Absent or Elevated Middle Ear Muscle Reflexes in the Presence of Normal Otoacoustic Emissions: A Universal Finding in 136 Cases of Auditory Neuropathy/Dys-synchrony

Charles I. Berlin*
Linda J. Hood*
Thierry Morlet*
Diane Wilensky*
Patti St. John†
Elizabeth Montgomery†
Melanie Thibodaux†

Abstract

We extracted a subpopulation of 136 patients (from our database of 257 AN/AD subjects) in whom middle ear muscle reflexes had been measured. None showed normal reflexes at all frequencies tested. Only three subjects showed any reflexes at 95 dB HL or below, but never at both 1 and 2 kHz in both ears whether ipsilaterally or contralaterally elicited. All the other reflex measures in these remaining 133 patients were either absent or observed above 100 dB HL, which is incongruous with their normal otoacoustic emissions throughout the frequency bands.

Therefore, we urge colleagues to test ipsilateral middle ear muscle reflex at least at 1 kHz and 2 kHz in any perinatal hearing screening that depends solely on otoacoustic emissions. If the emissions are present and the reflexes are absent or elevated, an ABR may be required to properly intervene, because the management of AN/AD patients often differs drastically from what the behavioral audiogram or the ABR suggest.

Key Words: Acoustic reflex, auditory brainstem response, auditory neuropathy/dys-synchrony, otoacoustic emissions

Abbreviations: ABR = auditory brainstem response; AN/AD = auditory neuropathy/dys-synchrony; MEMR = middle ear muscle reflex; MOCS = medial olivocochlear system; NICU = neonatal intensive care unit; OAEs = otoacoustic emissions

Sumario

Seleccionamos una sub-población de 136 pacientes (de nuestra base de datos de 257 sujetos con AN/AD) a quienes se le había medido sus reflejos de los músculos del oído medio. Sólo tres sujetos mostraron algún reflejo a 95 dB HL o menos, pero nunca en 1 y 2 kHz en ambos oídos, ya se tratará de estimulación ipsi o contralateral. Todas las demás mediciones de reflejos en los restantes 133 pacientes estuvieron ausentes o por encima de 100 dB HL, lo que fue incongruente con sus emisiones otoacústicas normales a lo largo de las bandas de frecuencia.

Por lo tanto, instamos a los colegas para que evalúen el reflejo ipsilateral del músculo del oído medio en 1 kHz y en 2 kHz, en cualquier tamizaje...
Auditory neuropathy/dys-synchrony (AN/AD) is commonly diagnosed when the auditory brainstem response (ABR) is absent or elevated middle ear muscle reflexes (MEMRs), but these are often bypassed in common audiological and neurological practice. At least ten percent (10%) of children who fail ABR screenings have normal OAEs (Norton et al, 2000), and a similar number in schools for the Deaf were found to have OAEs (Berlin et al, 2000, 2003; Tang et al, 2004). Rea and Gibson (2003) have observed as many as 40% of NICU (neonatal intensive care unit) infants may have this combination of symptoms secondary to hypoxia. Others relate the symptomatology to hyperbilirubinemia (e.g., Oysu et al, 2002). None of them would have been identified with a screening program that used only otoacoustic emissions (e.g., Bray and Kemp, 1987; White et al, 1994; Rea and Gibson, 2003).

This brief communication is designed to counteract the trend of bypassing MEMRs. Our data show that absent or elevated MEMRs are essential to the diagnosis. Furthermore, the inclusion of MEMRs as part of a diagnostic triage (Berlin et al, 2002) may help to uncover cases that masquerade as AN/AD (Berlin et al, 1978) or a few cases that have large cochlear microphonics (Coats and Martin, 1977; Berlin et al, 1998) that are not always in and of themselves incontrovertible signs of AN/AD.

**PHYSIOLOGIC RATIONALE**

The outer hair cell, presumably the source of OAEs, is currently viewed as an aid to the inner hair cell, to help it overcome its limited dynamic range (e.g., Ashmore, 1987; Ruggero, 1992). Despite statements to the contrary (e.g., Bonfils et al, 1988), normal OAEs in and of themselves do not always accompany completely normal cochlear function and/or normal ABRs or even normal behavioral audiograms. With the advent of universal screening, many more cases of absent ABRs and normal emissions will be reported if we are vigilant and set up our screening programs to identify them. Identification is critical because the management of these patients requires early language intervention; a later paper will show that hearing aids plus AVT (auditory/verbal therapy) have been the least successful management policy until after cochlear implantation, or unless the patient has combination problems such as a conductive or mixed loss superimposed on mild AN/AD (Berlin et al, 2004).

MEMRs are one of two efferent reflexes mediated by the inner hair cell, eighth nerve, and brain stem pathways. The other is the medial olivocochlear (MOCs) reflex, or modulation of OAEs by ipsilateral, contralateral, or bilateral noise (Collet et al, 1990; Berlin et al, 1993, 1995; Hood et al, 2003; Morlet et al, 2004). The latter (MOCs) reflex is also missing in AN/AD patients (Hood et al, 2003). Neither the MOCs nor the MEMR are seen at expected hearing levels (60–65 dB SPL for MOCs and 95 dB HL or below for MEMR) when either inner hair cell and/or auditory nerve function are directly impaired (Starr et al, 1996, 2001; Abdala et al, 2000; Hood et al, 2003; Berlin et al, 2004). In the presence of audiometric hearing loss of 60–65 dB HL, the emissions are expected to be absent while the MEMR is usually seen by 95 dB HL in outer hair cell losses.

The tonal MEMR is usually seen at 70–95 dB hearing levels when only outer hair cells...
are affected (OAEs are missing) and hearing loss is at 60 dB HL or less. Because the inner hair cell has a dynamic range of about 60 dB (e.g., Ashmore, 1987), it follows that when there are normal reflexes at 75–95 dB HL in the presence of 60 dB hearing levels, the inner hair cells are working properly together with the eighth nerve (e.g., Bennett and Weatherby, 1982). The absence, reduced contribution, or decoupling of inner hair cells vis-à-vis the auditory nerve has been cited as one likely cause of AN/AD (e.g., Starr et al, 1996, 2001; Deltenre et al, 1997, 1999; Kraus et al, 2000; Amatuzzi et al, 2001; Berlin et al, 2001; Varga et al, 2003) and is offered as one reason why the name "neuropathy" might be misleading (Berlin et al, 2001; Rapin and Gravel, 2003; Rance et al, 2004). Because MEMRs are often absent or elevated in the presence of desynchronizing lesions (e.g., Hannley et al, 1983), it follows that finding normal MEMRs at levels between 75 and 95 dB HL at 500, 1000, and 2000 Hz (Handler and Margolis, 1977; Wilson, 1981) confirms an intact pathway between the inner hair cells of the cochlea, the primary neural fibers, the brainstem and olivocochlear bodies, and the facial nerve, which in turn supplies the motor innervation to the stapedius tendon (Borg and Counter, 1989). It should also be kept in mind that when data were being collected on what was "normal threshold for MEMRs," the physiology of outer versus inner hair cells was not well known, and the reflexes were being interpreted with regard to how they related to the pure tone audiogram. This paper suggests that we should be looking at them from the point of view of how the reflexes reflect the physiology, and normal emissions are incongruous with absent or elevated middle ear muscle reflexes at the same frequencies (Berlin et al, 1993).

**DATABASE SOURCE**

The data on which this brief report is based are part of a larger study being prepared for peer review (Berlin et al, 2004). We collected OAEs, MEMRs, and ABR data from our patient population and from colleagues throughout the United States to develop a rational plan of action based on outcomes of many patients with AN/AD. This subpopulation dealing with MEMRs is being singled out for early dissemination because of the current activity of national organizations setting new guidelines for early hearing detection and intervention. Unless the MEMR test is included (e.g., Hannley et al, 1983; Hirsch et al, 1992), our data indicate that AN/AD patients with normal OAEs will be missed and/or may be misdiagnosed later in life with "central auditory processing disorders" or attention deficit disorders because of unusually poor hearing in noise (see sample patient later).

**SUBJECTS**

Data on the 136 patients with confirmed AN/AD on whom MEMR tests were performed were extracted from the Kresge Laboratory database of 257 AN/AD patients described above. Fifty-seven of the 136 subjects were tested on at least one occasion at Kresge Laboratory. Six of the 15 patients displaying some recordable MEMRs were seen at Kresge Laboratory, and these patients are noted with a "K" in Table 1. Some of these patients were also tested in the Audiology Clinic in the Department of Otolaryngology at LSU Health Sciences Center, which is related to Kresge Laboratory and uses the same test protocols.

Normal middle ear function was presumed based on the presence of OAEs coupled with type A tympanograms. There were three patients for whom tympanogram data were either not reported or inconclusive; in these patients, normal middle ear function was presumed based on the presence of OAEs.

One hundred twenty-eight of the patients had bilateral AN/AD, and eight had unilateral AN/AD. In four patients with bilateral AN/AD, data were available for only one ear. Patients ranged in age from two months to 74 years with a mean age of ten years, six months. Fourteen of the 136 patients received MEMR testing at age six months or under.

**METHODS**

Tympanograms and ipsilateral and contralateral MEMR thresholds were completed by us and by others who contributed to the database using standard clinical procedures and commercial clinical equipment. The probe frequency was typically 220 or 226 Hz. We reviewed probe frequency data and files for the 14 patients who were six months of age or younger at the time of MEMR testing. For these 14 patients, a 1000 Hz probe
frequency was used in two patients (both with absent MEMRs), 678 Hz for two patients (MEMRs absent), and 226 Hz probe in two patients (one with MEMRs present and one with MEMRs absent). Probe-frequency data were not specified for the remaining eight patients, and, since they were not tested at Kresge Laboratory, it is not possible to recapture the information. The four youngest patients were two months of age at testing, and all had absent MEMRs with probe frequencies of 1000 Hz in one patient, 678 Hz in one patient, and no probe frequency data available for the remaining two patients.

MEMRs were considered normal when thresholds were obtained for tonal stimuli at 95 dB HL or less for all frequencies tested. For patients with unilateral AN/AD, we report only MEMRs generated when the affected ear was stimulated.1

MEMR thresholds were not reported for all frequencies in all patients, though generally two to four frequencies (of 500, 1000, 2000, and 4000 Hz) were obtained. In the 136 patients studied, there were a total 260 ears (124 bilateral, eight unilateral AN/AD, and four bilateral AN/AD patients with only one ear meeting criteria for inclusion) x eight test frequencies (four frequencies by ipsi and contra MEMRs) yielding 2,080 possible reflex reports. For patients tested at Kresge Laboratory, MEMRs were obtained using a Grason-Stadler GS-33 Middle Ear Analyzer using a probe tone of 226 Hz. TEOAEs (obtained for all patients) were tested using Otodynamics ILO88 or ILO92 Echoport systems. Stimuli

### Table 1. Summary of MEMR Threshold Data in Subjects with Present Middle Ear Muscle Responses (n = 15)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right Age</th>
<th>Ipsilateral</th>
<th>Contra</th>
<th>stimulus ear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (K)</td>
<td>7 yr., 4 mo.</td>
<td>A A A A</td>
<td>110 A A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>2 (K)</td>
<td>2 yr., 11 mo.</td>
<td>105 105 A A</td>
<td>105 100 A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>3</td>
<td>2 yr., 4 mo.</td>
<td>A A A ND</td>
<td>ND ND ND</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>4 (K)</td>
<td>33 yr., 6 mo.</td>
<td>A A A A</td>
<td>110 105 110 A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>5</td>
<td>38 yr., 1 mo.</td>
<td>ND ND ND</td>
<td>ND ND ND</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>6</td>
<td>17 yr., 3 mo.</td>
<td>105 105 A A</td>
<td>A A A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>7</td>
<td>30 yr., 6 mo.</td>
<td>A A A ND</td>
<td>110 110 A ND</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>8</td>
<td>0 yr., 5 mo.</td>
<td>100 105 A A</td>
<td>100 A A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>9</td>
<td>41 yr., 11 mo.</td>
<td>100 95 A A</td>
<td>A A A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>10 (K)</td>
<td>54 yr., 0 mo.</td>
<td>105 100 95 A A</td>
<td>105 100 A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>11</td>
<td>0 yr., 3 mo.</td>
<td>105 A A A ND</td>
<td>ND ND ND</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>12 (K)</td>
<td>7 yr., 11 mo.</td>
<td>A A A ND</td>
<td>ND ND ND</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>13 (K)</td>
<td>2 yr., 2 mo.</td>
<td>90 85 A A</td>
<td>90 85 A A</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>14 (K)</td>
<td>3 yr., 1 mo.</td>
<td>110 115 A A</td>
<td>A A A A</td>
<td>500 1000 2000 4000</td>
</tr>
</tbody>
</table>

Note: Normal criterion reflexes were seen in only one patient (#14) at only 5 of 16 possible frequency and ear combinations. Patient 15 has unilateral AN/AD (right ear). Age is in years (yr.) and months (mo.). A = absent; ND = no data; K = tested at Kresge Lab.
were 80-microsecond electrical pulses presented in a "nonlinear" paradigm where every fourth click is reversed in polarity and 10 dB higher in intensity. This paradigm is used to reduce the stimulus artifact. The full 20 msec time window was used for all but three subjects; those three were tested with reduced low-frequency content and a shorter time window (the "Quikscreen" mode). DPOAEs were obtained in addition to TEOAEs in 19 subjects. For DPOAEs, stimulus levels were 65 dB for F1 and 55 dB for F2 with from two to eight points per octave (with fewer points obtained in younger patients due to available cooperative test time constraints). The frequency ratio between F1 and F2 was 1.2.

RESULTS

None of the patients evaluated demonstrated a normal pattern of MEMR thresholds at all frequencies. MEMRs were absent at 110 dB HL or higher for all test frequencies and conditions (ipsilateral, contralateral) tested in 113 of the 128 bilateral patients (88.3%). They were present at normal levels (95 dB HL or below) in only six ears of five patients (see the table) and never at 1 and 2 kHz together.

Distributions as a function of frequency and test condition for the 15 patients who showed any MEMRs are shown in Table 1. All of these patients had Type A tympanograms bilaterally. Fourteen of these patients showed bilateral AN/AD, and one patient had unilateral AN/AD. Only one patient with bilateral AN/AD, age 2½ years, demonstrated normal ipsilateral and contralateral MEMRs at 500 and 1000 Hz, while MEMRs were absent at 2000 and 4000 Hz. This patient, incidentally, shows no language delay and is developing speech and expressive language normally, despite his absent ABRs.

CASE STUDY

This case study is of a representative patient who was mismanaged as having "central auditory problems and aphasia or a specific language disorder" in part because MEMRs were not tested to cross-check his presumed-normal audiogram.

Patient JT1 was being treated from 1995–2001 for aphasia and a language disorder at a nearby facility that specializes in treating such children. He was placed there because his single polarity ABR was (mis)interpreted as representing normal waves and intervals at high intensities, and after an abnormal reaction to his immunizations, he appeared to ignore speech but respond to environmental sounds. This led to a diagnosis of "aphasoid behavior." No emissions were done, and he was screened as "normal in hearing" based on behavioral observations alone.

We tested him as follows:

- Tympanometry and MEMRs. Tympanometry was normal; however, his MEMRs were absent at all four frequencies both ipsilaterally and contralaterally.
- Transient Evoked OAEs. All of these were robust.

This triage of tympanometry, MEMRs, and OAEs has now become the standard intake protocol for all new audiology patients at the LSUHSC Otolaryngology Clinic (Berlin et al, 2002).

These results prompted us to perform an ABR with separate averages of positive and negative polarity clicks (Berlin et al, 1998).
These results, shown in Figure 1, support a diagnosis of AN/AD that was suggested first by the absent MEMRs in the presence of normal OAEs. Had MEMRs been tested, along with emissions, this child and his family could have been saved six years of misguided therapy, and he could have been directed toward cochlear implantation once the diagnosis was confirmed.

**DISCUSSION**

In only six of the 260 ears evaluated in our 136 subjects was the reflex seen at 95 dB HL or below, and never at all frequencies in both ears. This is so even in the one mildly affected patient who, so far, has required no intervention and is developing language normally. Two subjects (numbers 3 and 8) showed reflexes in one ear, albeit elevated, but not in the other.

Thus, when screening newborns with OAEs, finding an absent MEMR with normal OAEs should suggest that AN/AD may be present. At that point an ABR with separate averages to positive and to negative polarity clicks (Berlin et al, 1998) is needed to complete the diagnostic picture. MEMRs should not be skipped whenever OAEs are normal.

Looking back at our data, we see that no AN/AD patient with normal OAEs would have been mislabeled as normal in hearing if we had included at least the ipsilateral MEMR tonal data at 1000 and 2000 Hz. It is for this reason that we recommend to organizations active in screening with OAEs that they include at least these two MEMR frequencies in an ipsilateral screen (which can be completed when the OAE probe is in place) to reduce the false negatives generated by an OAE screen that misses AN/AD. Alternatively, broad-band noise can be considered as a practical screen because thresholds are generally lower than for tones (Margolis et al, 2003) and the normal emissions suggest that there should be good hair cell sensitivity to stimulation.

Whether a higher tympanogram frequency is called for in screening is not clear (see Margolis et al, 2003, for additional discussion). We are aware of the reports (e.g., McMillan et al, 1985; Sprague et al, 1985) that say middle ear muscle reflexes are often not visible with a 220 Hz probe tone in newborns. The implication is that the "artifactually normal tympanogram" arising from collapsing canal walls does not "see" obstructive middle ear residue blocking the recording of the reflex. However, if the emissions can pass through unobstructed, it is not reasonable to think that the reflexes would be obstructed while the emissions would not. In addition, with Rea and Gibson (2003) reporting a 40% incidence of what may be AN/AD in the NICU, the need for a higher probe frequency to detect the reflex should be reexamined. Whatever the outcome, our data show that middle ear muscle reflexes need to be added to a screening program that is entirely dependent on OAEs. If a child passes OAEs and does not show normal reflexes, some form of ABR testing should follow.

Some infants with absent ABRs and present OAEs in fact develop normal ABRs and auditory function within about 16 months. None have been included in this sample, but infants with stormy neonatal histories or serious prematurity sometimes completely outgrow all their symptoms and develop normal ABRs (Roberts et al, 1982). By contrast, 7% of our 257 patient sample developed normal speech and language but continued to show absent or disorganized ABRs. We have yet to develop any methods for differentiating the AN/AD subjects from the neural immaturity subjects, unless the presence of MEMRs will differentiate them—a fact we can neither support nor dispute at this time.²

On the other hand, some children with AN/AD spontaneously lose their OAEs and outer hair cell function as part of the disorder, which may be part of the otoferlin-mediated course of certain varieties of AN/AD (see Varga et al, 2003, for discussion of otoferlin mutations). This does not override their fundamental loss of synchrony and perforce make them hearing aid candidates. We have seen two patients with mild AN/AD develop middle ear disease and need amplification to help them return to a mild AN/AD status; hearing aids should not be denied simply because AN/AD is present. However, it is the expectation that the hearing aids in and of themselves will "correct the audiogram and allow normal language development" that needs to be carefully scrutinized on a case-by-case basis.

**SUMMARY AND CONCLUSIONS**

Based on their underlying physiology and middle ear mechanics, OAEs and MEMRs
should generally be present together (Hirsch et al, 1992). When the OAEs are present and the MEMRs are absent, a strong suspicion of AN/AD should be raised. At that point, an ABR should be completed to confirm the diagnosis. The ABR test should be done with separate averages to positive and negative polarity clicks to identify the cochlear microphonic and separate neural from hair cell events (Berlin et al, 1998).

With the advent of universal hearing screening, proper identification and management are essential, and the psychophysics and management of AN/AD has been shown to be quite different from the management and psychophysics of more commonly understood outer hair cell hearing loss (Zeng et al, 1999; Rance et al, 1999, 2004; Kraus et al, 2000; Shallop et al, 2001; Berlin et al, 2003). Therefore, proper triage is essential, especially for programs that screen only with OAEs (e.g., White et al, 1994; Gorga et al, 2000; Rea and Gibson, 2003).

NOTES

1. Our observations of MEMRs with unilateral patients taught us that the absence of reflexes in AN/AD patients is secondary to an afferent deficit rather than efferent failures. This was clear when MEMRs could be elicited in the AN/AD ear at normal levels when the normal ear was stimulated, but not the other way around.

2. Some patients with AN/AD lose their OAEs over time; this does not mean that the dys-synchrony has disappeared and that hearing aids can now be expected to "correct the audiogram according to the rules of Articulation Index" and improve speech perception by improving audibility. The loss of OAEs does not "trump" the underlying lack of neural synchrony from whatever cause.

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