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Cochlear Receptor (Microphonic and Summating Potentials, Otoacoustic Emissions) and Auditory Pathway (Auditory Brain Stem Potentials) Activity in Auditory Neuropathy

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Objective: To define both auditory nerve and cochlear receptor functions in subjects with auditory neuropathy (AN).

Design: We tested 33 AN subjects (66 ears) and compared them with 21 healthy subjects (28 ears). In AN subjects, the average pure-tone (1, 2, and 4 kHz) threshold loss was 57 dB HL. Click stimuli were used to elicit transient evoked otoacoustic emissions (TEOAEs), cochlear microphonics (CMs), and auditory brain stem responses (ABRs). Both cochlear and ABR potentials were recorded from surface electrodes (vertex-ipsilateral mastoid) using averaging procedures. The amplitudes and latencies of CMs and ABRs and the amplitude of the TEOAEs were analyzed.

Results: CM amplitudes recorded from normal ears decreased as a function of subject age. CMs recorded from AN subjects fell within the normal age-adjusted range in 60% of the subjects and were >2 SEEs (standard error of estimate) above the age-adjusted normal regression in 40% of the subjects. TEOAEs were absent in 19 (30%) AN ears (bilaterally in eight, and unilaterally in three subjects) and were present in 44 ears. In AN subjects, correlations among CM amplitude, TEOAE amplitude, and pure-tone average thresholds were not significantly related. CM amplitudes were not significantly different whether TEOAEs or ABRs were present or absent. The ABR was present in 21% of AN subjects and consisted of a low-amplitude Wave V without a preceding Wave I. Measures of CM amplitude and PTA hearing loss were not significantly different in those AN ears with a preserved ABR compared with ears with absent ABRs. Summating potentials to transient click stimuli were of small amplitude (<0.1 μ V) and detectable in approximately 50% of the AN and healthy control subjects limiting formal analysis of summating potentials.

Conclusions: In a significant proportion of AN subjects, we found abnormalities of cochlear receptor function, including elevated CM amplitudes and absence of TEOAEs. These two abnormalities occurred independently of each other. A low amplitude Wave V of the ABR was found in approximately

one-fifth of AN subjects, evidence that neural synchrony can be partially preserved in some subjects with this disorder.

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Physiologic measures of cochlear and auditory nerve function such as otoacoustic emissions (OAEs), cochlear microphonics (CMs), and auditory brain stem responses (ABRs) may be of assistance in distinguishing between hearing disorders due primarily to auditory nerve disorders from those due primarily to cochlear receptor disorders. OAEs are faint sounds generated by outer hair cells that can be detected in response to sound stimuli (transient or distortion products) in most normal-hearing subjects using a microphone in the external ear canal (Kapadia & Lutman, 1997; Kemp, 1978; Probst, Lonsbury-Martin, & Martin, 1991). These sound-evoked OAEs are absent or reduced in hearing losses thought to be of cochlear origin (Prieve et al., 1993). CMs are potentials generated by activation of both inner and outer hair cells (Dallos & Cheatham, 1976) and their absence is compatible with impaired hair cell function. ABRs are generated by auditory pathway structures with Waves I and II in humans representing activity of the auditory nerve and Waves III, IV, and V representing activation of brain stem auditory structures (Moller, Janneta, & Sekhar, 1988). An absence or severe abnormality of ABRs when OAEs and/or CMs are preserved indicates disordered auditory nerve function in the presence of normal cochlear hair cell functions (Berlin, Hood, Cecola, Jackson, & Szabo, 1993; Chisin, Perlman, & Sohmer, 1979; Park & Lee, 1998; Starr et al., 1991).

Patients with abnormal ABRs in the presence of preserved cochlear receptor measures have pure-tone audiograms that are typically of a flat or rising configuration (Rance et al., 1999; Starr, Picton, Sininger, Hood, & Berlin, 1996). Speech perception is impaired out of proportion to the elevation of the pure-tone threshold and auditory percepts dependent on temporal cues are particularly disrupted (Starr et al., 1991; Zeng, Oba, Garde, Sininger, &

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Starr, 1999). Acoustically activated brain stem reflexes involving middle ear muscles and olivocochlear bundle (OCB) are typically absent (Berlin et al., 1993; Starr et al., 1996).

The clinical picture of disordered auditory nerve function and preserved cochlear outer hair cell activity has been termed "auditory neuropathy" (AN), because many of these patients also have an accompanying axonal or demyelinating neuropathy of their peripheral nerves (Butinar et al., 1999; Starr et al., 1996) and evidence of vestibular nerve impairments (Fujikawa & Starr, 2000). However, disordered auditory nerve function in the presence of preserved OAEs and/or CMs could occur if the auditory nerves were normal but inner hair cells and/or synapses linking inner hair cells to the dendrites of healthy auditory nerve fibers were impaired. These latter conditions have not yet been identified in hearing-impaired subjects.

The preservation of OAEs and CMs in AN has been considered evidence that cochlear outer hair cell function is normal in this disorder (Deltenre, Mansbach, Bozet, Clercx, & Hecox, 1997; Kaga, Nakamura, Shinogami, Tzuzuku, Yamada, & Shindo, 1996; Starr et al., 1996; Stein, Tremblay, Pasternak, Banerjee, Lindemann, & Kraus, 1996). However, there are several findings that could represent abnormal cochlear outer hair cell function. First, CMs in subjects with AN have been noted to be especially prominent and to persist several milliseconds after a transient click stimulus (Berlin et al., 1998; Deltenre et al., 1997; Starr et al., 1991), findings not reported in normal-hearing subjects. Second, transient evoked otoacoustic emissions (TEOAEs) may be absent in a number of patients (Deltenre et al., 1999; Rance et al., 1999) who otherwise fulfill criteria for AN (Starr et al., 1996). There are only a few reports (Deltenre et al., 1997; Starr, Sininger, Winter, Derebery, Oba, & Michalewski, 1998) of summing potentials (SPs) in patients with AN without clarification of whether the SPs were normal.

We have made a systematic study of cochlear receptor activity (CMs, SPs, TEOAEs) in 33 AN and 21 control subjects. CMs were abnormally increased in amplitude in 13 AN subjects, all of whom were less than 10 yr of age. AN subjects, 10 yr or older, had normal amplitude CMs. TEOAEs were absent in 30% of patients independent of age, and SPs were detected in approximately 50% of both patients and healthy controls.

METHODS

Subjects

Thirty-three (12 female, 21 male) AN subjects ranging in age from 4 mo and 64 yr and 21 healthy subjects (8 female, 13 male) between 1 wk and 43 yr

of age were tested. Pure-tone audiograms were available for 57 of the 66 affected ears. A total of 28 control ears were tested for CMs. TEOAEs were not tested in the control subjects. ABR test results were available for 57 AN ears and 28 control ears. All testing followed university guidelines for approved projects involving human subjects. Subjects, or their parents or guardians gave signed consent for participation in the study.

Otoacoustic Emissions

We used the published norms for TEOAEs (Abdala, 1996) to define abnormal values in the present study. The emissions were recorded with an ILO-92 OAE system using nonlinear click levels ranging from 80 to 86 dB peak SPL. Emissions in response to as many as 260 stimuli were averaged over a 20 msec window. The presence of normal OAEs in the 2.5 to 20 msec poststimulus period was determined by an overall response amplitude signal to noise ratio of at least 4 dB and waveform reproducibility in at least three octave bands of >75%. An analysis of TEOAE amplitude as a function of spectral bands was not performed.

Cochlear Potentials

Square wave pulses (0.1 msec) activated a transducer (Etymotic ER-3, Etymotic Research, Inc., Elk Grove, Illinois) coupled to the ear canal by a section of 10 cm-long plastic tubing and a foam ear insert. The tubing and insert introduced a 0.85 msec delay between electrical activation of the transducer and the appearance of the acoustic waveform at the end of the insert. The latencies of the recorded potentials were adjusted to take into account this transmission delay. The stimulus intensity used, 110 dB peak SPL, was determined in separate experiments to be approximately 20 dB above the threshold of healthy ears for the detection of CM using our recording methods and instrumentation. Clicks of a single polarity (condensation and rarefaction) were presented at approximately 20/sec. The polarity of the initial phase of the acoustic waveform was determined by connecting the end of the foam ear insert to a 1-cc coupler and recording the acoustic waveform with a condenser microphone and Bruel and Kjaer sound level meter. The amplified output of the sound level meter was displayed on an oscilloscope and the voltage polarity of the initial acoustic wave was compared with that obtained when a known pressure displacement (increase) was introduced into the coupler.

Recordings

Subjects were tested in a sound attenuating chamber while reclining in a comfortable armchair. AN subjects, under 6 yr of age, who would not sit quietly, were sedated with chloral hydrate. Cochlear and auditory brain stem potentials were recorded with electrodes placed at Cz and the mastoid ipsilateral to the ear being stimulated. A ground electrode was placed at Fz. The impedance measured between any two-electrode sites was below 5 k Ω . Amplification was 100,000 times at a band pass of 30 Hz (or 100 Hz) to 3000 Hz. In approximately two-thirds of the ears tested, averaging was terminated when the noise level as determined by the single point variance was reduced to 0.04 μ V (Don & Elberling, 1996). In the remainder, averaging was terminated when the signal (CM) was visually determined to be present above background recording noise. The A/D (16-bit) sampling rate was 100 kHz. The presence of a stimulus artifact in the average was minimal for those patients tested with the click transducer in a shielded box. The same transducer without a shielded box produced a transient stimulus artifact of approximately 1 msec before the first occurrence of CM components.

Data Reduction and Analysis

Cochlear Potentials • Superimposed potentials in a normal-hearing subject to condensation (C) and to rarefaction (R) click stimuli (Fig. 1 top, C & R) revealed short latency (approximately 0.4 msec) components that had a phase inversion with polarity reversal of the stimulus. Clamping the plastic tube resulted in the loss of these components distinguishing them as biologic in origin rather than a recording artifact of the electrical input to the earphone. Summing the separate averages to C and R stimuli (C + R in Fig. 1) resulted in a cancellation of the CM leaving neural components (Waves I to V) with a small SP on the rising slope of Wave I. When the traces were subtracted (C - R in Fig. 1), CMs were enhanced because of their phase reversal whereas in-phase neural and SPs were attenuated. Subtraction did not result in cancellation of all neural potentials because the latter shift slightly in latency and morphology as a function of click polarity (see the superimposed C - R traces in Fig. 1). The latency of the initial peak of the phase-reversed CMs occurred at 0.42 ± 0.2 msec in 74/85 recordings (47 of 57 neuropathy ears and 27 of 28 control ears). In the other 11 recordings the initial phase reversed component occurred earlier at 0.26 ± 0.02 msec (10 neuropathy ears and 1 control ear). The phase of the initial microphonic potential (0.26 or 0.42 msec) to condensation stimulus was mastoid negative in 71 of

Cochlear and Auditory Brainstem Potentials

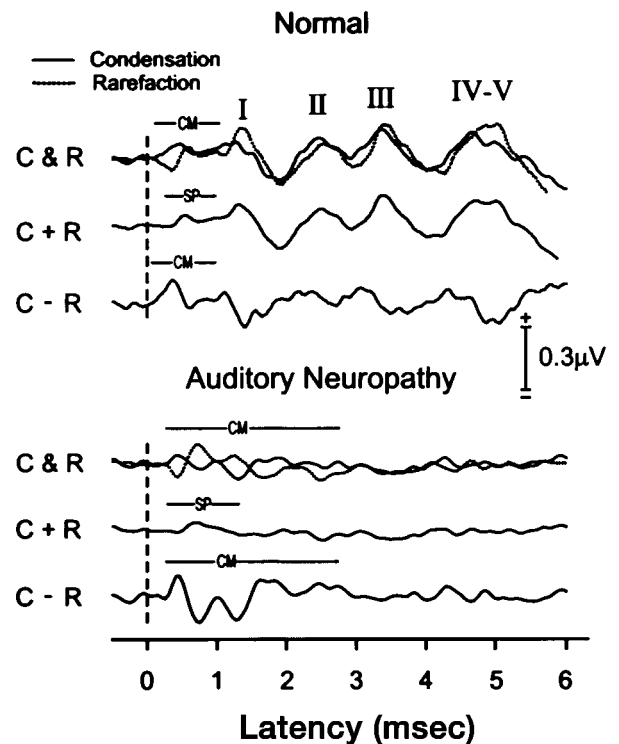


Figure 1. Auditory brain stem responses from a healthy control (8-yr-old, top) and an auditory neuropathy subject (5-yr-old, bottom) recorded from vertex to the mastoid ipsilateral to the acoustic stimulus are superimposed in the top traces (C & R) of each record to separately presented condensation (C) and rarefaction (R) click stimuli. Roman numerals (I through V identify neural components), and cochlear microphonics (CM) are identified by their phase reversal. Phase reversed components are attenuated when the two averages are added (C + R) and enhanced when the averages are subtracted (C - R). A summating potential (SP) on the rising slope of Wave I is marked in the C + R trace. Zero ("0") in the time base refers to the time of arrival of the sound stimulus at the eardrum. Note the presence of CM and SP in both subjects and the presence of neural components only in the healthy control.

the 84 ears tested. The exceptions were in 10 neuropathy and three control ears. We did not monitor the acoustic waveform in the ear canal to determine whether differences of CM onset phase and latency were the result of changes in acoustic stimulus (spectrum and/or phase) introduced by the stimulus delivery system or the ear canal.

We measured the amplitude of the CM in both patients and healthy controls in the subtracted averages to C and R stimuli (C - R) as the difference between adjacent peaks occurring between 0.4 and 0.6 msec, the latency domain at which CM amplitudes were maximal in 50 of 57 AN and all normal

ears. In seven AN ears the maximum amplitude of CM occurred between 0.7 and 1.2 msec. In healthy controls, we did not use out-of-phase components after 0.7 msec to avoid inclusion of Wave I that can shift in latency with click polarity to resemble out-of-phase CM components (Stockard, Stockard, Westmoreland & Corfits, 1979). CMs defined in the C – R processed traces were twice that of the CMs found in the separate averages to C or R stimuli.

Summating Potentials • The identification of an SP was made on the C + R traces (Fig. 1) by the appearance of a low amplitude deflection ($0.1 \mu\text{V}$) at a mean latency of 0.7 msec. For healthy controls, the amplitude of the SP was defined between baseline and the SP at the point where it blended with the ascending portion of Wave I (see the SP in the C + R in Fig. 1). Wave I was absent in all AN subjects so SP amplitude was defined between the peak of the potential and the preceding baseline period (see Fig. 1). The transient SP was of low amplitude and could only be distinguished as a component from background recording “noise” by its latency of approximately 0.7 msec. In healthy controls, the identification of a SP was aided by its position on the rising phase of Wave I.

ABRs • Auditory brain stem potentials were examined for the presence of neural components and the latency (click onset and tube delay) and amplitude (maximum peak relative to prestimulus baseline period) measures were computed.

Analyses • The amplitude values of both SP, and Wave V were measured in the (C + R)/2 traces. CM amplitude was considered abnormal if greater than 2 SEEs (standard error of estimate) above the age-adjusted regression line relating CM amplitude and age for the normal-hearing control subjects.

Analysis of variance procedures for repeated measurements were used to separately evaluate CM amplitude for the variables of group (AN, normal), gender (male, female), and ear (left, right). Separate *t*-tests were also used to evaluate differences for group, gender, ear, and measures of CM amplitude and latency, TEOAE, ABR, and PTA. Correlation and regression procedures were used to examine relationships among the variables of age, CM amplitude, TEOAE amplitude, and PTA. Differences of $p < 0.05$, or better, were considered significant.

RESULTS

The average amplitude of CMs, TEOAEs, average PTAs, and diagnoses are summarized for AN subjects in Table 1. The average pure-tone hearing loss (at 1, 2, and 4 kHz) for AN subjects was 58.2 dB for the right ear and 56.7 dB for the left ear. No significant gender (male, female) or ear differences

(left, right) were indicated for measures of CMs, TEOAEs, or average pure-tone thresholds in AN subjects, or for measures of CMs in controls.

CM Potentials

Recordings from an 8-yr-old healthy control and from a 5-yr-old AN subject are shown in Figure 1. In both subjects, the initial phase reversed component (C & R) peaked at approximately 0.4 msec. In the AN subject, phase reversed components continued out to 3 msec whereas in the healthy control phase reversed components after 0.7 msec could not be distinguished as CMs from latency-shifted neural components. Addition of the averaged potentials to condensation and to rarefaction clicks (C + R) cancelled the phase reversed components (CM) in both patient and the healthy control to reveal a small potential at approximately 0.7 msec compatible with a transient SP. Neural components (Waves I to V) also were evident in the healthy control but not in the AN subject. Phase-reversed components were enhanced in the C – R traces. Overall, CM amplitudes were significantly larger in AN subjects than normals for measures of the maximum amplitude as well as the amplitude at 0.4 msec latency.

Graphs showing the amplitude of the maximum

TABLE 1. Cochlear microphonics (CMs), transient evoked otoacoustic emissions (TEOAEs), degree of hearing loss (PTA), and diagnoses in auditory neuropathy

CMS	Ears (n)	Mean	(SD)
Present	57		
Not available	9	0.42 μV	± 0.29
TEOAEs	63	9.5 dB ^a	± 7.3
Not available	3		
Present	44	18.2 dB ^a	± 4.8
Absent	19	0.0 dB ^a	± 0.0
PTAs ^b	57	57.0 dB HL	± 28.0
CM if TEOAE present	37	0.46 μV	± 0.29
CM if TEOAE absent	17	0.38 μV	± 0.31
CM if PTA > 57	23	0.50 μV	± 0.32
CM if PTA < 57	26	0.40 μV	± 0.28
PTA if TEOAE present	39	54.6 dB HL	± 30.3
PTA if TEOAE absent	17	62.6 dB HL	± 23.4
Diagnoses			
Genetic	12		
Idiopathic	10		
Neonatal	9		
Hyperbilirubinemia	5		
Prematurity	7		
Peripheral neuropathy	6		

Note: One patient had a unilateral auditory neuropathy that developed following a viral infection; results from the unaffected ear were not included in the analyses.

None of the differences between (1) CMs with TEOAE present or TEOAE absent, (2) CMs if PTA > 57 or < 57, and (3) PTA if TEOAE present and PTA if TEOAE absent were significant.

^a dB peak SPL.

^b A total of 57 PTA measures were available; 9 PTA measures were judged technically compromised.

CM component as a function of age are shown in Figure 2 for both normal-hearing control subjects (upper) and AN subjects (lower). The 1 SEE and 2 SEE bands of the regression for normals are indicated in both graphs. There was a significant negative correlation between age and CM amplitude in normals ($p = 0.01$, $r = -0.54$). Amplitudes of CMs, adjusted for age, were abnormally elevated (>2 SEEs above the mean of healthy subjects) in 13 AN subjects (21 ears), all less than 10 yr of age comprising 54% of the AN subjects in this age group. There was no significant correlation between CM amplitude and degree of hearing loss (PTA). Clinical features such as the presence of neonatal risk factors, peripheral neuropathy, and the presence of AN in other family members were related with subject

Cochlear Microphonics

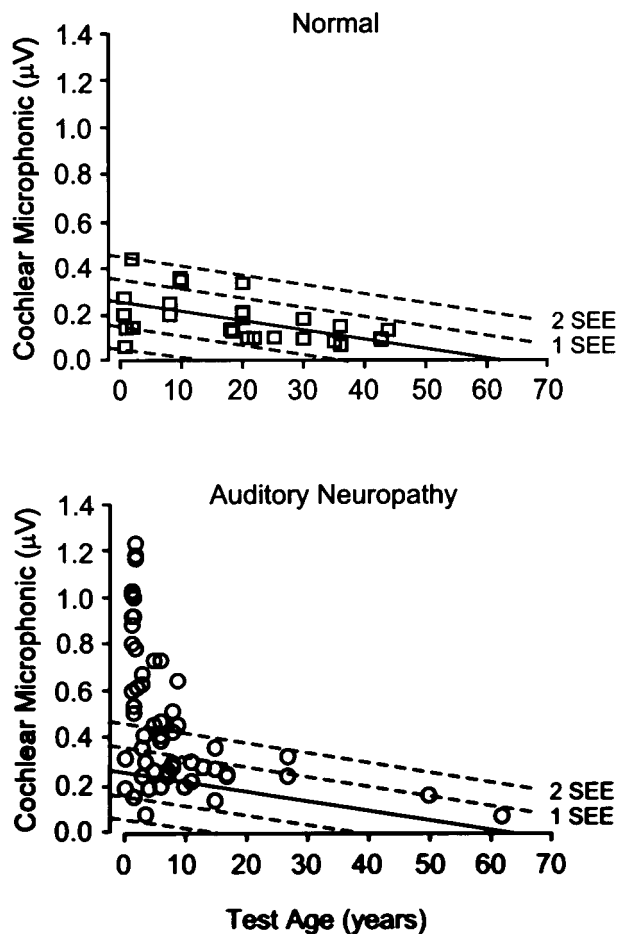


Figure 2. Maximum cochlear microphonic (CM) amplitude from 25 control ears (upper graph) and 57 auditory neuropathy (AN) ears (lower graph) as a function of subject age. In controls, there was a significant negative linear change of CM amplitude and age; 1 and 2 SEEs for controls are indicated. In AN subjects there was a clustering of abnormally elevated CM values for subjects younger than 10 yr of age.

age but did not separately distinguish between AN subjects with normal and abnormally elevated CMs.

CM averages from 25 subjects (from the left ear) with AN ranging from 1 to 50 yr of age are shown in Figure 3A. The potentials to condensation and rarefaction stimuli are superimposed. Note that phase reversed components persisted for several milliseconds and that CM peaks were larger in the younger than older patients. The grand averages of the CMs to condensation and rarefaction stimuli are shown in Figure 3B.

There were 24 AN subjects with CM recordings from both ears. The amplitudes were normal bilaterally in 13, abnormally increased bilaterally in 8, and abnormally increased unilaterally in 3. The maximum amplitudes of CM between the two ears of these 24 AN subjects were significantly correlated ($p < 0.001$; $r = 0.65$).

Otoacoustic Emissions

TEOAEs were present in 44 of the 63 test ears (total = 66, 3 ears not available) of AN subjects and absent in 19 (30%). There were eight AN subjects with bilateral absence of TEOAEs and three AN subjects with a unilateral absence. There was no significant relationship between PTA and the pres-

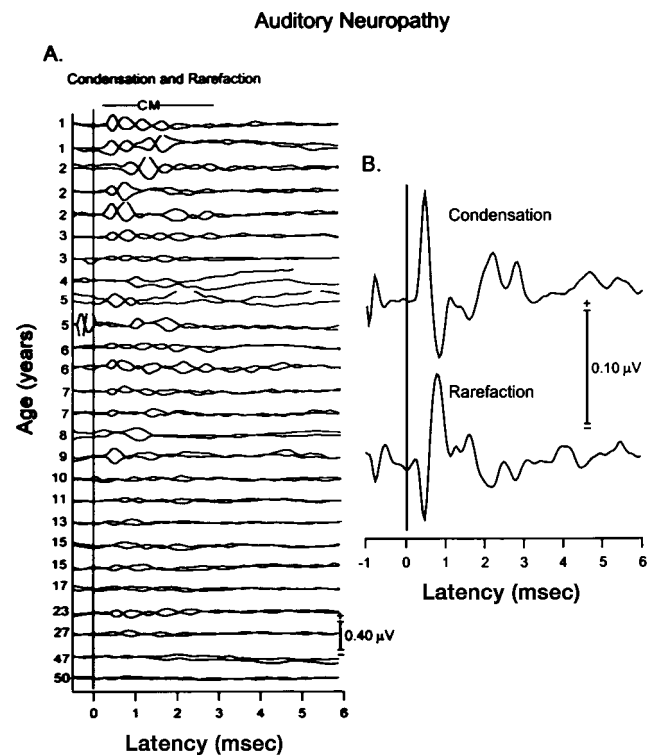


Figure 3. Superimposed averaged potentials to separately presented condensation and rarefaction clicks from 25 patients ranging in age from 1 to 50 yr are shown in (A). The grand averages from these 25 patients are shown in (B).

ence or absence of TEOAEs. Nine of the AN subjects with absent TEOAEs had preserved TEOAEs on an earlier evaluation. All of the AN subjects with absent TEOAEs had a history of using hearing aids in the past. The two AN subjects with absent TEOAEs on the initial evaluation had normal tympanograms and the TEOAE recordings were judged technically acceptable. CMs were present in all ears without TEOAEs with an average amplitude of $0.43 \mu\text{V}$ that was not significantly different than the average CM amplitude of $0.52 \mu\text{V}$ found in ears with preserved TEOAEs.

There was a significant negative relationship of TEOAE amplitude and age ($r = -0.38$, $p < 0.01$, intercept at 14.7 dB) in those ears with preserved TEOAEs. The correlation between the amplitudes of TEOAEs and CMs from the same ear when TEOAEs were present ($N = 33$), was also significant ($r = 0.45$; $p < 0.01$).

Summating Potential

A SP was identified in approximately 50% of both AN (28 out of 57) and healthy control ears (15 out of 27). The average peak amplitude of the SP in AN was $0.11 \mu\text{V}$ with a peak latency of 0.75 msec. C + R tracings from an AN subject showing a SP at 0.7 msec are shown in Figure 4 (also Fig. 1). We were unable to draw any conclusions about whether SPs to a transient click stimulus were abnormal in AN subjects because of the relatively low incidence of detection in both AN and healthy controls.

Auditory Brain Stem Potentials

Wave V, without a preceding Wave I, was identified in the ABR from 13 (21%) of the 60 AN test ears. Seven of the AN subjects with preserved ABRs had been tested bilaterally; four had a Wave V from stimulating each ear, and three had a Wave V from stimulating only one of the ears. The mean amplitude of Wave V when present (16 AN ears) was $0.10 \mu\text{V}$, significantly ($p < 0.01$) less than the mean amplitude of Wave V in normals ($0.51 \mu\text{V}$). Wave V latency in AN was delayed in 10 of the 16 recordings (6.0 msec to 8.5 msec). CM amplitudes were not significantly different between subjects with or without a preserved Wave V in the ABRs.

DISCUSSION

Measures of cochlear hair cell function, CMs, and TEOAE can be abnormal in AN. CM amplitudes were of abnormally large amplitude (more than 2 SEEs above the normal regression line amplitude) and/or TEOAEs were absent in approximately 50% of AN subjects. These results appear contrary to the

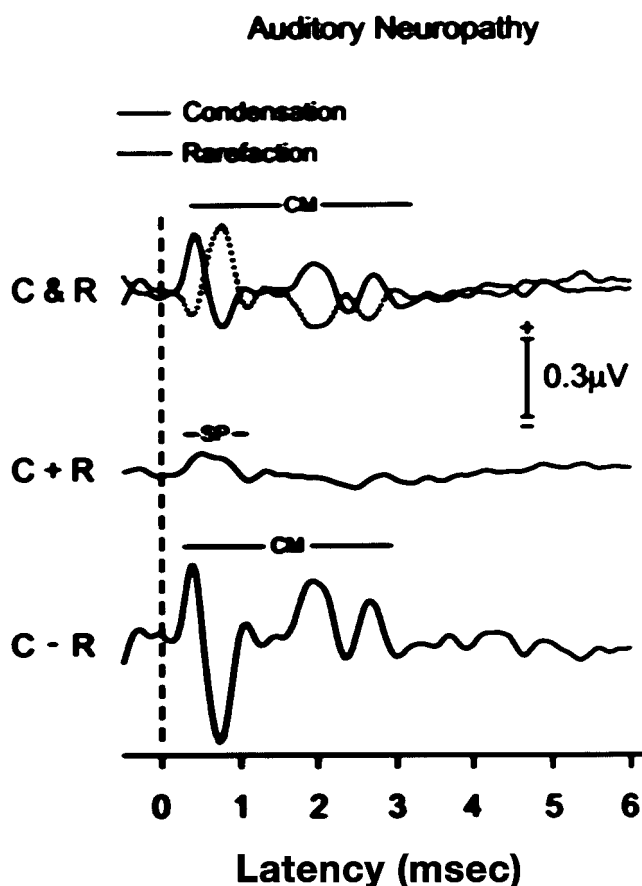


Figure 4. Auditory brain stem responses recorded from a 4-yr-old patient with auditory neuropathy who demonstrated cochlear microphonics and summating potential are illustrated.

proposition that AN is a disorder of auditory nerve function in the presence of preserved cochlear hair cell activity (Starr et al., 1996). CMs in AN have been previously characterized as prominent and long lasting (Berlin et al., 1993; Deltenre et al., 1997; Starr et al., 1991) without being identified as normal or abnormal. Recently, TEOAEs have been reported absent in some AN subjects, but all had CMs as evidence of preserved hair cell function (Deltenre et al., 1999; Rance et al., 1999).

Cochlear Microphonics

In the present study, abnormally increased CMs were found only in those AN subjects less than 10 yr of age. None of the patients above age 10 had abnormally increased CMs. Our "healthy" control group included 28 ears; three were newborns tested during their first week of life, five were in children between 3 mo and 10 yr of age, and 17 comprised the age range between 11 and 45 yr of age. The four young children we did test (ages 4, 15, 18, and 24 mo) were sedated for ABR evaluation of a possible

hearing loss. Their ABRs were normal, and we were able to do additional ABR measures while they were still sedated to define CMs. Analysis of the results from the controls showed CM to decrease with subject age similar to the relationship of TEOAE amplitude and age (Prieve et al., 1993). Additional CM measures from young children with normal ABRs would allow further characterization of the extent to which CM amplitudes change with maturation and refine guidelines for abnormality of CM as a function of age. The need for sedation in young children and the concomitant risks of the medications currently limit the ability to collect significant numbers of control subjects for such a study.

There are several mechanisms that might account for an increase of CMs. First, graded contractions of the middle ear muscles can selectively enhance transmission of certain tonal frequencies and effect a slight increase in CMs (Pilz, Ostwald, Kreiter, & Schnitzler, 1997; Starr, 1969). Middle ear muscles of patients with AN can contract to a variety of nonacoustic stimuli even though their acoustically activated middle ear muscle reflexes are typically absent (Gorga, Stelmachowicz, Barlow, & Brookhouser, 1995; Starr et al., 1998). We have no evidence that graded middle ear muscle contractions participate in the increased amplitudes of CM found in some subjects with AN. Second, in experimental animals activation of the efferent OCB can lead to a doubling of amplitude of the CM (Fex, 1962; Galambos, 1956). OCB activation causes hyperpolarization of outer hair cells with an accompanying increase in receptor potentials and a decrease in neural activity of the VIIIth nerve (Fex, 1967). The OCB has been implicated in humans for the attenuation of OAEs when sound is applied to the contralateral ear. Crossed suppression of OAEs in AN is absent (Berlin et al., 1993) suggesting that OCB function is altered in this disorder. If the disorder of the OCB system took the form of tonic overactivity, CMs would be of large amplitude. Finally, pharmacologic agents, such as acetylsalicylic acid, can influence hair cell metabolism leading to an increase in CM amplitudes (Aran & de Sauvage, 1976). It may be that some AN subjects harbor a metabolic disorder of hair cells leading to enhanced CMs and an accompanying impairment of afferent auditory nerve activity.

Otoacoustic Emissions

TEOAEs were absent in approximately one-third of the AN subjects (10 of 33) independent of age; bilaterally in eight and unilaterally in three. The diagnosis of an auditory nerve disorder was established up to 3 yr earlier in all (but two instances) by

preserved TEOAEs and absent or severe abnormalities of the ABR. In one of the patients with absent TEOAEs, the diagnosis of an auditory nerve disorder was not made until a younger sibling developed a hearing loss with preserved OAEs and absent ABRs. ABRs were retested in the older sibling without TEOAEs, and CMs were demonstrated.

We are reluctant to ascribe the absence of TEOAEs in AN subjects with certainty to a hair cell disorder because absent TEOAEs may be found in normal-hearing subjects. TEOAEs can be absent in a significant proportion of children with normal hearing due, perhaps, to subtle hair cell changes that do not affect hearing thresholds (Grenner, Tiedeholm, Hinriksdottir, & Carlborg, 1997). OAEs could also theoretically be absent if there were changes in middle ear function that were sufficient to disrupt the detection of OAEs but below the threshold for clinical detection. All of the AN subjects with absent TEOAEs have risk factors for either middle ear disorder or hair cell damage. Two of the eight AN subjects without TEOAEs had prior middle ear disorders (infections and/or the placement of transtympanic tubes) and all used hearing aids in the past. However, all subjects with absent TEOAEs had technically satisfactory recordings and normal tympanic membrane motility.

Even with the above limitations, we are of the opinion that the CM and TEOAE alterations found in AN subjects in this and other studies (e.g., Deltenre et al., 1999; Rance et al., 1999) provide a strong presumption that cochlear functions can be involved in this disorder. We are unable to distinguish whether the alterations of cochlear hair cell functions are a cause or a consequence of disordered auditory nerve activity in these patients. We have proposed (Butinar et al., 1999; Starr et al., 1996) that the auditory nerve was the site of disorder in many patients with AN because of 1) the absence of auditory nerve and auditory brain stem pathway evoked potentials when cochlear outer hair cell functions (intact OAEs and CMs) were preserved; and 2) the occurrence of a concomitant peripheral neuropathy in a significant number of these patients. However, auditory nerve function would also be impaired if the site of disorder were the inner and perhaps outer hair cells and/or the synapse between inner hair cell and VIIIth nerve dendrite (Berlin et al., 1993; Harrison, 1998). The finding in this report of abnormal CMs and TEOAEs in some subjects with AN can be used as an initial effort to distinguish different possible types of AN. For instance, none of the patients with abnormal CMs or TEOAEs in the present study had evidence of a peripheral neuropathy, suggesting the possibility that the dysfunction of auditory nerve was the result of a disorder

der of inner hair cells or their synapses with auditory nerve.

Summating Potentials

The identification of a short latency potential compatible with an SP in approximately 50% of the patients with AN complements earlier reports of its presence in certain individuals with AN (Aran & de Sauvage, 1976; Starr et al., 1998). However, we were only able to define a SP in approximately 50% of the normal-hearing individuals we studied. The SP was of small amplitude and was difficult to distinguish from background recording noise. Additional measures of SP using ear canal or tympanic membrane recordings may be necessary if we are to define whether this cochlear event is normal in AN. The measure is important because the generators for SP include both types of hair cells, with inner hair cells considered the principal generator (Durrant, Wang, Ding, & Salvi, 1998; Zheng, Ding, McFadden, & Henderson, 1997).

Auditory Brain Stem Potentials

Finally, the finding of a preserved though low amplitude Wave V in a minority of AN subjects suggests that the disorder of temporal synchrony may be graded in AN. AN subjects also show gradations of impairments affecting degree of hearing loss (Rance et al., 1999; Zeng et al., 1999) and, in the present experiment, receptor functions, and auditory pathway responses. These and other observations may be useful in identifying the varieties of hearing loss that comprise the condition labeled "AN."

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