Auditory neuropathy/dyssynchrony
Its diagnosis and management
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Otoacoustic emissions, middle ear muscle reflexes, and auditory brain stem response (ABR) often are presented as “objective and infallible hearing screening tools.” They are not. Although a normal ABR with a normal latency-intensity function usually accompanies normal peripheral hearing, an absent or grossly abnormal ABR is not always associated with deafness. In contrast, a hearing loss of 30 dB or more usually predicts absent otoacoustic emissions, but normal emissions can be seen in some patients whose behavioral audiograms imply total deafness. Under circumstances that may occur in at least 10% of children with language and hearing problems, ABR and middle ear muscle reflexes can be absent while emission results are normal. This combination seriously affects management guidelines and, therefore, should be part of the screening procedure for every new patient. This article reviews the underlying auditory physiology that makes these tests useful and potentially misleading, and recommends steps to be considered by primary care physicians and other professionals to compensate for the vulnerabilities of each of the procedures.

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Fig. 1. (A) Transient evoked otoacoustic emissions in the left ear of a child born at 31 weeks. Tympanometry was normal, and the middle ear muscle reflexes were absent. (B) ABRs in the same child showed long ringing CMs that reversed polarity when click polarity was inverted. Abbreviation: FFT, Fast Fourier Transform.
**Definition**

Auditory neuropathy/dyssynchrony (AN/AD) most commonly is recognized when the first three items on the following list are observed:

1. Otoacoustic emissions are, or at one time were, present (they sometimes disappear with time or with hearing aid use).
2. ABR is absent or grossly abnormal. The ABR also can be misinterpreted as present when in fact a cochlear microphonic (CM) or hair cell response is masquerading as a neural response (see below).
3. Middle ear muscle reflexes are absent.

Thus, if only otoacoustic emissions are used as an initial screener, 10% of children who have normal emissions also may have serious auditory synchrony problems (see Fig. 1A, B). Similarly, if only alternating polarity or single polarity ABR is used an initial screener, approximately 10% of children with flat or abnormal ABRs will have normal emissions and may not respond well to hearing aids and auditory verbal therapy or strictly aural management with little or no visual support. Therefore, if ABR is the first tool of choice, abnormal ABRs should be followed up with emissions tests. If only emissions are used, they should be coupled with middle ear muscle reflex tests. Normal emissions and absent reflexes are a hallmark of AN/AD, and an ABR can be requested rationally [1].

Because patients often go through some metamorphoses, it is useful to initially perform an ABR with one positive and one negative polarity click (as described above) to differentiate hair cell from neural responses [2], and thereafter, in the follow-up of patients, to establish that:

4. Efferent suppression of otoacoustic emissions is absent.
5. Masking level differences are absent.
6. Speech perception, which may be surprisingly good in some patients in quiet surroundings, is seriously compromised in noisy surroundings.

Despite a totally absent ABR, approximately 7% of infants and children will act as if they have no hearing problems. Some actually develop with no apparent speech problems. Also, parents’ reports that their children’s hearing seems to come and go should be taken seriously. Thus far, these children have had histories of hyperbilirubinemia, and some actually develop with no apparent speech or hearing problems despite their absent ABRs.

**Underlying physiology**

There are five well-studied electroacoustic events in the cochlea (see Berlin et al [3] and the CD-ROM accompanying that book). They are:

1. The endocochlear potential, a +80 MV battery without which the cochlea essentially stops working [4]; note that clinically the patient will appear to
have a “sensorineural loss,” but initially there will be normal hair cells and nerve fibers (see Fig. 8-1 in Berlin et al [3]).

2. The CM, which is the reflection of the electrical activity emanating from both outer and inner hair cells. The CM generally lasts as long as the stimulus, so that if the stimulus is a click, the CM usually is quite brief (see Fig. 8-2 in Berlin et al [3]). The polarity of the stimulus determines the polarity of the recording, a phenomenon that is not seen in neural responses. In the early days of ABR and electrocochleography, especially when standard over-the-ear phones were used, alternating polarity clicks were commonly used to minimize, if not eliminate, both electrical artifact and the CM—which was considered irrelevant to the ABR interpretation. The focus of many ABR users was on wave V and its latency-intensity function (see Fig. 8-6 in Berlin et al [3], which shows a normal ABR latency-intensity function along with a normal inverting CM when the click polarity is inverted).

3. The compound action potential, which is wave I of the ABR as well as N1 of the electrocochleogram. This potential is the sum of synchronous discharges of many onset sensitive single units in response to a click or transient.

4. The summating potential (SP), which is a DC offset and part of the AC CM. The SP lasts as long as the stimulus, so that if a click is used, it is very brief. If a long tone burst is used, the SP lasts as long as the CM and the tone burst.

5. Otoacoustic emissions, which are acoustic output from hair cells, ascribable to both mechanical distortion products and direct echoes [5].

Clinical diagnosis and management: collaboration with audiologists

Patients with AN/AD, who exhibit no ABR and both normal emissions or normal CMs, have followed some well-described paths that range along a continuum from total behavioral deafness to a minimal penetration. We have noted that, at times, this penetration is so mild that it allowed some of our patients to develop superficially normal hearing, speech, and language and finish college and professional schools, including law school and medical school [6]. The behavioral pure-tone audiograms of patients with AN/AD are far less predictive than those of patients with ordinary conductive or common sensorineural loss that ordinarily would be responsive to hearing aids and auditory verbal management. The most common behavior that we have seen in almost 200 patients [6] is unpredictable hearing loss, interspersed with parental reports of “flashes of normal hearing”—sometimes interpreted by professionals as “the parent’s denial of deafness” or “wishful thinking.” In these cases, a mistake could be made by treating the test results instead of the child.

The pathophysiology of AN/AD varies. Some patients may have genetic or congenital absence of inner hair cells [7,8] that often are accompanied by anoxia or exchange transfusions, whereas others may have demyelinating diseases of the VIIIth nerve and other peripheral nerves in the body [9]. Many patients have mild hyperbilirubinemia (12–15 mEq dL) in their histories, and
there may be a gene involved that makes some patients—and their siblings—hypersensitive to bilirubin.

The value of preaudiometric triage

By testing each new patient with tympanometry, reflexes, and otoacoustic emissions, the diagnostician can save enormous amounts of time and diagnostic energy. This pretesting regimen will predict the audiologic results almost before they are obtained and, if the observed behavioral audiometry is at odds with the physiology, the wise tester will take the time to discover why [3]. For example, in a three-test triage, there are six possible combinations, as outlined in Table 1. If emissions are normal and reflexes are absent, there is almost always some form of auditory neuropathy. In this case, a carefully crafted ABR must be performed—not as a hearing test, but as a physiologic test of synchrony. Under this condition, any audiometry that is collected will not be useful for management without an ABR.

The danger of classifying patients by pure-tone audiometry alone

Some patients with AN/AD can have normal or nearly normal audiograms. If the assumption is made that a normal audiogram always generates normal ABRs and reflexes, many children with AN/AD will be missed. For example, Fig. 2 shows the pure-tone audiogram of a child who was previously misdiagnosed as being a malingerer and then having a central hearing loss. Ultimately, both he and his sister were found to have Charcot-Marie-Tooth (CMT) disease, in part, because of absent reflexes and absent ABRs. Patients with CMT quite likely have true auditory neuropathies as part of their systemic neuropathies.

Other procedures of interest

In addition to ABR and middle ear muscle reflexes, there are several other tests of auditory synchrony. One physiologic procedure is the study of efferent medial olivocochlear function. An auditory stimulus elicits an otoacoustic emission and is modified in the presence of noise, whether ipsilateral or contralateral to the stimulus. Patients with AN/AD show virtually no activation of this reflex, primarily because of the failure of the afferent nerve fibers to activate central structures with enough synchrony to bring about an efferent response [10]. This is true whether the AN/AD is bilateral (most common) or unilateral (we know of 12 cases).

Also of interest is a behavioral procedure called the masking level difference or MLD [11,12]. In this procedure, target tones are presented in the presence of noise in both ears and a threshold of hearing in noise is determined. Once this threshold has been determined, the phase angle of either the tones or the noise to one ear is reversed. In a normal system, the target tones become more audible by 10 to 14 dB, presumably because of cancellation of signals from both ears based on common synchrony. We have yet to see an AN/AD patient with a normal
<table>
<thead>
<tr>
<th>Tympanometry Reflexes</th>
<th>Normal hearing</th>
<th>Auditory neuropathy</th>
<th>Conductive loss</th>
<th>Sensory loss</th>
<th>Nonorganic loss or central auditory disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emissions</td>
<td>Normal</td>
<td>Normal, Absent</td>
<td>Abnormal</td>
<td>Normal, Elevated or absent</td>
<td>Normal Present</td>
</tr>
<tr>
<td>Auditory brain stem response to ± clicks if used</td>
<td>Present at 75–90 dB ipsilateral and contralateral</td>
<td>Present, absent</td>
<td>Usually present if loss does not exceed 75–80 dB</td>
<td>Absent or diminished</td>
<td>Usually present if loss does not exceed 75–80 dB</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Present and often robust</td>
<td>Absent or diminished</td>
<td>Normal, by bone conduction; delayed, by air conduction</td>
<td>Absent or diminished</td>
</tr>
<tr>
<td></td>
<td>Follows latency-intensity curve, cochlear microphonic at the beginning is seen to invert</td>
<td>Present and often robust</td>
<td>Normal, by bone conduction; delayed, by air conduction</td>
<td>Normal, by bone conduction; delayed, by air conduction</td>
<td>Normal latency-intensity function, just as in normal-hearing patients</td>
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MLD. Unfortunately, this is not an easy test to perform on anyone who cannot take a valid and reliable pure-tone audiogram.

Management

Spontaneous recovery or no obvious symptoms of an absent ABR

Children with AN/AD are being found more frequently because of the proliferation of newborn ABR-based hearing screening programs. Not every child with an absent ABR will act or grow up deaf. For reasons that are not yet understood, 7% to 10% of the AN/AD patients we have seen have had no observable symptoms other than an absent ABR, or have developed normal speech and language with only complaints of mild difficulty in language learning or poor hearing in noise. We urge our colleagues to cross-check every abnormal ABR with reflexes and emissions and to not manage the child as deaf until those tests show absent emissions and absent reflexes. In addition, it is important to be aware of the diagnosis of “central auditory processing disorder” or “language disorder” in the presence of “normal hearing.” Unless normal hearing is confirmed by tympanometry, normal reflexes, and normal emissions, there may be an underlying AN/AD that can be revealed by an ABR using one complete average with positive polarity clicks and another with negative polarity clicks. The resultant waveforms in AN/AD invert completely and reveal the lack of
neural synchrony. ABR usually is not necessary on every such patient when both middle ear muscle reflexes and emissions are present.

Amplification

Testing with a behavioral audiogram, and attempting to correct the audiogram with hearing aids, usually has been unproductive in our AN/AD patients, although the recent papers by Rance et al [13,14] promote hearing aid trials. Rance et al do admit that about half of their patients never obtain any benefit, but claim some benefit for the others. It may be that they are not observing the patients who did benefit from hearing aid trials in noise or for long enough periods. We, too, tried hearing aids at first and were encouraged by improved behavioral audiograms and improved “alertness.” Some parents also wanted these devices to work and were quick to embrace their efficacy. After a 20-year span of following close to 200 of these patients, however, we have noted that although some of our patients seemed to improve their detection and awareness with aids, none has ever adopted hearing aids and oral language as a successful lifelong strategy in the same way as does a conventional hard-of-hearing child, who has some residual ABR and reflexes, and shows full hearing aid benefits. Surprisingly, cochlear implants have been remarkably successful even in adults and children whose audiograms are not consistent with severe-to-profound deafness. In AN/AD, the pure-tone audiogram does not actually predict hearing abilities [15] and should be interpreted in a conventional manner only if emissions are absent and ABR or middle ear muscle reflexes imply a good residual neural complement.

Language learning and acquisition via oral, auditory, or visual means

The educational and language paths that a hard-of-hearing or deaf child might take are among the most controversial in our field. If the parents’ goal in raising a deaf child is to create a “literate taxpayer” (a concept that we learned from the parent of one of our most successful patients), deaf parents of deaf children will have the easiest time if they and their families are all signers. In our culture, the predominant sign language is American Sign Language [ASL]. ASL is neither English nor does it reproduce English sounds on the hands, but rather an entirely different language structure in which English is best learned as a second language. Many ASL users are both literate and well employed, and some of our AN/AD patients have been raised and educated successfully in Deaf Culture. Surprisingly, they may demonstrate among the best speech and lip-reading skills (even though ASL is usually promoted as a voice-off tool) because they hear speech when it is offered, although the speech they hear is usually quite garbled. (For an example of how it sounds, go to http://www.bsos.umd.edu/hesp/zeng/simulations.html or visit our Web page at www.kresgelab.org. From there, click on Information about Deafness and then go to Links to Other Web Sites. There you will see some examples that were produced by Drs. Fang Geng Zeng and
Arnold Starr that simulate the desynchronized sounds of speech when a patient has AN/AD. These simulations were based on psychophysical tasks completed on adult AN/AD patients.)

Cochlear implantation

Because the term “auditory neuropathy” implies to the casual listener that the patient must have pathologic or even nonfunctioning auditory nerves, we initially thought cochlear implants would not be useful; however, on the contrary, they are. They serve to activate available nerve fibers under nonfunctioning inner hair cells, or synchronize those neural elements that cannot discharge in a suitable manner [16]. Hence, our addition of the modifying term “auditory dyssynchrony” [17] to describe the problem as one of poor synchrony regardless of the etiology and signify that implants will work to restore or establish synchrony.

Children with AN/AD born to deaf parents often live very productive and comfortable lives in the Deaf World; they are sometimes surprisingly good lip readers because they hear a great deal of the speech envelope. In contrast, the most productive and desirable methods for educating a hard-of-hearing or deaf child to enter the parents’ hearing world are auditory-based methods (such as Auditory Verbal Therapy) in which the child learns language by ear and speaks as clearly as possible. These methods have not worked well for children with AN/AD and, unfortunately, if they are offered services and are categorized by their audiograms alone, the children get lost in the system and some hearing parents may feel that they are “failures” because their children have to enter the Deaf World instead of the hearing world. Although auditory therapies are not particularly successful as a sole means of management preimplant, they are ideal after cochlear implantation.

The take-home message for the primary care physician

Currently available “hearing tests” have their shortcomings. Many patients with AN/AD will continue to be missed if diagnosticians rely solely on behavioral audiometry. Certainly tympanometry alone—the tool most often used for detecting middle ear fluid—cannot detect AN/AD. The triage trio of tympanometry, reflexes, and emissions, however, is a formidable screening procedure that can detect virtually all patients who have normal emissions and absent reflexes. Unfortunately, over time, many children lose their emissions, either because of changes in the cochlea that have yet to be explained, middle ear disease, or surgery. In fact, some lose their emissions as a result of hearing aid use. Thus, the screening procedure loses its effectiveness if the emissions are masked.

Emissions and reflexes should be used together to rule out AN/AD. If the reflexes are absent and the emissions are present, AN/AD is highly likely. Working with audiologists who know and understand these issues and will perform an ABR with one complete average to positive polarity clicks and one complete average to negative polarity clicks is important. If the waveforms invert
completely, the diagnosis of AN/AD is complete and management should be tempered by watchful waiting with a skilled speech language pathologist who can monitor language comprehension growth and development to determine whether intervention is actually needed [3,18].

References