild/moderate sensorineural hearing loss and are frequency-specific. Despite earlier suggestions to the contrary, it now seems that DP OAE thresholds are not a reliable predictor of actual hearing thresholds, although correlation between the two is better for the higher frequencies [19]. In particular, 14.8% of ears with normal DP OAEs were reported to have abnormal hearing and 8% with no DP OAEs had normal hearing. Again the test is quick to carry out, but is difficult among the unco-operative children where it would be most valuable.

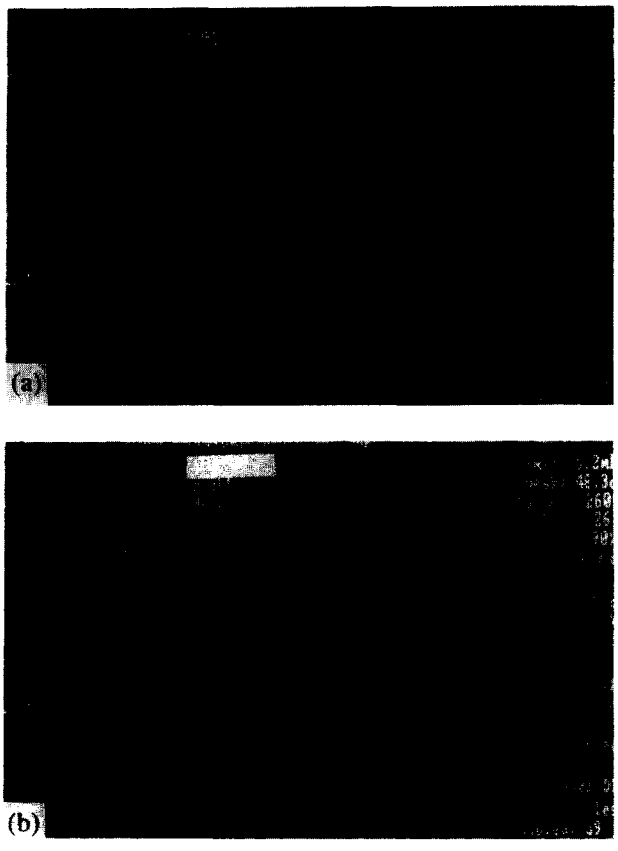

Figure 3. (a) Normal evoked oto-acoustic emissions. (b) High frequency loss of emissions.

MIDDLE EAR DISEASE

When monitoring the hearing levels of young children, it is important to assess middle ear function on each occasion. Middle ear disease, and in particular otitis media with effusion (OME), is no less common in children on chemotherapy than in the general population. This can be seen on otoscopy and confirmed by admittance methods, showing a negative middle ear pressure or flat response on tympanometry. OME produces a fluctuating conductive hearing loss, which means that bone conduction, as well as air conduction, thresholds need to be carried out to obtain sensorineural hearing levels. Reliable bone conduction thresholds frequently require masking, which prolongs the test session, and many children under the age of 5–6 years are unable to undertake this technique. In addition, results are not reliable above 4 kHz. Thus, test results may be somewhat limited, even in co-operative children. Children with persistent OME or recurrent infections may benefit from the insertion of ventilation tubes to improve hearing and reduce the incidence of acute otitis media.

MANAGEMENT

As a general principle, monitoring of any type is only justifiable if the results of the test will benefit the patient. There are two ways in which an abnormal hearing response may affect patient management. The first is in reconsideration of the therapeutic regime and the second is in the provision of auditory rehabilitation.

If the overall regime can be modified to reduce ototoxicity, this is clearly preferable. If the drug in question is proving effective clinically and there is no valid alternative, then counselling and monitoring of the increasing hearing loss is needed. Parents find it far easier to cope with a hearing problem if they have been kept fully informed of the hearing status during treatment, and been counselled regarding management. It is important for non-audiological clinicians to have a way of assessing likely hearing disability. A practical grading system has been suggested to aid understanding [20]. The timing of auditory rehabilitation has to take into consideration a child's age and prognosis as well as the level of hearing. In general, young children and their families are not aware of any disability from a recent high frequency loss. It is important that they are informed of any hearing impairment and are given general advice to minimise any auditory disability. However, it is rarely justifiable to introduce hearing aids, with all their attendant problems during treatment or in the immediate post treatment period. Occasionally, an older child may be aware of difficulty in hearing clearly, and rehabilitation, including amplification, can be initiated as soon as the child requests it. Four to 6 months after the end of treatment, the prognosis for the child is usually clearer, and those children who remain well at this time will benefit from the introduction of rehabilitation, including amplification if necessary.

CONCLUSION

Some hearing loss following treatment with cisplatin has been reported in 77% patients [13, 21]. This is not always severe, but between 18–36% of children have been reported to have a loss sufficient to warrant amplification [20, 22]. Similarly, problems have been noted with carboplatin and combination therapies. Other factors such as cranial radiation and mode of drug administration can increase susceptibility. Ototoxicity can thus be recognised to be a significant practical problem and there is widespread agreement that monitoring of hearing is necessary [23–25].

A pretreatment assessment should be carried out whenever feasible. Monitoring should ideally be carried out after each course of treatment, and becomes essential with a cumulative cisplatin dose of 330 mg/m^2 or over, or where ototoxicity may be increased by mode of drug administration or other factors.

Pretreatment screening should include pure-tone audiometry or VRA in all but the very young, and at all ages tympanometry and OAEs. If there is any doubt about hearing levels prior to therapy, ABR may be necessary. Monitoring will include tympanometry to check middle ear function, stapedial reflex thresholds and, if appropriate, OAEs. Audiometry should concentrate on the higher frequencies of 3–8 kHz to identify early changes in hearing. Following the end of treatment, the child should be re-assessed when well enough to co-operate, and by this stage most children will be old enough to co-operate with pure-tone audiometry or VRA. Middle ear function and speech discrimination tests should also be included. If there remains any doubt regarding hearing thresholds, frequency specific ABRs can be carried out at this stage. Rehabilitation, including amplification, can then be introduced if necessary at an appropriate time, balancing the individual child's disability against prognosis.

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