

# AUDITORY NEUROPATHY/DYS-SYNCHRONY: DIAGNOSIS AND MANAGEMENT

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Auditory brainstem responses (ABRs) and otoacoustic emissions (OAEs) are objective measures of auditory function, but are not hearing tests. Normal OAEs reflect normal cochlear outer hair cell function, and an ABR indicates a synchronous neural response. It is quite possible for a patient to have normal OAEs but absent or grossly abnormal ABR and a behavioral audiogram that is inconsistent with either test. These patients, who may constitute as much as 10% of the diagnosed deaf population, have auditory neuropathy/dys-synchrony (AN/AD). To diagnose AN/AD accurately, ABRs are obtained in response to condensation and rarefaction clicks to distinguish cochlear microphonics (CM) from neural responses. Appropriate management is confounded by variation among patients and changes in auditory function in some patients over time. Recommendations for management include visual language exposure through methods such as American Sign Language (ASL), Cued Speech, or baby signs, and closely following patients.

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MRDD Research Reviews 2003;9:225–231.

**Key Words:** auditory neuropathy/dys-synchrony (AN/AD); auditory brainstem response (ABR); otoacoustic emissions (OAEs); cochlear microphonic (CM); middle-ear muscle reflexes (MEMRs)

## INTRODUCTION AND ORIENTATION—ABR AND OTOACOUSTIC EMISSIONS ARE NOT INFALLIBLE HEARING TESTS

The casual reader of auditory screening literature might be led to believe that otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs) are in and of themselves objective tests of hearing. *They are not.* When normal OAEs are present, they reflect normal outer hair cells in the cochlea and imply a normal middle ear. However, some very deaf patients have normal otoacoustic emissions but have either absent inner hair cells or compromised neural synchrony. This should not be interpreted as a brainstem or brain disorder but more peripherally as part of a disruption of the inner hair cell nerve fiber junction or the nerve trunk itself [Starr et al., 1996; AmatuZZi et al., 2001].

Similarly, a patient may have an absent ABR and *not* be deaf, a phenomenon which may occur in about 10% of all the people diagnosed and managed as deaf in this country [Berlin et al., 2001b]. However, OAEs and ABRs are very powerful indices when used together. Normal otoacoustic emissions and a normal ABR showing a normal increase of latency with a decrease in intensity certainly implies normal peripheral hearing and indicates that hearing aids and speech and ordinary inter-

vention are not appropriate. Absent ABRs and absent OAEs in the presence of normal tympanometry (confirming a normal middle ear system) strongly indicate peripheral hearing impairment requiring intervention. Absent ABRs with present otoacoustic emissions, normal tympanometry, and absent middle-ear muscle reflexes (MEMRs) strongly suggest auditory neuropathy/dys-synchrony (AN/AD). ABRs should be obtained separately for positive and negative polarity clicks; comparison of these responses is useful in identifying the cochlear microphonic and separating it from the neural response [Berlin et al., 1998].

We have seen a few of these patients develop hearing, speech, and language normally who would never have been identified had their initial screening not included an ABR. Some develop into normal hearing and speaking adults who show little trouble other than difficulty hearing in noise; they are sometimes later mis-diagnosed as having “Central Auditory Processing Disorders” or even Attention Deficit Disorders because their ability to attend to signals in noise is inordinately poor. Some others act and live a Deaf life. The majority fall somewhere in between, showing distinct auditory problems but also showing periods of sporadic hearing or having difficulty in hearing far beyond that predicted by their pure tone audiograms.

## DEFINITION OF AUDITORY NEUROPATHY/DYS-SYNCHRONY

When ABRs and middle-ear muscle reflexes are absent, but otoacoustic emissions are present (or have been at one time), the patient is at great risk for auditory neuropathy/dys-synchrony. Data from such patients are summarized in Figures 1, 2, and 3. The rationale for the additional term is expanded upon in another publication [Berlin et al., 2001] but is reviewed briefly here. The name “auditory neuropathy” implies a confirmed pathology of the VIIIth N., when in fact evidence supports multiple etiologies and multiple locations ranging from the inner hair cell itself [AmatuZZi et al., 2001] to kernicteric deposits

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Published online in Wiley InterScience (www.interscience.wiley.com).  
DOI: 10.1002/mrdd.10084

[Shapiro and Nakamura, 2001] anywhere from the spiral ganglion fibers to the brainstem, to a paucity of myelinated fibers in the VIIIth N. per se [Starr et al., 2001]. The term was initially agreed upon by Drs. Arnold Starr, Terence Picton, Linda Hood, and Charles Berlin in 1996 when we reviewed our first five cases in common at a private meeting in New Orleans [Starr et al., 2001; Berlin et al., 2001]. At that time, the Louisiana State University (LSU) contingent had collected transtympanic electrocochleographic<sup>1</sup> data on other patients who showed *no* primary compound action potential (CAP) but a large and persistent cochlear microphonic in response to inverted polarity clicks<sup>2</sup> [Berlin et al., 1998]. This observation, coupled with the neurologists' [Drs. Starr and Picton] observation that all but one of the patients had elevated or impaired deep tendon and/or ankle reflexes, suggested some form of peripheral neural disease. One, in fact, was already diagnosed with Charcot-Marie-Tooth Disease. Subsequent PET scans on two of these patients [Lockwood et al., 1999] have shown no brain response to sound in one patient and a weak response in the other. Both of these patients have recordable OAEs, absent ABRs, and no speech discrimination in noise, despite mild pure tone hearing losses.

Other audiological tests show no masking level difference (MLD; release from masking)<sup>3</sup>, no efferent suppression of transient evoked otoacoustic emissions in response to noise in one or both ears [Berlin et al., 1993; Hood and Berlin, 2001], and variable pure tone audiograms over a huge range. At one extreme, we

see what appears to be total deafness despite normal otoacoustic emissions. At the other extreme, we see nearly normal audiograms with no auditory complaints except in noise despite a totally absent ABR. Examples of three patients are shown in Figures 1, 2, and 3. If one screens for and rules out deafness *only* with otoacoustic emissions, an additional mis-diagnosis of either mental retardation or central auditory disorders might be invoked to account for absent language in the presence of normal outer hair cells.

## COCHLEAR EVENTS

We can deduce that, when normal, otoacoustic emissions are *not* tests of hearing. Conversely, absent ABRs are *not* guarantors of deafness. Let's see why by briefly reviewing some fundamentals of cochlear physiology. These principles are elucidated in a book chapter and companion CD video as part of a text entitled Hair Cell Micromechanics and Otoacoustic Emissions [Berlin et al., 2002] and also available from articles on our Web Page: [www.kresgelab.org](http://www.kresgelab.org).

There are five fundamental electro-acoustic events commonly measured from mammalian cochleae:

1) The endocochlear potential (EP) is an 80 mv battery which is in part mediated by the stria vascularis and ion transport across barrier membranes in the inner ear. This potential is the master source of all cochlear energy; when it is depleted, all other electrical activities quickly cease [Konishi, 1961].

2) Cochlear microphonics (CM), or cochlear hair cell potentials, are polarity-sensitive electrical events which reflect electrical activity emanating from *both* outer and inner hair cells [Withnell, 2001]. When the polarity of the stimulus changes, the polarity of the recordable waveform reverses. It is for this reason that we recommend using one positive and one negative polarity click in each high-intensity ABR recording. In cases of AN/AD, a five-peak waveform often appears which has all the latency characteristics of a normal ABR. But when the polarity of the click is reversed, the polarity of the waves also inverts. If the waves were indeed neural responses (see next item), they would maintain essentially the same appearance but change latency by the width of the pulse (usually 100 microseconds).

3) The compound action potential (CAP) represents the sum of the neural elements in the cochlea discharging to a brief pulse with a rapid rise time. Its size and latency are determined in part by the synchrony of discharge of cochlear hair

cell/nerve fiber units, speed of the traveling wave, rise/fall time of the stimulus, and frequency content of the stimulus. The CAP is also Wave I of the ABR and the action potential (AP) of the electrocochleogram. It is absent in cases of auditory neuropathy/dys-synchrony. We know its appearance is related to synchrony more than hearing per se because, when we use an audible tone burst with a slow rise time (10 milliseconds or more), a CAP cannot be measured.

4) The summing potential (SP) is a direct current (DC) offset from the baseline which reflects the presence of hair cells (usually, but not always, outer hair cells in the case of AN/AD).

5) Otoacoustic emissions (OAEs) are acoustic energy coming from outer hair cells either spontaneously or evoked by transients or pairs of stimulating tones.

If we mentally split the organ of Corti into outer and inner hair cell segments, we can see that OAEs test the outer hair cell segment, and ABRs test the inner hair cells and nerve fiber junctions and the nerve fibers themselves. In a patient with the more commonly understood forms of deafness where there are few if any inner and outer hair cells remaining, we see no emissions, no ABR, and no middle ear muscle reflexes. Where only outer hair cells remain, we see emissions but no synchronous firing of the neural elements emanating from inner hair cells, the hallmark of AN/AD. The presence of emissions and CM also tells us by inference that the endocochlear potential is intact.

## COCHLEAR VERSUS NEURAL EVENTS

Comparison of ABRs obtained with condensation to those obtained with rarefaction stimuli allows separation of cochlear from neural events. This is demonstrated in Figure 4, which displays an ABR intensity series from a normal individual (upper panel) and an AN/AD patient (lower panel). Both condensation and rarefaction clicks were used at the highest intensity in the normal listener. There is a small inverting CM at the beginning of the trace (shaded), but the rest of the tracings show similar responses regardless of polarity and a normal waveform latency increase with decreasing intensity. In contrast, the response to a single polarity stimulus in the AN/AD patient leads to a misleading result. Comparison of the results shown in the lower panel of Figure 4 (single polarity) to those in the right panel of Figure 5 (condensation and rarefaction polarity) reveals that the waves are *not* the neural responses one ex-

<sup>1</sup>Also known as ECochG. An electrode is placed on the promontory of the cochlea and the ear is stimulated with a brief click. The ensuing electrical discharges are recorded and amplified and offer a powerful insight into the synchrony of the hearing nerve. The ECochG usually reflects hair cell activity within the first 0.8 msec after the click and neural activity from 1.5 msec or later. However, in AN/AD the hair cell response sometimes "rings" for an inordinately long time and mimics an ABR. This "impostor ABR" can be unmasked by changing the polarity of the click.

<sup>2</sup>A click is a brief pulse which pushes the diaphragm of the earphone inward and then pulls it outward for a brief period of time. The usual period is 100 µsecs or 100 millionths of a second. A condensation pulse is a pulse that pushes inward first and pulls outward second. A rarefaction pulse does just the reverse. . .pulls outward first and pushes inward second. A response from the hair cells will invert when the click polarity inverts. A response from the nerve fibers will not change materially when the click is inverted.

<sup>3</sup>The Masking Level Difference is obtained by presenting two identical tones to each ear. Masking noise is then added to both ears until the tones are inaudible. At that point, the phase angle of either the tones or the noise is reversed. In a normal auditory system, the thresholds of detection improve by 10–13 dB. In patients with AN/AD, they receive no benefit from the phase changes.

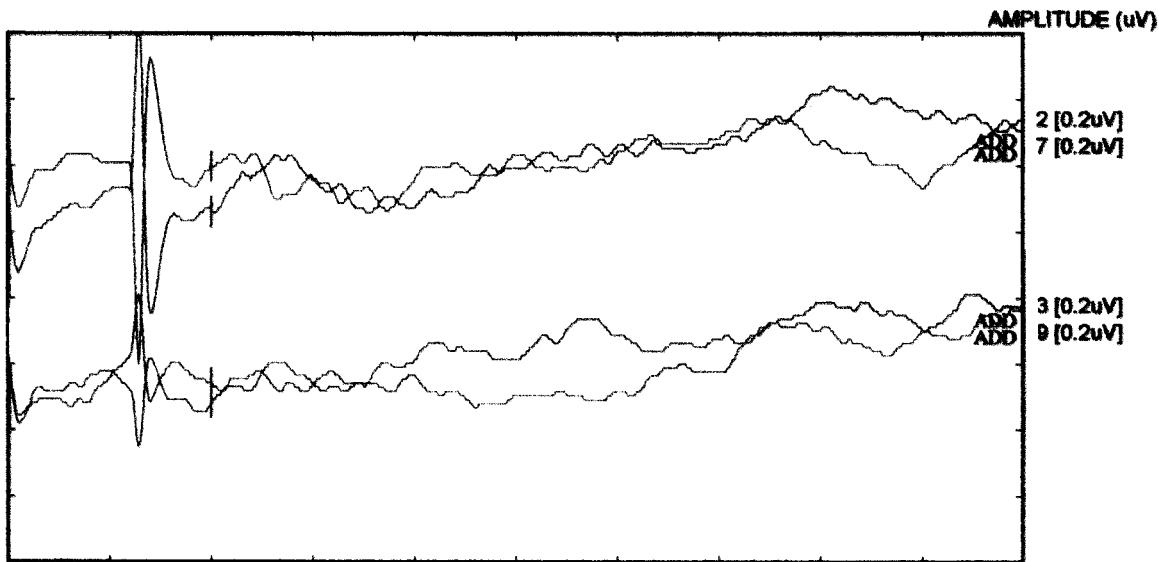
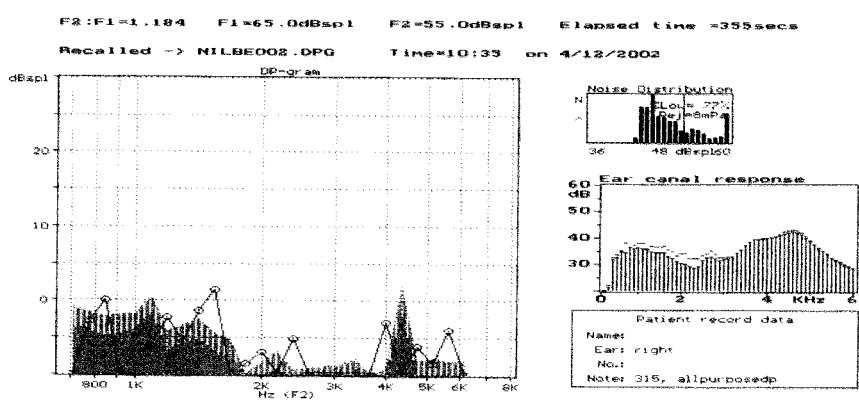
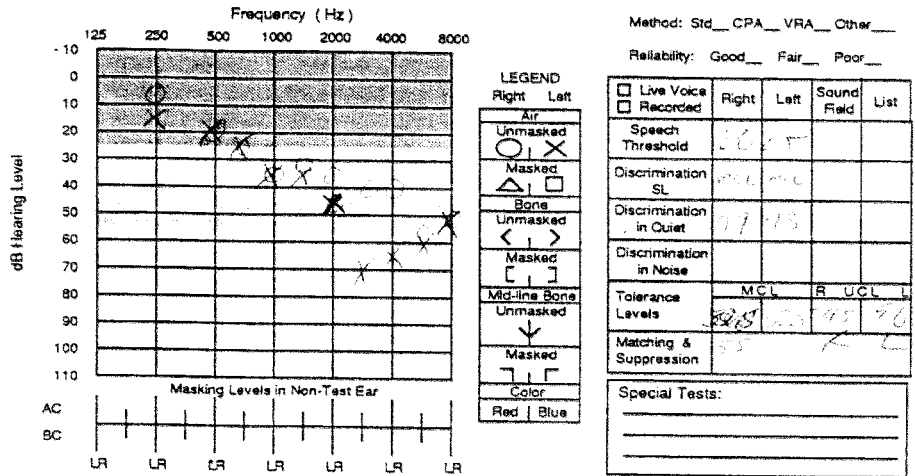


Fig. 1. AN/AD Patient 1. This is a 33-year-old adult who demonstrates fair word recognition ability in quiet, despite no ABR. Distortion product otoacoustic emissions are reduced with the possibility of some residual OAEs in some frequency regions (right ear response shown in the middle panel). ABRs obtained with condensation and rarefaction stimuli show that a small CM is present (shown to the right of the small vertical line in the lower panel). This patient reports great difficulty in situations with background noise but has managed quite well with lip-reading and represents a "milder" form of AN/AD.

pects from an ABR but are polarity-sensitive hair cell responses, or cochlear microphonics, whose latency remains constant despite decreasing intensity.

**VARIATION AMONG AN/AD PATIENTS**

In over 100 patients [Berlin et al., 2001], we have seen the following six

categories which teach us to treat the patient rather than the test results:

- 1) Some are incorrectly labeled "Deaf" because of flat ABRs but de-

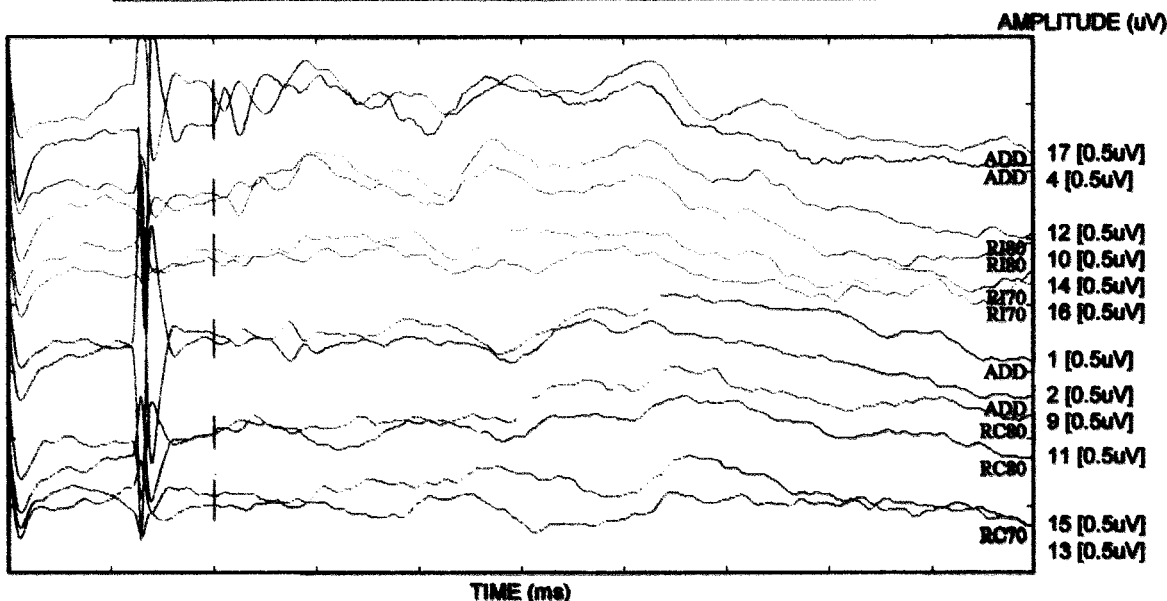
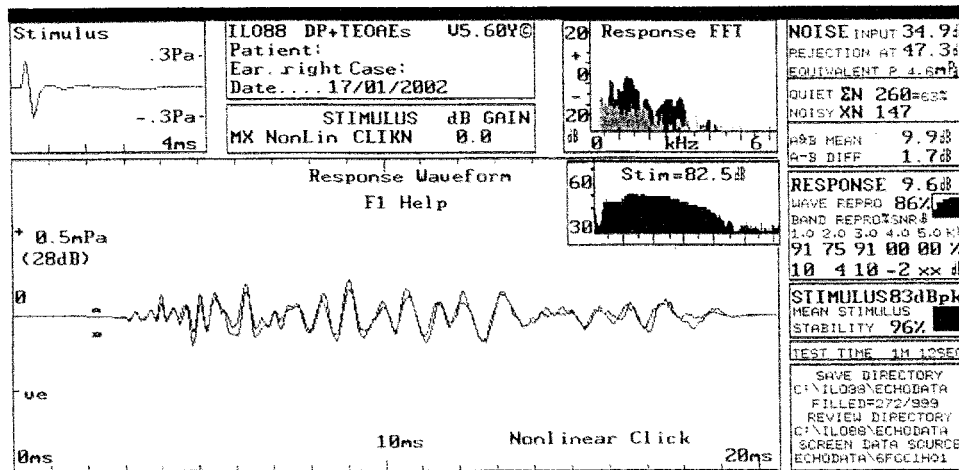
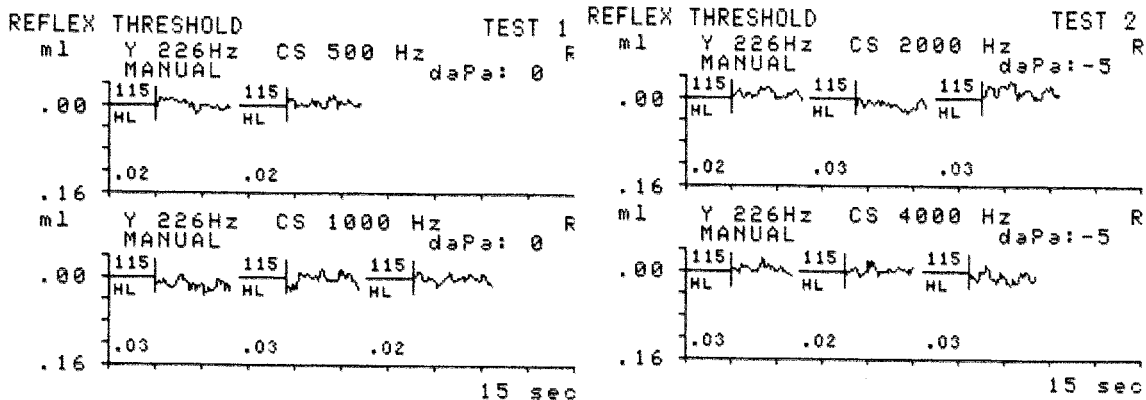


Fig. 2. AN/AD Patient 2. This two-month-old infant shows absent MEMRs (upper panel) and present OAEs in both ears (right ear shown in the middle panel). ABRs obtained with condensation and rarefaction stimuli show that a CM is present (shown to the right of the small vertical line in the lower panel) at the higher intensity levels. There is also some evidence of neural response later in the ABR tracings where the responses do not invert with stimulus polarity. This patient will be followed to monitor the ABR for signs of neuromaturation of the response.

velop normally and start hearing and speaking within a year to 18 months (7/100 in one sample). *If it were not for ABR screenings, they may never have been ear-marked or behaved as at-risk for hearing or language disorders.* Many such children grow into adults whose only real

complaint is a problem hearing in noise; they are often mis-diagnosed as having a central auditory disorder. They can be easily identified: patients with AN/AD have never been seen with middle-ear muscle reflexes at normal levels. (See Category 6 below.)

2) Some patients lose their emissions and cochlear microphonics but behave as if they have severe/profound hearing loss with occasional but fleeting episodes of hearing sensitivity.

3) Other patients lose their emissions but *not* their cochlear microphonics

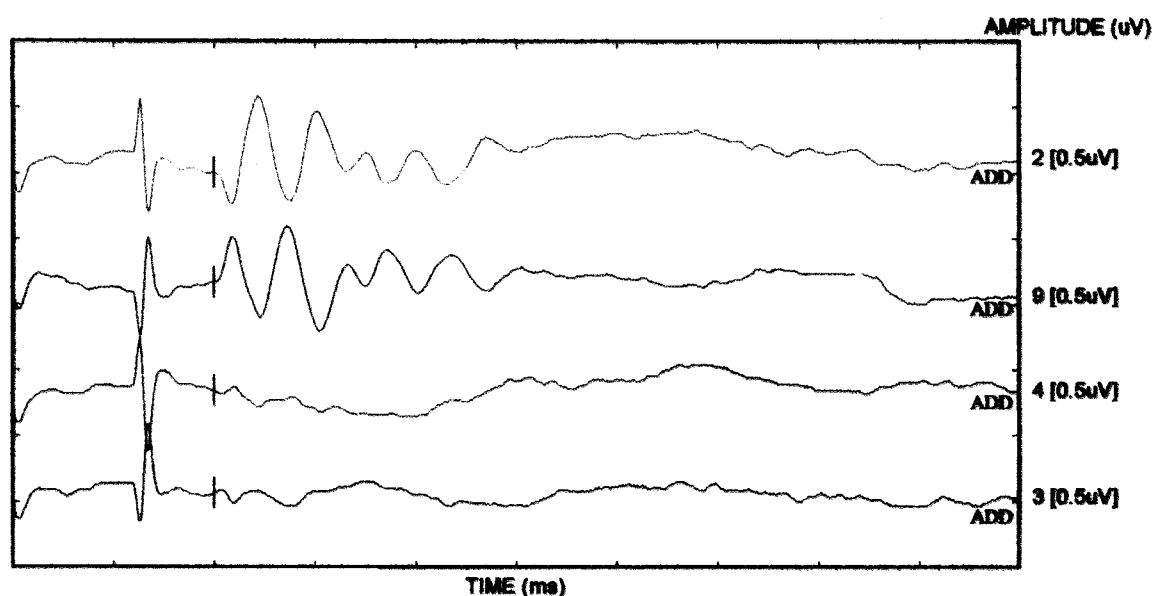
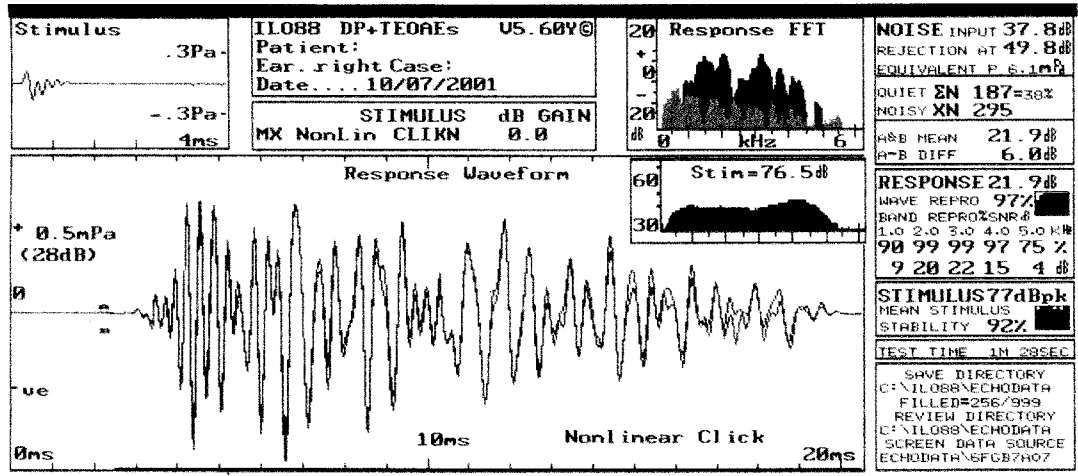
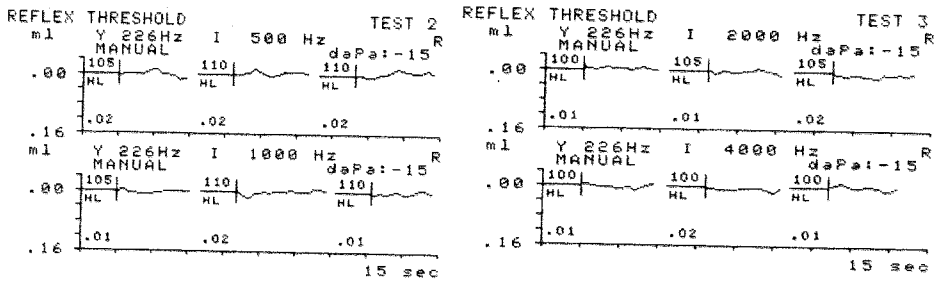


Fig. 3. AN/AD Patient 3. This 10-year-old male shows absent MEMRs (upper panel) and present OAEs in both ears (right ear shown in the middle panel). ABRs obtained with condensation and rarefaction stimuli indicate a robust CM (shown to the *right* of the small vertical line in the lower panel) at the higher intensity level. Recommendations for this patient included visual language training and consideration of a cochlear implant.

while behaving anywhere from deaf to occasionally showing unexpected hearing abilities.

4) Some patients stay the same and behave very deaf all the while. These are usually genetic in origin, and we have 12/100 subjects who have familial AN/AD

with *no* accompanying peripheral neuropathy.

5) Some AN/AD patients (12/100) develop peripheral neuropathies, such as Charcot-Marie-Tooth disease, later in life. This latter category more commonly describes later onset

AN. These patients quite likely have true auditory neuropathies as part of their systemic neuropathies. They develop speech and language normally but slowly lose speech comprehension, especially in noise or in less-than-ideal listening conditions.

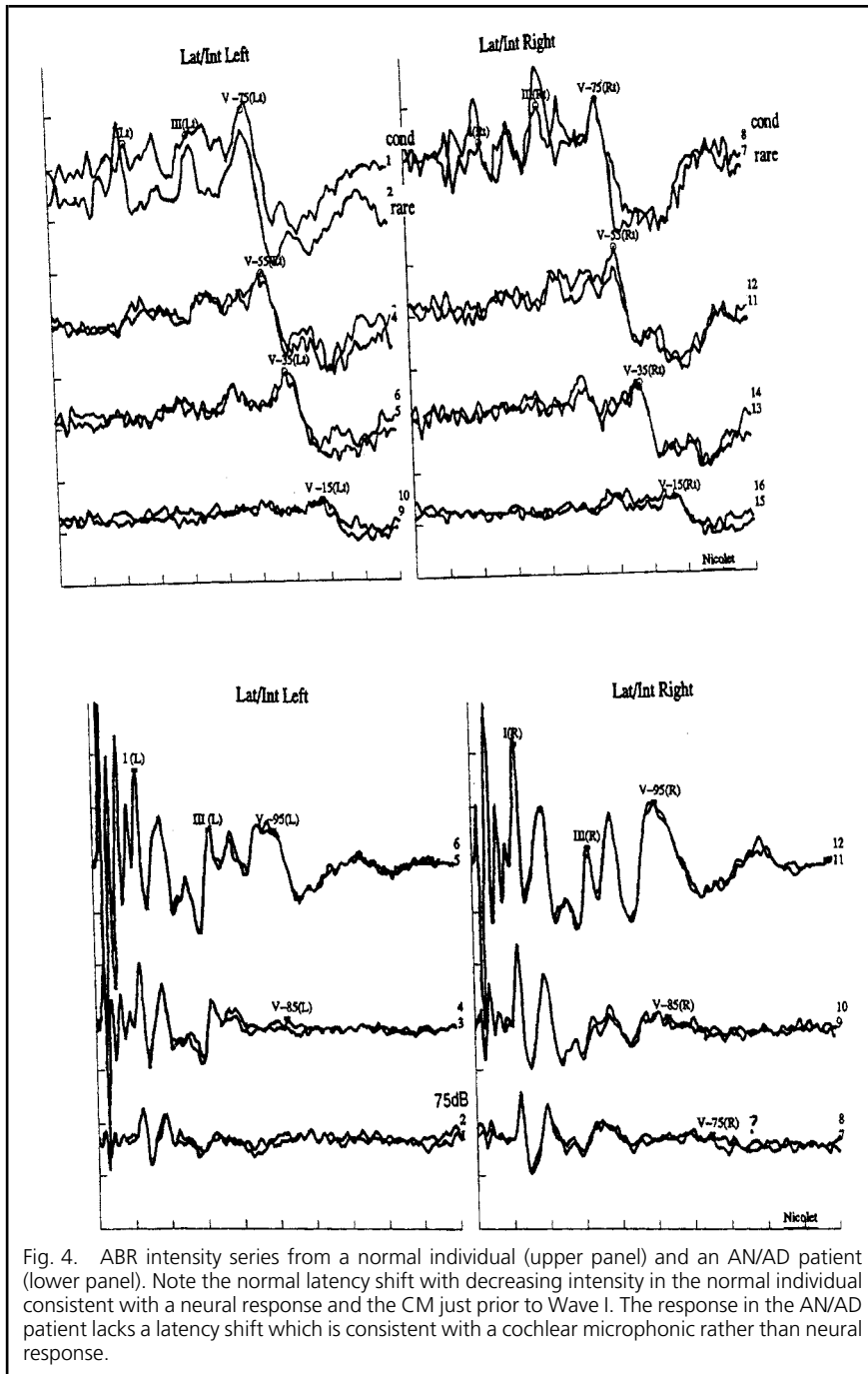


Fig. 4. ABR intensity series from a normal individual (upper panel) and an AN/AD patient (lower panel). Note the normal latency shift with decreasing intensity in the normal individual consistent with a neural response and the CM just prior to Wave I. The response in the AN/AD patient lacks a latency shift which is consistent with a cochlear microphonic rather than neural response.

6) Some patients go through life without complaining of *any problem*, developing speech and language normally, and would never have been discovered if no one had done an ABR as part of either a screening or research project. These may be the adult results of infant patients in Category 1 above. At present, we have no idea how many people like this exist or how many develop neuropathies much later in life, since we saw our first patient with this symptomatology in 1982. We saw him again 20 years later, after he finished law school and entered his own private practice. His only com-

plaints were that he could not hear in noise and kept failing hearing screenings after which he was regularly advised to wear hearing aids because of what appeared to be a mild high-frequency loss.

#### MANAGEMENT OF AN/AD PATIENTS

How do we recommend managing patients who are likely to have such an unpredictable course? The clinician should first take a history, including a family pedigree. If the etiology is likely to be genetic, recovery has yet to be seen in such children, whereas prematurity and

histories of hyperbilirubinemia suggest that maturation and autolysis of kernicterus might be expected to lead to some, if not total, decline in hearing loss behaviors. However, ABRs have not always reflected the hearing behaviors of the children (as noted on the AN/AD parent/patient listserve at groups.yahoo.com/group/AuditoryNeuropathy). We have learned from experience to follow a regimen that offers visual language first, coupled with observation of the child. In our hands, hearing aids make the child more aware of environmental sounds but do not lead to learning language auditorily. The drawback to using powerful hearing aids is that they may destroy outer hair cell function and, if the child is on the road to recovery, may cause a preventable high-frequency sensory loss.

For visual language exposure, in families who do not use ASL or other variants of sign language, we recommend Cued Speech [Cornett and Daisy, 1992; Fleetwood and Metzger, 1998]. This combination of hand positions and mouth shapes allows the child to visually eavesdrop on any and all languages spoken in the home. Using simple baby signs will help the baby express his or her needs and reduce everyone's frustration and enhance attachment, a state of affairs essential for normal language and personality growth.

#### SUMMARY

Auditory neuropathy/dys-synchrony patients have normal emissions and cochlear microphonics, and absent ABRs and absent middle ear muscle reflexes. Using *only* ABR or *only* otoacoustic emissions as a screening tool will subject you to a 10% error in one direction or the other. That is to say, 10% of children who fail an ABR screen and continue to show poor or no ABR may have auditory dys-synchrony and *not* respond well to hearing aids. Conversely, children with AN/AD have normal otoacoustic emissions and, therefore, cannot be identified by an emission-only screening test. Since AN/AD was not a target in the recently published guidelines [JCIH, 2000], clinicians and program administrators must be sensitized to this situation.

#### ACKNOWLEDGEMENTS

Research at Kresge Hearing Research Laboratory is supported by: NIH National Institute on Deafness and Other Communication Disorders, U.S. Department of Defense, American Hearing Research Foundation, National Organization for Hearing Research, Deafness Research Foundation, Oberkotter Foundation, Kam's Fund for Hearing Re-

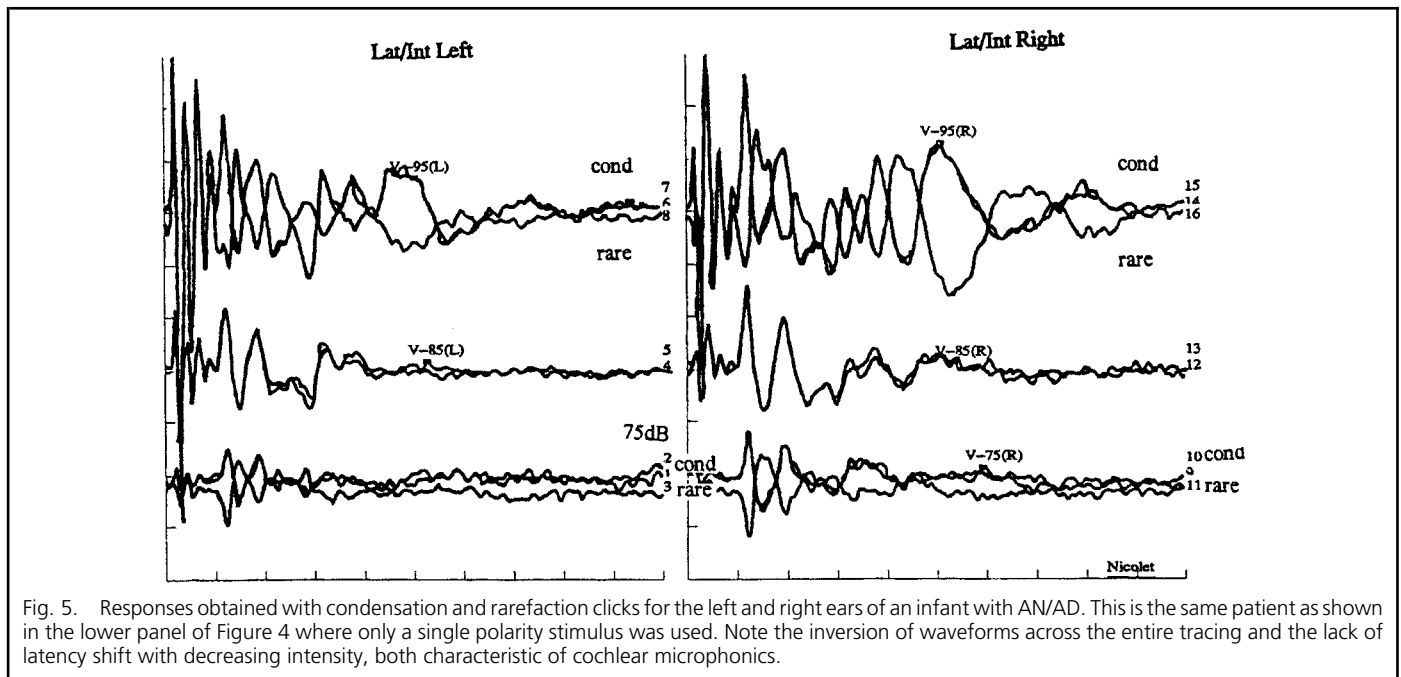


Fig. 5. Responses obtained with condensation and rarefaction clicks for the left and right ears of an infant with AN/AD. This is the same patient as shown in the lower panel of Figure 4 where only a single polarity stimulus was used. Note the inversion of waveforms across the entire tracing and the lack of latency shift with decreasing intensity, both characteristic of cochlear microphonics.

search, Marriott Foundation, and Louisiana Lions Eye Foundation.

Contributions to the study of patients with AN/AD at Kresge Hearing Research Laboratory were made by the following individuals: Harriet Berlin, M.A., Leah Goforth-Barter, M.S., Annette Hurley, M.S., Jennifer Jeanfreau, M.C.D., Elizabeth Montgomery, M.S., Patti St. John, M.C.D., Sonya Tedesco, M.C.D., Han Wen, M.S.B.E., and Diane Wilensky, M.S. ■

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