Patients with Auditory Neuropathy/Dys-synchrony Lack Efferent Suppression of Transient Evoked Otoacoustic Emissions

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Abstract

Function of the olivocochlear reflex, measured by suppression of transient evoked otoacoustic emissions, is assessed in nine patients with bilateral auditory neuropathy/dys-synchrony and compared to matched control subjects with normal auditory function. TEOAEs were acquired using 65 dB peak sound pressure linear clicks with and without the presence of broad-band noise presented binaurally, ipsilaterally, or contralaterally in a forward masking paradigm. Efferent suppression differed significantly between subject groups (p < .0001). Mean suppression was less than 0.22 dB across all suppressor noise conditions for the auditory neuropathy/dys-synchrony subjects. TEOAE suppression averaged 4.47 (binaural), 2.41 (ipsilateral), and 1.52 (contralateral) dB in the control subjects. Suppression characteristics across the three suppressor conditions were also assessed in one patient with unilateral auditory neuropathy/dys-synchrony. The results suggest that poor efferent responses are related to compromised afferent input to the OCR pathway and support the use of efferent suppression of otoacoustic emissions as a differential measure of auditory function in patients with auditory neuropathy/dys-synchrony.

Key Words: Auditory brainstem response, auditory dys-synchrony, auditory neuropathy, efferent system, forward masking, hearing disorder, human, middle-ear muscle reflex, olivocochlear reflex, otoacoustic emissions

Abbreviations: ABR = auditory brainstem response, AN/AD = auditory neuropathy/dys-synchrony, MEMR = middle-ear muscle reflex, MOC = medial olivary complex, OAE = otoacoustic emissions, OCR = olivocochlear reflex, TEOAEs = transient-evoked otoacoustic emissions

Sumario:

Se evaluó la función del reflejo olivo-coclear (OCR), medido por medio de la supresión de las emisiones otoacústicas evocadas por transitorios, en nueve pacientes con una neuropatía o una dis-sincronía auditiva bilateral, y los resultados fueron comparados con un grupo equiparado de sujetos control con función auditiva normal. Las TEOAE se obtuvieron mediante clicks lineares de 65 dB de pico de presión sonora, con y sin la presencia de un ruido de banda ancha, presentado en forma binaural, ipsilateral o contralateralmente, utilizando un paradigma de enmascaramiento anterógrado. La supresión eferente fue significativamente diferente entre los grupos (p<0.0001). La supresión...
Auditory neuropathy/dys-synchrony (AN/AD) describes a set of auditory characteristics shared by patients, ranging in age from infants to adults, who exhibit normal outer hair cell function and abnormal neural function and demonstrate significant hearing difficulty, particularly in situations with background noise. Normal outer hair cell function is demonstrated by the presence of otoacoustic emissions (OAEs) and cochlear microphonics. Abnormal neural function is reflected in measures of VIIIth nerve and brainstem function such as absent middle-ear muscle reflex (MEMR) responses despite normal tympanograms, auditory brainstem responses (ABRs) demonstrating a lack of synchronous response to click stimuli, and no masking level differences. Other clinical findings in patients with an AN/AD indicate variable pure-tone thresholds ranging from normal sensitivity to the severe or profound hearing loss range (e.g., Berlin et al., 1993a; Berlin et al., 1994; Gorga et al., 1995; Kaga et al., 1996; Starr et al., 1991, 1996). Speech recognition is quite variable though generally much poorer than expected and is particularly poor in noise or with competing messages.

A disruption in neural function in patients with AN/AD is further indicated by the lack of an olivocochlear reflex (OCR), as demonstrated by contralateral suppression of transient-evoked otoacoustic emissions (TEOAEs) (Berlin et al., 1994). The origin of otoacoustic emissions is ascribed to functions associated with active cochlear processes and the mechanical motion of the outer hair cells. Changes to emissions in the presence of a suppressor noise are thought to be modulated through the efferent auditory pathways via the olivocochlear system (Kemp, 1978; Kemp and Chum, 1980). Efferent auditory fibers travel from the olivocochlear bundle at the level of the olivary complex in the brainstem through the vestibulocochlear (VIIIth) nerve to the cochlea. The medial olivocochlear (MOC) fibers terminate primarily on the outer hair cells while the lateral olivocochlear fibers terminate mainly on primary auditory neurons at the base of the inner hair cells (Warr and Guinan, 1978; Warr et al., 1986). Thus, the influence of the MOC system on cochlear function can be measured by introducing an external suppressor stimulus and measuring its effect on otoacoustic emissions (e.g., Collet et al., 1990; Ryan et al., 1991; Berlin et al., 1993b). The MOC pathways have crossed and uncrossed fibers where the contralaterally responsive pathway is thought to involve primarily uncrossed MOC fibers and the ipsilaterally responsive pathway primarily crossed MOC fibers.

Most studies of suppression of TEOAEs have used continuous contralateral noise (e.g., Berlin et al., 1993b; Collet et al., 1990; Ryan et al., 1991).
commonly used measure of OAE suppression, continuous contralateral noise generates the smallest result (Berlin et al., 1995). To study efferent function more fully and to assess both the crossed and uncrossed MOC pathways as well as effects of binaural stimulation in humans, Berlin and colleagues (1995) applied a forward masking paradigm in normal subjects using suppressor stimuli presented to one or both ears. In a forward masking paradigm, the suppressor precedes, in time, the click or toneburst used to elicit the TEOAE that allows study of contralateral, ipsilateral, and binaural suppressor effects on TEOAEs. Our studies of subjects with normal hearing sensitivity and normal MOC function have consistently demonstrated a suppression effect that is greater for binaurally presented suppressor stimuli than for ipsilaterally or contralaterally presented suppressor stimuli (Berlin et al., 1995).

To date, OAE suppression results in patients with AN/AD have been reported with contralateral suppressor stimuli (Berlin et al., 1994; Starr et al., 1996) and anecdotal in single case studies for contralateral, ipsilateral, and binaural suppression (Berlin et al., 1996; Hood and Berlin, 2001). Since ipsilateral and binaural suppression paradigms appear to activate different or additional efferent pathways and yield higher suppression effects than contralateral suppressor stimuli, it is important to systematically test the OCR under these conditions as well. It is possible, though hypothesized unlikely, that some patients with AN/AD might display suppression under these more robust suppression conditions. Also, because of the broad variability among patients with AN/AD on some measures (e.g., pure-tone thresholds, word recognition) but not others (e.g., MEMR and ABR), we wished to test a group of subjects with AN/AD and compare them statistically to a group of carefully matched control subjects. Therefore, the purpose of this study was to compare OCR characteristics in patients with AN/AD to matched control subjects via suppression effects on TEOAEs measured using binaural, ipsilateral, and contralateral suppressor stimuli.

**METHOD**

**Subjects**

Ten subjects with documented AN/AD were studied. Characteristics of AN/AD were defined by the presence of OAEs and the absence of ABRs. All subjects were evaluated at the Kresge Hearing Research Laboratory and followed over time periods from one to 20 years. IRB-approved consent was obtained. Subjects with bilateral AN/AD ranged in age from 8 to 51 years with a mean age of 28 years. Subject demographics are shown in Table 1. Nine subjects had bilateral AN/AD while one subject had unilateral AN/AD. Subjects included in this analysis series all completed ipsilateral, contralateral, and binaural TEOAE suppression paradigms in one (n=1) or both ears (n=9). The nine experimental subjects with bilateral AN/AD were compared to control subjects matched for age and gender. Control subjects (seven females, two males) ranged in age from 14 to 49 with a mean age of 28 years. All control subjects had normal hearing sensitivity; some of these subjects were drawn from a previous normative study of TEOAE suppression (Hood et al., 1997).

**Procedures**

Efferent suppression of TEOAEs was assessed using 65 dBA peak sound pressure (SP) single-polarity, 80-microsecond clicks with and without the presence of 65-70 dBSPL broad-band noise. The stimulus levels are based on studies that demonstrated greater suppression effects for lower rather than for higher intensity clicks (Veuillet et al., 1991; Hood et al., 1996; Ryan and Kemp, 1996). Also, these intensities maximize the suppression effect while guarding against the use of intensity levels that may evoke a middle-ear muscle response. Click stimuli that employ all clicks with the same polarity are recommended to avoid distortions in response amplitude (Berlin et al., 1995; Collet et al., 1990). The suppressor noise, 400 milliseconds in duration, was presented either binaurally, ipsilaterally, or contralaterally in a forward-masking paradigm with 10 msec separating the offset of the noise from the onset of the click. Six suppressor conditions were tested: OAE measurement in the right ear with binaural, ipsilateral, and contralateral suppressor stimuli and OAE measurement in the left ear with binaural, ipsilateral, and contralateral suppressor stimuli. These suppressor conditions were interleaved with conditions where OAEs were obtained without the presence of suppressor stimuli. Two or three “without noise” and two or three of each of the “with noise” conditions were interleaved to minimize effects of subject
and stimulus level changes over time. The suppressor level was monitored with a low-noise probe microphone in the ear canal to ensure that accurate and constant suppressor intensity was maintained throughout testing.

**Data Analysis**

Data were initially analyzed using the Kresge EchoMaster Program (Wen et al., 1993) to quantify TEOAE amplitude, replicability of like (i.e., first without vs. subsequent without) responses, and suppression effects across time and frequency (Hood et al., 1999). Statistical analyses (repeated measures ANOVA) compared experimental and control groups with TEOAE amplitude and suppression amplitude from 8 to 18 msec, suppression amplitude in discrete 2-msec time periods from 2 to 20 msec, and suppression spectral amplitude across six frequency bands from 195 to 6000 Hz as the dependent variables. Suppression amplitude is plotted as dB differences in emission amplitude between conditions with and without suppressor signals. The focus on 8 to 18 msec in quantifying overall suppression amplitude is based on previous observations that the maximum suppression effects are concentrated in the time period between 8 and 18 msec (Berlin et al., 1993a; Hood et al., 1996).

**RESULTS**

TEOAE amplitude, obtained without suppressor noise, did not differ significantly between the two groups. Mean rms amplitude from 8 to 18 msec was 8.98 and 8.50 dB SPL for patients with AN/AD and 10.18 and 10.68 dB SPL for control subjects for the right and left ears, respectively.

**Overall Suppression in the 8- to 18-msec Time Period**

Suppression measured across the 8 to 18 msec time period was significantly lower
in the AN/AD patient group than the control subjects for all three suppressor noise conditions (binaural: \( p < .001, F = 27.006, \text{df} = 1,16 \); ipsilateral: \( p < .001, F = 23.368, \text{df} = 1,16 \); and contralateral: \( p = .003, F = 11.622, \text{df} = 1,16 \)). Mean suppression amplitude in the 8 to 18 msec time period and one standard deviation are depicted in Figure 1. Mean suppression for the patients with AN/AD was less than 0.22 dB across all suppressor noise conditions. Mean suppression for the control subjects was 4.57 and 4.37 dB (for binaural noise), 2.67 and 2.15 dB (for ipsilateral noise), and 1.65 and 1.39 dB (for contralateral noise) for the right and left ears, respectively. No significant differences in suppression were observed between the right and left ears.

To obtain an estimate of within subject variation, or test-retest variability, differences between "like" averages (e.g., two without suppressor noise conditions) were compared. Also shown in Figure 1 are horizontal arrows at the right and left edges of the graph depicting the average difference between two "without" conditions for the AN/AD (solid arrow) and control (dashed arrow) subject groups. The arrows to the left of the graph are for right ear data, and the arrows to the right are for left ear data. The average differences for the AN/AD group were 0.584 and 0.606 dB for the right and left ears, respectively. The average differences for the control group were 0.418 and 0.335 dB for the right and left ears, respectively. The average inter-run variation is well below the mean suppression values in the control subjects. In the AN/AD subjects, the average suppression did not exceed the inter-run variation.

### Suppression rms Amplitude in 2-msec Time Intervals

Suppression in the AN/AD and control groups was compared by discrete 2-msec intervals from 2 to 20 msec. Patients with AN/AD have significantly less suppression than control subjects for all suppression conditions across the 2- to 20-msec time window (Figures 2a-f). Significant group differences were observed for binaural, ipsilateral, and contralateral suppressors for the right and left ears (binaural RE: \( p < .001, F = 24.337, \text{df} = 1,16 \); ipsilateral RE: \( p = .001, F = 14.937, \text{df} = 1,16 \); contralateral RE: \( p = .047, F = 4.638, \text{df} = 1,16 \); binaural LE: \( p < .001, F = 34.252, \text{df} = 1,16 \); ipsilateral LE: \( p = .001, F = 14.869, \text{df} = 1,16 \); contralateral LE: \( p = .003, F = 12.788, \text{df} = 1,16 \)).

The amount of suppression varied among the 2-msec time periods with significant differences \( (p < .001) \) observed for the binaural and ipsilateral conditions. The greatest suppression occurred in the 8- to 18-msec time periods, consistent with previous findings (e.g., Berlin et al., 1993a; Hood et al., 1996). Also, in the control subjects, suppression was greatest for the binaural suppressor noise condition, which is consistent with previous studies (Berlin et al., 1995).

### Suppression Spectral Amplitude in Six Frequency Bands

Comparisons between groups were also made as a function of frequency characteristics of suppression. Spectral amplitude data were grouped into six frequency bands with widths of 1000 Hz and center frequencies of 0.5, 1.5, 2.5, 3.5, 4.5, and 5.5 kHz (Figures 3a-f). Consistent with the results for amplitude
across time, the AN/AD group showed significantly less suppression than control subjects across all frequency bands for all suppressor conditions (binaural RE: \( p < .001, F = 32.143, df = 1,16 \); ipsilateral RE: \( p < .001, F = 21.266, df = 1,16 \); contralateral RE: \( p = .002, F = 14.356, df = 1,16 \); binaural LE: \( p < .001, F = 56.392, df = 1,16 \); ipsilateral LE: \( p = .002, F = 14.251, df = 1,16 \); contralateral LE: \( p = .018, F = 6.952, df = 1,16 \)). Differences in suppression spectral amplitude were observed among frequency bands that are consistent with previous reports indicating stronger suppression in the 1 to 3 kHz range (e.g., Hood et al., 1996; Goforth et al., 1997).

**Figure 2.** Mean suppression RMS amplitude (and one standard deviation) across time in 2-msec intervals for patient and control groups for (a) right binaural, (b) left binaural, (c) right ipsilateral, (d) left ipsilateral, (e) right contralateral, and (f) left contralateral suppressor noise.
Comparison of Suppression Amplitude and Pure-Tone Thresholds

Control subjects in this study all had normal pure-tone thresholds. Behavioral threshold responses to pure-tones varied widely among the patients with AN/AD, with pure-tone averages (0.5-4kHz) ranging from 15 to 95 dB HL.

The amount of suppression was small for all auditory neuropathy subjects, despite differences among subjects in behavioral thresholds. There were no significant relationships between suppression amplitude and pure-tone average (Figure 4). In other words, those patients with AN/AD with poor pure-tone thresholds did not show suppression that was different than those

Figure 3. Mean suppression spectral amplitude (and one standard deviation) across six frequency bands for patient and control groups for (a) right binaural, (b) left binaural, (c) right ipsilateral, (d) left ipsilateral, (e) right contralateral, and (f) left contralateral suppressor noise.
patients with AN/AD with normal or nearly normal pure-tone thresholds.

Unilateral Auditory Neuropathy/Dysynchrony

Unilateral auditory neuropathy/dysynchrony offers an opportunity to gain insight into afferent and efferent contributions to OAE suppression. The same test paradigms as reported for the bilateral patients with AN/AD and control subjects were completed on a patient with normal auditory function in one ear and AN/AD on the other side. This patient was referred to us at age 12 years with reported learning problems and suspicion of a possible central auditory processing disorder. She had not complained of a hearing loss, and the hearing abnormality was first noted on a school hearing screening test.

Audiometric testing indicated normal pure-tone thresholds across the frequency range for the right ear and thresholds in the profound hearing loss range for the left ear, with no response to pure-tones in that ear with appropriate masking in the normal ear. Word recognition in quiet was consistent with the hearing loss, that is, 100% in the right ear and 0% in the left ear. Ipsilateral and contralateral MEMRs were normal upon stimulation of the right ear and absent for stimulation of the left ear. The ABR for the right ear showed normal absolute and interwave latencies and normal response thresholds, with increasing latency, for clicks and 500-Hz tonebursts. The ABR was absent for the left ear under all test conditions. OAEs were present and robust for both ears as well as cochlear microphonics that inverted with reversal of the stimulus polarity and were larger and longer in duration for the left ear. These findings were consistent with normal outer hair cell function bilaterally and the presence of AN/AD in the left ear.

TEOAE suppression yielded a combination of present and absent responses. When the right (normal) ear received the suppressor stimulus (RE binaural, RE ipsilateral, and LE contralateral conditions shown in Figure 5), suppression was present. The only other condition where suppression was present was in the LE binaural condition where both the left and right ears were stimulated. When suppressor stimuli were delivered to the left (profound loss ear) ear only, suppression was below normal regardless of the click location. The similarity in amplitude between the LE binaural and LE contralateral conditions suggests that only the right ear is processing the suppressor stimulus effectively, and thus the absence of the olivocochlear reflex in patients with AN/AD is most likely traceable to an afferent deficit.

Figure 4. Suppression magnitude is shown in comparison to pure-tone thresholds (0.5-4 kHz average) for the right (a) and left (b) ears of AN/AD patients. The amount of suppression does not vary systematically with threshold sensitivity.
DISCUSSION

TEOAE Suppression in Patients with Auditory Neuropathy

Patients with AN/AD examined in the present study demonstrated significantly reduced suppression of TEOAEs for binaural, ipsilateral, and contralateral suppressor stimulus conditions. In fact, there was a general lack of an OCR in this patient group, despite variation in other auditory and non-auditory characteristics. This finding is consistent with reports of a lack of contralaterally induced suppression in patients with AN/AD (Berlin et al., 1993a; Starr, 2001).

In normal subjects, binaurally presented noise produces significantly greater suppression than ipsilateral or contralateral noise. In assessing suppression in patients with AN/AD, the most robust test would use binaural stimuli where the largest OCR would be expected. The finding of the lack of an OCR for all three suppressor conditions suggests an overall dysfunction of the OCR, regardless of the suppressor stimulation paradigm. To further ensure that we were able to identify even subtle suppression effects, analyses were completed using the detailed EchoMaster analysis method. Even with this highly sensitive method of demonstrating suppression effects, there was little evidence of efferent suppression in these patients.

TEOAE Suppression in Patients with Auditory Nerve Disorders

Patients with AN/AD can be differentiated from those with radiologically or surgically documented space-occupying or other lesions of the VIIIth nerve because patients with AN/AD have normal CT and MRI results. However, absence of OAE suppression has been reported in both types of disorders. For example in patients with VIIIth nerve lesions who retain OAEs, a lack of efferent suppression is reported (Maurer et al., 1992; Prasher et al., 1994; Liang et al., 1997). A lack of OAE suppression also has been demonstrated in patients who undergo vestibular neurectomy (Williams et al., 1994; Giraud et al., 1995). This procedure involves sectioning the inferior vestibular fibers that carry both medial and lateral efferent bundles with the goal of alleviating vertigo while preserving hearing. Since the efferent fibers are targeted in vestibular neurectomy, the lack of suppression found in their studies provides supporting evidence for the role of the efferent system in OAE suppression.

Comparison of Control Group to Previous Normal Studies on OCR Characteristics

The control subjects in this study showed the greatest suppression effect (an average of about 4.5 dB) for the binaural suppressor condition, the least suppression with contralateral noise (about 1.5 dB), and slightly greater suppression with ipsilateral than contralateral stimulation. This is a pattern and magnitude that we have consistently observed in normal subjects (e.g., Berlin et al., 1995; Hood et al., 1997). This pattern of MOC reflex strength also is consistent with the distribution of auditory efferent fibers reported in the cat (Warr et al., 1986) where a greater number of crossed than uncrossed fibers are observed. Remember, of course, that the crossed olivocochlear fibers cross the midline and return to terminate on the outer hair cells of the homolateral ear.

Figure 5. TEOAE suppression results in a patient with unilateral AN/AD.
Potential Problems and Other Considerations

Middle-ear muscle reflexes and acoustic cross-talk or crossover of sound through the head can contaminate measurement of efferent suppression. However, the observation that weaker suppressors generate more suppression than more intense suppressors demonstrated by Veuillet and colleagues (1991) and Hood and colleagues (1996), reduces the domination of the middle-ear muscle reflex and crossover. If suppression were related to either of these phenomena, then suppression would be expected to increase at higher stimulus intensities. In addition, suppression has been observed in patients who lack stapedius muscle function due either to Bell’s Palsy or stapedius tendon section during stapedectomy. Nevertheless the consideration of subclinical middle-ear reflex intrusion cannot be entirely ruled out without some of the precautions suggested by Guinan (2002). These potential problems, however, underscore the importance of monitoring stimulus and suppressor levels during testing.

Potential Sites of Abnormality Contributing to the Abnormal/Absent OCR in Patients with AN/AD

The auditory system has two reflexes mediated through the brain stem pathways that are measurable clinically in humans. These are the middle-ear muscle reflex that results in contraction of the stapedius muscle via stimulation from the seventh cranial (facial) nerve and the olivocochlear reflex (OCR) where activation of the medial olivocochlear (MOC) pathways alters otoacoustic emissions (OAEs). For TEOAEs, the effect is generally referred to as suppression, based on the characteristic decrease in OAE amplitude in the presence of a suppressor stimulus.

Patients with AN/AD characteristically show an absence of both the MEMR and OCR. Evidence suggests that the lack of these reflexes is most likely related to a breakdown in the afferent portion of the reflex arc. When the MEMR is tested with non-acoustic facial tactile stimulation, patients with AN/AD demonstrate contraction of the stapedius muscle (Berlin et al., 1994; Gorga et al., 1995; Starr et al., 1998). Furthermore, Shallop and colleagues (2001) have shown stapedius muscle contraction in patients with AN/AD to auditory signals following cochlear implantation. In AN/AD, it is possible that the auditory nerve may not achieve discharge rates high enough to activate either middle-ear muscle or olivocochlear reflexes (Starr, 2001; Starr et al., 2001).

It is also possible that sufficient synchrony cannot be achieved to allow representation of auditory nerve and brainstem responses via the ABR, activation of auditory reflex responses, or other processes dependent upon temporal synchrony. The suggested possible sites of abnormality in AN/AD include an absence or dysfunction of inner hair cells, synaptic abnormalities, and axonal loss or demyelination. Each of these could contribute to poor neural synchrony or a lack of neural discharge sufficient to accurately convey auditory information (Kraus et al., 2000; Berlin et al., 2001).

Unilateral AN/AD: Do Suppression Patterns Support an Afferent or Efferent Problem?

Patients with unilateral AN/AD may provide insight into the influence of afferent versus efferent neural function on suppression. These patients have intact OAEs in both ears but absent ABRs and MEMRs on one side. The efferent suppression patterns found for binaural, ipsilateral, and contralateral noise provide insight into the influence of afferent and efferent pathways on suppression.

Suppression results for the patient with unilateral AN/AD indicate that TEOAE suppression is present upon stimulation of the normal (right) ear but is not enhanced (in the binaural condition) by addition of the suppressor noise to the left ear. The finding of similar suppression for the RE binaural and RE ipsilateral conditions suggests that the RE binaural condition might effectively be only an ipsilateral-like condition. The presence of suppression in the affected (left) ear when the suppressor stimulus is presented to the normal ear, though smaller in amplitude than in the normal ear, suggests that the efferent system is functioning. The absence
of suppression only when the affected ear is stimulated with the suppressor noise strongly implicates a defect in afferent function.

SUMMARY

This paper describes characteristics of the OCR, measured by efferent suppression of otoacoustic emissions in patients with AN/AD and matched control subjects. TEOAE suppression was significantly poorer in patients with AN/AD than in age and gender matched controls for all stimulus and suppressor conditions. Consideration of acoustic and non-acoustic MEMRs and the pattern of OCR amplitude in a patient with unilateral AN/AD suggests that the lack of TEOAE suppression is due to a disruption in afferent input to the auditory pathway. Efferent suppression of TEOAEs appears to be a sensitive measure of auditory function in patients with auditory dys synchrony/ neuopathy and should provide insight into the underlying mechanisms.

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