Auditory Neuropathy Characteristics in Children with Cochlear Nerve Deficiency

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Objective: **To describe a group of children exhibiting electrophysiologic responses characteristic of auditory neuropathy (AN) who were subsequently identified as having absent or small cochlear nerves (i.e., cochlear nerve deficiency).**

Design: **A retrospective review of the clinical records, audiological testing results, and magnetic resonance imaging (MRI) studies. Fifty-one of 65 children with AN characteristics on auditory brain stem response (ABR) testing had MRI available for review. Nine (18%) of these 51 children with ABR characteristic of AN have been identified as having small (*N* = 2; 4%) or absent (*N* = 7; 14%) cochlear nerves on MRI.**

Results: **Of the nine children with cochlear nerve deficiency, five (56%) were affected unilaterally and four (44%) bilaterally. Eight of nine presented after failing a newborn infant hearing screening, whereas one presented at 3 yr of age. On diagnostic ABR testing, all 9 children (9 of 13 affected ears; 69%) had evidence of a cochlear microphonic (CM) and absent neural responses in at least one ear. In the unilateral cases, AN characteristics were detected in all affected ears. In bilateral cases, at least one of the ears in each child demonstrated the AN phenotype, whereas the contralateral ear had no CM identified. Only one ear with cochlear nerve deficiency had present otoacoustic emissions as measured by distortion-product otoacoustic emissions. In children with appropriate available behavioral testing results, all ears without cochlear nerves were identified as having a profound hearing loss. Only 4 (31%) of the 13 ears with cochlear nerve deficiency had a small internal auditory canal on MRI.**

Conclusions: **Children with cochlear nerve deficiency can present with electrophysiologic evidence of AN. These children frequently refer on newborn screening examinations that use ABR-based testing methods. Similar to other causes of AN, diagnostic ABR testing will show a CM with absent neural responses. Given that 9 (18%) of 51 children with available MRI and electrophysiologic characteristics of AN in our program have been identified as having cochlear nerve deficiency makes this a relatively common diagnosis. These findings suggest that MRI is indicated for all children diagnosed with AN. Moreover, electrophysiologic evidence of unilateral AN in association with a profound hearing loss should make the clinician highly suspicious for this problem. Although children with cochlear nerve deficiency who have a small nerve may benefit from cochlear implantation or amplification, these interventions are obviously contraindicated in children with completely absent cochlear nerves.**

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INTRODUCTION

Auditory neuropathy (AN) is a clinical syndrome characterized by the presence of otoacoustic emissions (OAEs) and/or cochlear microphonics (CM) suggesting normal outer hair cell function in conjunction with absent or grossly abnormal auditory brain stem responses (ABRs) (Starr, Picton, Sininger, et al., 1996). AN is thought to account for up to 10% of newly diagnosed cases of hearing loss in children (Madden, Rutter, Hilbert, et al., 2002). Less than 10% of AN cases are thought to involve only one ear. With bilateral presentation, patients exhibit a wide range of auditory capabilities. Hearing thresholds for pure-tone detection can range from normal to profound levels (Madden, Rutter, Hilbert, et al., 2002; Rance, Beer, Cone–Wesson, et al., 1999; Starr, Sininger, & Pratt, 2000). Recent studies in older children and adults suggest that these patients' perceptual abilities can be severely impaired for both pitch discrimination in the low frequencies as well as temporal processing tasks (Rance, McKay & Grayden, 2004; Zeng, Kong, Michalewski, et al., 2005). It has been hypothesized that lesions in the inner hair cells, the synapse between the inner hair cell and the auditory nerve, and the auditory nerve itself may account for the clinical findings (Berlin, et al., 2003; Berlin, Morlet & Hood, 2003; Fuchs, Glowatzki & Moser, 2003 Starr, Picton, Sininger, et al., 1996).

The term cochlear nerve deficiency is used to refer to those cases in which the nerve is either small or absent on MRI (Glastonbury, Davidson, Harnsberger, et al., 2002). Cochlear nerve deficiency can presumably occur as a result of failure of the nerve to develop either partially (hypoplasia) or completely

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(aplasia or agenesis) or as a result of post-developmental degeneration. Cochlear nerve deficiency has been described in studies of human temporal bones in association with inner ear malformation, internal auditory canal (IAC) stenosis, and occasionally in the presence of a normal IAC morphology (Felix & Hoffmann, 1985; Nadol & Xu, 1992; Nelson & Hinojosa, 2001; Spoendlin & Schrott, 1990; Ylikoski & Savolainen, 1984). Both Jackler et al. (1987) and Shelton et al. (1989) suggested that the presence of IAC stenosis on computed tomography (CT) scan images was indicative of cochlear nerve aplasia and poor performance with a cochlear implant; they recommended that IAC stenosis absolutely contraindicated cochlear implantation. More recently, numerous investigators have demonstrated cochlear nerve deficiency using magnetic resonance imaging (MRI)-based cross-sectional imaging techniques of the IAC (Casselman, Offeciers, Govaerts, et al., 1997; Glastonbury, Davidson, Harnsberger, et al., 2002). Although only limited audiologic data have been reported for this group of patients, most have demonstrated profound hearing loss in association with cochlear nerve agenesis and/or no response after cochlear implantation (Ito, Suzuki, Murofushi, et al., 2005; Jackler, Luxford & House, 1987; Shelton, Luxford, Tonokawa, et al., 1989).

The present study reports on a group of pediatric patients with cochlear nerve deficiency who presented with electrophysiologic characteristics of AN. This previously unreported association has substantial clinical implications: Both amplification and cochlear implantation may be contraindicated in these ears. These findings support the routine use of MRI, with special attention to the cochlear nerves as the primary imaging modality when evaluating children with profound sensorineural hearing loss, especially those with ABR responses characteristic of AN.

MATERIALS AND METHODS

Subjects

Currently, more than 1000 hearing-impaired children are being treated with either conventional amplification ($n \sim 500$) or cochlear implants ($n \sim 500$) at the University of North Carolina at Chapel Hill (UNC). A retrospective review of the databases of the Division of Audiology at the UNC Hospitals and the W. Paul Biggers Carolina Children's Communication Disorders Program (CCCDP) in the Department of Otolaryngology–Head and Neck Surgery at UNC was undertaken. The Biomedical Institutional Review Board of UNC approved this study.

To date, 65 children with electrophysiologic responses characteristic of AN have been identified at our institution. Of these, 33 (51%) are either being followed expectantly with periodic testing or have received amplification, whereas 23 (35%) have undergone cochlear implantation. Starting in 2001, MRI has gradually supplanted CT imaging as the preferred imaging modality at our institution for all children with sensorineural hearing loss. Of the 65 children identified with AN characteristics on ABR testing, 51 have undergone an MRI as described below. Most children without MRI were evaluated before 2001, were older and had a stable hearing loss, were scheduled for the study that is still pending, or their parents have refused such an evaluation.

Since 2001, 14 children who have presented for evaluation of suspected hearing loss have been identified as having cochlear nerve deficiency on MRI. Nine of these 14 children with MRI confirmation of cochlear nerve deficiency have had an appropriate ABR performed. This report details these 9 children. Thus, from a group of 51 children with AN characteristics on ABR testing that have had an MRI performed, 9 (18%) have been identified as having cochlear nerve deficiency.

Diagnosis of Auditory Neuropathy

Auditory neuropathy is a generic diagnostic term that describes any condition in which gross discrepancy exists between measures of cochlear and neural function in the auditory system. Classically, this discrepancy is most evident in cases in which OAEs and/or CM (indicative of normal hair cell function) are present with absent or abnormal ABRs.

The diagnostic protocol currently in use at UNC for children with suspected hearing loss, including AN, incorporates a battery of audiologic tests that includes measurements of immittance, OAEs, ABR, auditory steady-state responses (ASSR), and behavioral testing. The protocols for ABR, OAEs, and behavioral testing are described briefly below.

Otoacoustic Emission Testing

The OAE test of choice is the distortion-product OAE (DPOAE). DPOAEs are measured in each ear for pairs of primary tones ($f1$ and $f2$), with a fixed ratio of $f2/f1 = 1.2$, and fixed levels of 65 dB SPL (L1) and 55 dB SPL (L2). The frequency of $f2$ is typically stepped through the range 1500 to 6000 Hz to yield a 6-point DPGram. Presence of a valid DPOAE at each frequency step is determined by a combination of criteria including signal-to-noise ratio $\geq$10 dB and absolute noise level ≤ -15 dB SPL.

DPOAE testing is usually undertaken using the GSI 70 OAE system (Grason-Stadler; Madison, WI).

Auditory Brain Stem Response Testing

The ABR testing for each child occurs under one of three environments: natural sleep, conscious sedation, or general anesthesia. Infants younger than about 3 mo of age are tested in natural sleep if possible. Babies older than this without other medical contraindications are sedated before testing. After medical clearance by a physician, a nurse from the hospital's pediatric sedation team administers a sedative and remains at bedside to monitor the entire session. Sedation is typically accomplished with chloral hydrate delivered orally, or midazolam (Versed®) is delivered intravenously. In cases in which the infant is scheduled for a procedure under general anesthesia (e.g., surgery or imaging), the evoked potential testing is incorporated into the procedure sequence if appropriate. Test time is usually dictated by the test environment, ranging from about 30 minutes in the operating room to over an hour under conscious sedation.

The ABR protocol includes at a minimum two main stimulus types: a 100-μsec click and a "single-cycle" 250-Hz tone burst. The single-cycle 250-Hz tone burst is shaped by a Blackman window with 2-msec rise/fall times and no plateau. Although nominally centered at 250 Hz, spectral analysis shows this stimulus to include energy broadly distributed below about 500 Hz. A 2-channel recording is undertaken (F_z – A_1 or A_2, referenced to F_{pz}), using a bandwidth of 100 to 3000 Hz (clicks) or 30 to 3000 Hz (250-Hz tone bursts) and a time window of 20 msec. The stimulation rate is 37.7 Hz, and 1500 sweeps per average are collected. The protocol calls for single-polarity stimulation to identify the CM, if present. CM is distinguished from neural response by two criteria: (1) the polarity of the CM will invert with stimulus polarity inversion; and (2) the latency of the CM will remain constant with changes in stimulus level. Accordingly, when a response suspected to be the CM is noted (typically at a relatively high stimulus level), recordings are made with both rarefaction and condensation stimulus phase, and—for a constant phase—two recordings are made 10 dB apart. Special care is required in identifying the CM, because, as a consequence of monophasic stimulation, all stimulus-phase–dependent components present at the electrodes—including stimulus artifact—will emerge during the averaging process. To distinguish CM from stimulus artifact, the sound tubing coupling the transducer to the insert earphone is disconnected without altering the relative positions of the electrodes and transducers. If the stimulus-phase–dependent component disappears in this case, it is the CM; if it remains, it is stimulus artifact.

For each stimulus type, a level series is undertaken to estimate threshold. The physiologic ABR threshold is taken as the lowest stimulus level at which a wave V response can be visually detected in the response. At least two runs are collected at each stimulus level to verify waveform identification. ABR testing is usually undertaken by using the Biologic Traveler system.

Behavioral Testing

Behavioral audiometric measures are obtained by using insert earphones (attached to the child's earmolds if fit with hearing aids). The measurement technique for babies and toddlers ages approximately 6 to 24 mo uses Visual Reinforcement Audiometry (VRA), where visual reinforcement (animated toy or video) is used to condition the baby to respond to sound. Usually the baby is seated on the mother's lap in a sound-treated room, with one audiologist in the room to maintain the baby's visual focus while another audiologist delivers the test stimuli from the attached control room. Behavioral testing is initiated as soon as the baby is developmentally capable; a complete, accurate audiogram for both ears usually requires at least two visits.

For older children younger than approximately 5 yr of age, behavioral testing is undertaken by using play audiometry. Here, the audiometric testing is couched in an age-appropriate play activity where, for example, the child places a peg in a peg-board or a ring on a ring stand in response to hearing a stimulus. The child is taught to attend to the listening task and to make the play response only when a stimulus is perceived. Usually an assistant is present with the child to dispense the game pieces and to ensure that the child remains on task.

Diagnosis of Cochlear Nerve Deficiency

MRI is used for the evaluation of most children with sensorineural hearing loss at UNC. This modality allows for complete evaluation of: (1) cochlear and vestibular labyrinthine morphology and patency, (2) the IAC and cisternal segments of the facial and cochleovestibular nerves, and (3) a thorough brain assessment. When cochlear implantation is considered, this imaging provides an MRI of the child's brain that may not be easily attainable after surgery. For surgical planning, further imaging is usually unnecessary unless significant inner ear malformations are identified. In those cases, CT imaging is considered.

MRI Technique

All patients are scanned on our 1.5-T MRI (Magnetom Sonata, Avanto, Vision, or Symphony; Siemens Medical Solutions, Inc., Malvern, PA) machines. The MRI technique currently in use at the study institution has been described in detail previously (Glastonbury, Davidson, Harnsberger, et al., 2002). Briefly, after performing an axial ADC localizer scan, axial T1, T2, and FLAIR sequences are supplemented by axial 3D continuous interference in a steady-state (CISS) images. The CISS images are then reconstructed in a coronal oblique plane traversing the IAC in a perpendicular orientation, producing images that visualize the four cranial nerves (facial, cochlear, superior vestibular, and inferior vestibular nerves) traversing the IAC. Contrast is currently not used in the scanning protocols for most children with hearing loss. The findings of a normal ear are shown in Figure 1 (left ear).

The term cochlear nerve deficiency is used to refer to either small or absent cochlear nerves on MRI. After Glastonbury et al. (2002), we designated the nerve absent when it could not be identified on axial, coronal, or reconstructed coronal oblique IAC images. An extremely small nerve below the limits of resolution of MR imaging would appear absent in this context. The nerve is considered small when the nerve is evident but substantially smaller than the other nerves in the IAC or smaller than the cochlear nerve in the contralateral ear. The terms aplasia, hypoplasia, agenesis, or degeneration are avoided so as to not imply a mechanism or causality, because this remains speculative. A small IAC is defined as $\leq$3 mm on cross-sectional diameter (Olivares & Schuknecht, 1979; Sakashita & Sando, 1995). The various inner ear malformations have been described previously (Buchman, Copeland, Yu, et al., 2004).

RESULTS

Table 1 shows a summary of the findings for the nine children with cochlear nerve deficiency. To date, there are six boys and three girls, with a mean age of 35 mo (range, 19 to 72 mo). Eight of nine children with cochlear nerve deficiency were referred on the basis of their automated, newborn infant hearing screen examination, whereas one child reportedly passed, and presented at 3 yr of age with a sudden hearing loss. The mean age at diagnosis of cochlear nerve deficiency was 17 mo (range, 9 to 46 mo). Excluding the one child with a delayed diagnosis at 3 yr, the mean age at identification of cochlear nerve deficiency, using MRI, was 14 mo (range, 9 to 22 mo). Of the nine children, three have known syndromes that include hearing loss: Hall-Hittner (CHARGE variant), CHARGE, and Down syndrome. None of the children had a history of prematurity, hypoxia, hyperbilirubinemia, or other central nervous system disorder. No child had a family history of hearing loss.

Magnetic Resonance Imaging

Five (56%) of the nine children with cochlear nerve deficiency were affected in only one ear, whereas four (44%) had bilateral involvement. Of the 9 children affected by cochlear nerve deficiency, 11 (61%) of the 18 cochlear nerves were characterized as absent, 2 (11%) small, and 5 (28%) had a normal complement and configuration of nerves. One of the two ears with a small cochlear nerve was in a child with an absent contralateral cochlear nerve; the other ear with a small cochlear nerve was in a child with a normal neural complement in the contralateral ear. Figure 1 shows the MRI of a child with a full complement of nerves in the left ear and an absent cochlear nerve in the right. The IAC and inner ear are of normal size and morphology, bilaterally.

Malformation of the cochlea was identified in only 3 (23%) of 13 ears (2 of 9 children; 22%) with cochlear nerve deficiency and in none of the ears having a full complement of nerves. Vestibular labyrinthine abnormalities were identified bilaterally in 4 patients (8 ears). Of these 8 ears with vestibular labyrinthine anomalies, 7 exhibited cochlear nerve deficiency whereas 1 had a normal cochlear nerve. Internal auditory canal configuration was considered normal in 14 (78%) of 18 ears, overall. Thus, only 4 (31%) of the 13 ears with cochlear nerve deficiency had a small IAC.

Auditory Brain Stem Response and Otoacoustic Emission

Figure 2 shows the click-evoked ABR tracings for all 9 children (18 ears). Both the condensation and rarefactions runs are shown for the ear affected by cochlear nerve deficiency as well as the contralateral ear. Waveforms that invert when the click polarity is changed (rarefaction $\leftrightarrow$ condensation) indicate the presence of a CM, implying hair cell function. Normal ABR morphology and thresholds were evident in only 2 ears of 2 patients (#2 right ear and #7 left ear); both had contralateral, absent cochlear nerves. Two ears demonstrated clear evidence of neural responses on ABR testing; one of these two ears had absent DPOAEs and a threshold of 55 dB, implying a cochlear hearing loss in the ear unaffected by cochlear nerve deficiency. The other subject (#4 left) had an apparent CM followed by a delayed neural component designated as V/VI.

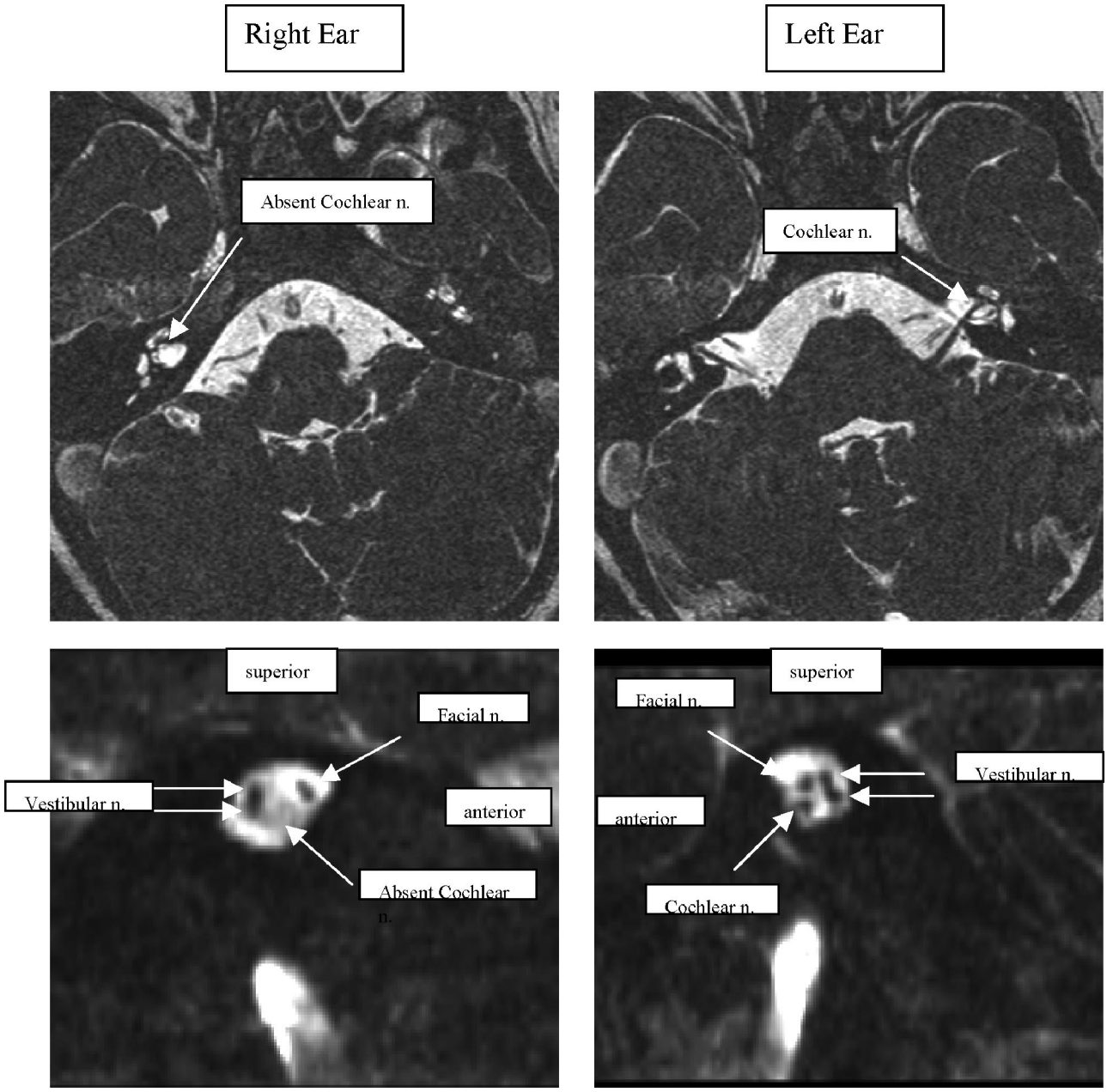

Fig. 1. Axial (top) and parasagittal (lower) T2-weighted MRI through the internal auditory canals of one child (case 5) with unilateral cochlear nerve deficiency. The parasagittal images represent a cross section taken approximately at the level of the cochlear nerve (arrow seen on the axial images). Normally, the facial nerve lies in the antero-superior aspect of the canal, whereas the cochlear nerve occupies an antero-inferior location. The superior and inferior vestibular nerves (fused in the picture) occupy their respective locations, posteriorly in the canal. The right cochlear nerve is absent, its expected position being marked by the labeled arrow. The left ear has a normal-size cochlear nerve, as marked by the labeled arrow.

A CM was present in 10 (56%) of 18 ears. A variety of CM morphologies were evident (Fig. 2). Nine (69%) of 13 ears with cochlear nerve deficiency had a CM present on ABR testing. In the unilateral cases of cochlear nerve deficiency, AN characteristics (present CM and absent neural responses) were detected in all affected ears. In bilateral cases, at least one of the ears demonstrated the AN phenotype, whereas the contralateral ear had no CM or neural responses identified. Only one (11%) of nine ears with a CM and associated cochlear nerve deficiency had an associated cochlear malformation, whereas four (44%) had vestibular malformations. One ear of a child with contralateral cochlear nerve deficiency (and a CM present) had present ABR waveforms and CM present (case 4).

DPOAE results were available for 8 of 9 children (16 ears total). DPOAEs were present in only three

TABLE 1. Anatomic and electrophysiologic findings in children with cochlear nerve deficiency

Subject	Age at MRI (mo)	Ear	CN	IAC*	Cochlea	Vestibular	ABR	CM	OAE	Syndrome
1	22	Right	Absent	1 mm	Normal	Absent HSCC	NR	Absent	Absent	
		Left	**Absent**	**1 mm**	**Normal**	**Absent HSCC**	**NR**	**Present**	**Absent**	
2	11	Right	Normal	6 mm	Normal	Normal	Normal	Absent	Present	
		Left	**Small**	**6 mm**	**Normal**	**Normal**	**NR**	**Present**	**Absent**	
3	9	Right	Normal	5 mm	Normal	Absent SCCs	Normal†	Absent	Absent†	Hall-Hittner
		Left	**Absent**	**4 mm**	**Normal**	**Absent SCCs**	**NR**	**Present**	**Absent**	
4	15	**Right**	**Absent**	**1 mm**	**Normal**	**Normal**	**NR**	**Present**	**NA**	
		Left	Normal	4 mm	Normal	Normal	Present‡	Present	NA	
5	46	**Right**	**Absent**	**7 mm**	**Normal**	**Normal**	**NR**	**Present**	**Present**	
		Left	Normal	8 mm	Normal	Normal	NR	Absent	Absent	
6	12	**Right**	**Absent**	**4 mm**	**Hypo**	**Absent HSCC**	**NR**	**Present**	**Absent**	
		Left	Absent	4 mm	Hypo	Absent HSCC	NR	Absent	Absent	
7	12	**Right**	**Absent**	**4 mm**	**Normal**	**Normal**	**NR**	**Present**	**Absent**	Trisomy 21
		Left	Normal	5 mm	Normal	Normal	Normal	Absent	Present	
8	13	Right	Absent	3 mm	Hypo	Normal	NR	Absent	Absent	
		Left	**Absent**	**5 mm**	**Normal**	**Normal**	**NR**	**Present**	**Absent**	
9	16	**Right**	**Absent**	**4 mm**	**Normal**	**Absent SCCs**	**NR**	**Present**	**Absent**	CHARGE
		Left	Small	4 mm	Normal	Absent SCCs	NR	Absent	Absent	

CN, Cochlear nerve; IAC, internal auditory canal; ABR, auditory brain stem response; CM, cochlear microphonic; OAE, distortion-product otoacoustic emission; HSCC, horizontal semicircular canal; SCC, semicircular canal, hypo-hypoplasia.

**A small IAC is defined as ≤ 3 mm in cross-sectional diameter (Olivares & Schuknecht, 1979; Sakashita & Sando, 1995).*

†ABR thresholds of 55 for clicks with Normal morphology.

‡ABR neural responses were present with a delayed latency (labeled V/VI). Bold type indicates the "AN phenotype."

(19%) ears of the entire cohort with available tests; two of these ears had normal cochlear nerves and one had an absent cochlear nerve with a CM present on ABR. For the 13 ears without DPOAEs present, 11 (85%) had cochlear nerve deficiency, whereas 2 (15%) had normal cochlear nerves. One of these two ears with normal cochlear nerves and absent DPOAEs had a sensorineural hearing loss; behavioral audiometric testing results are currently unavailable for the other ear (i.e., patient). In all, only

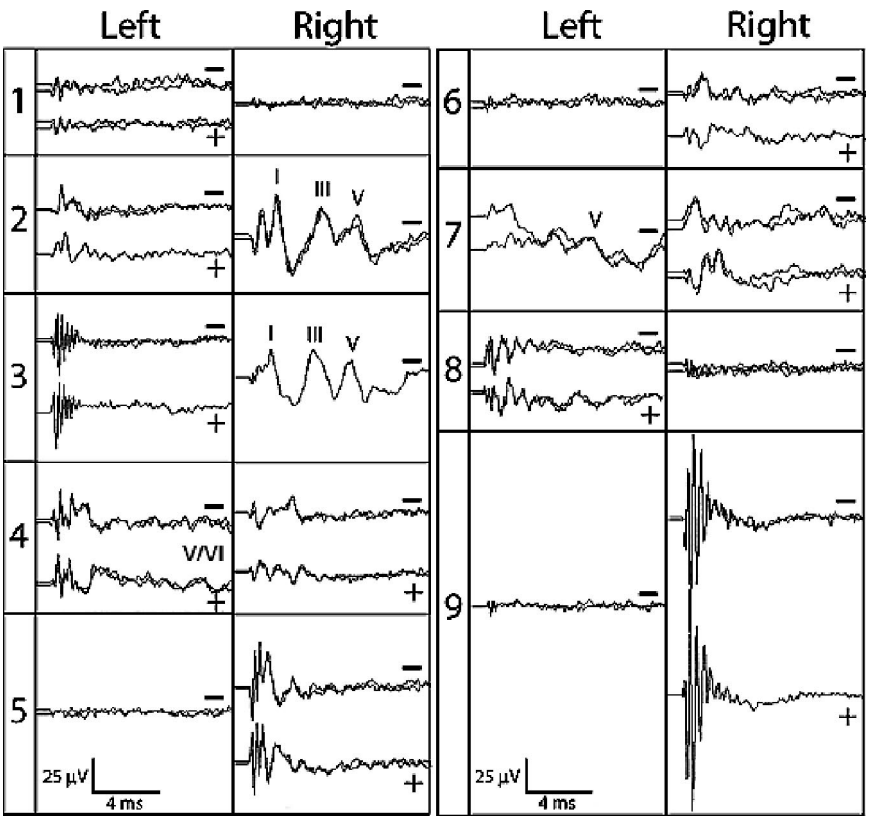

Fig. 2. Auditory brain stem response tracings for the nine children with absent cochlear nerves. The cochlear microphonic (CM) is distinguished from neural response by two criteria: (1) the polarity of the CM will invert with stimulus polarity inversion; and (2) the latency of the CM will remain constant with changes in stimulus level. To distinguish CM from stimulus artifact, the sound tubing coupling the transducer to the insert earphone was disconnected without altering the relative positions of the electrodes and transducers. The stimulus-phase–dependent component disappeared in each case, indicating it was the CM rather than stimulus artifact. (+) indicates condensation stimulus; (–), rarefaction stimulus.

one (13%) of eight ears with cochlear nerve deficiency and a CM present had DPOAEs.

Behavioral Audiometry

Complete behavioral audiograms with ear-specific data and appropriate masking are currently available for 5 (56%) of 9 children (8 of 13 ears; 62%) with cochlear nerve deficiency. The children without such audiograms are still too young to complete this type of testing. To date, all 8 ears (100%) with cochlear nerve deficiency and available behavioral data have had profound sensorineural hearing loss in the affected ear. Of interest, on more than one occasion, young children with clear evidence of cochlear nerve deficiency that were appropriately conditioned for behavioral testing were found to respond consistently to low frequency (250 and 500 Hz) pure tones in the severe to profound range, implying a vibrotactile response in some cases.

Management

Two children with bilateral cochlear nerve deficiency, absent neural responses on ABR, and profound bilateral hearing loss have undertaken sign language as their communication mode. Another child with bilateral nerve deficiency was implanted in an ear because of clear, reliable behavioral responses at 95 to 100 dB HL. This child has subsequently gained no responses from stimulation and is now beginning to integrate sign language for communication. Two children with normal hearing in their unaffected ear by either ABR and/or audiometry have been observed with periodic testing. Three children with variable degrees of measurable hearing in their unaffected ear are using amplification effectively. Finally, one child (case 5; Fig. 2) was initially implanted in the ear without a cochlear nerve (right) and exhibited no intracochlear evoked compound action potentials (ECAPs) and very limited benefit. The child subsequently received an implant in the contralateral ear that had clear evidence of a cochlear nerve on MRI (Fig. 2, left), with good responses on both ECAP and behavioral testing.

DISCUSSION

The etiology of AN appears to be multifactorial. Mutations in a number of genes (*MPZ, NDRG1, PMP22, OTOF, AUNA1*) have now been characterized in hereditary cases of AN (Chapon, Latour, Diraison, et al., 1999; De Jonghe, Timmerman, Ceuterick, et al., 1999; Kalaydjieva, Gresham, Gooding, et al., 2000; Maier, Castagner, Berger, et al., 2003; Starr, Isaacson, Michalewski, et al., 2004; Starr, Michalewski, Zeng, et al., 2003; Varga, Kelley, Keats, et al., 2003; Yasunaga, Grati, Cohen–Salmon, et al., 1999). Associations have also been made between infectious (measles, mumps), metabolic (diabetes, hyperbilirubinemia, hypoxia), and neoplastic processes (acoustic neuroma) as well as prematurity (Starr, Sininger, Nguyen, et al., 2001). In most children with AN, the cochlear nerve is known to be anatomically present because residual hearing abilities exist. Most of these affected individuals have varying levels of pure-tone thresholds with disproportionately poor speech perception abilities. Because some children with AN who have received cochlear implants have had robust ECAPs and good performance (Buss, Labadie, Brown, et al., 2002; Madden, Hilbert, Rutter, et al., 2002; Mason, De Michele, Stevens, et al., 2003), the abnormal hearing that these children have is thought to be due to disordered signal transduction at the inner hair cells, hair cell–dendrite synapse, or the cochlear neurons (i.e., auditory dys-synchrony) (Berlin, Morlet & Hood, 2003; Fuchs, Glowatzki & Moser, 2003; Starr, Picton, Sininger, et al., 1996).

Results of the present study demonstrate the novel finding that children with cochlear nerve deficiency can have electrophysiologic characteristics of AN on ABR testing. Thus, children with small or absent cochlear nerves may still have hair cell function. Since 2001, 9 (18%) of the 51 children identified as having AN in at least one ear on ABR testing that have undergone MRI have ultimately been diagnosed with cochlear nerve deficiency. Of the 13 ears with absent or very small cochlear nerves, nearly 70% have demonstrated a CM in addition to absent ABR waveforms in the affected ear. Behavioral testing ultimately documented a profound hearing loss in all of the ears affected by cochlear nerve deficiency. Thus, in some children, the AN phenotype may result from, or be related to, an absent or very small cochlear nerve. None of these children had a medical history or family history that would suggest any known AN risk factors.

The findings of the present study are consistent with the temporal bone histopathology findings of Nelson & Hinojosa (2001). They showed two cases of unilateral cochlear nerve deficiency in the presence of normal organ of Corti structure. As in 9 (69%) of the 13 ears with cochlear nerve deficiency in our study, one of their patients had normal IAC structure. Thus, normal IAC morphology, even in the presence of electrophysiologic evidence of cochlear function, does not guarantee the existence of a cochlear nerve.

For clinicians who treat children with hearing loss, especially those who perform diagnostic ABR testing, understanding these facts is critical. After a

failed newborn hearing screening, diagnostic ABR testing is usually carried out to detect thresholds and make recommendations for amplification. When a CM with absent neural responses has been documented, the diagnostic evaluation should proceed to a thorough search for cochlear nerve deficiency. This requires the child undergo an MRI with attention to the brain, IACs, cochleovestibular nerve complexes, and inner ears.

Opinions regarding treatment of children with AN vary widely. When hearing loss has been documented, conservative amplification has been proposed (Rance, Cone-Wesson, Wunderlich, et al., 2002). On the contrary, other investigators believe that the distorted speech perception abilities resulting from AN precludes effective use of amplification (Berlin, Hood, Morlet, et al., 2003). Regarding the utility of cochlear implantation in children with AN, limited data have demonstrated efficacy, implying that electrical stimulation may restore neural synchrony in some of these patients (Buss, Labadie, Brown, et al., 2002; Madden, Hilbert, Rutter, et al., 2002; Mason, De Michele, Stevens, et al., 2003; Peterson, Shallop, Driscoll, et al., 2003; Sininger & Trautwein, 2002). The decision to fit amplification or proceed with cochlear implantation in children with AN who have little or no residual hearing should be made only after definitive evidence of a cochlear nerve on an MRI.

For a child with the diagnosis of AN associated with a congenitally absent cochlear nerve(s), the treatment scheme is unique. In our program, behavioral testing is still attempted to confirm the electrophysiologic and anatomic findings. For unilateral cases, continued observation of the unaffected ear is indicated to detect possible delayed neural loss or other auditory pathologies. In fact, one child in our program with a unilateral absent cochlear nerve and profound hearing loss had development of contralateral hearing loss in a progressive manner. MRI in the ear with progressive loss was found to have cochlear nerve hypoplasia (small), suggesting ongoing neural pathology. This child has ultimately done well with a cochlear implant. Unfortunately, detailed ABR data are lacking for this child. Nonetheless, the concern for progressive neural loss remains. Another child (subject 4) with unilateral absent cochlear nerve and CM has a CM present in his ear with residual hearing. Obviously, progressive neural loss in this ear is a major concern for the future. Finally, children with bilaterally absent cochlear nerves are clearly not candidates for amplification or cochlear implantation. In these children, the introduction of alternative forms of communication is strongly encouraged. Although the auditory brain stem implant has been used in a limited capacity in children with cochlear nerve aplasia, its use for this indication has not been approved by the US Food and Drug Administration (FDA) and thus remains investigational (Colletti, Carner, Fiorino, et al., 2002).

Cochlear nerve deficiency is probably not as uncommon as previously thought. Our center began using MRI as the primary imaging modality for all children with sensorineural hearing loss in 2001. The fact that we now have accumulated 14 cases over a period of 3 yr is noteworthy. We are also aware of at least 3 additional children from our program, with CT imaging as their only imaging modality, who have failed to demonstrate any signs of stimulation after uncomplicated cochlear implantation. These children are now suspected to have the same condition. Govaerts et al. (2003) have recently described 17 children with cochlear nerve deficiency over a 6-yr period of evaluation. Aside from their study and the results reported herein, only isolated case reports exist otherwise. This may be the due to the lack of MRI utilization for screening children with hearing loss rather than other factors. MRI does take longer to acquire the images, requires general anesthesia in young children, and is more costly than CT imaging. It is interesting to note that to date, all of the reports regarding cochlear nerve deficiency except one (Glastonbury et al., 2002) have come from centers outside of the United States. Anecdotal evidence suggests that centers in the United States are much less likely to use MRI imaging protocols for children with hearing loss than centers abroad.

In the present study, the finding of a present CM but absent DPOAEs is not paradoxical. First, any minor disruption to the conductive mechanism is more likely to affect DPOAE recording than CM recording. DPOAEs require normal middle ear function for their reverse transmission to the sealed ear canal, and they are elicited with lower intensity level stimuli than the CM in these measurements. The electrical CM response is volume-conducted directly to the surface electrodes. Second, the frequency-specific DPOAE response represents outer hair cell activity at very localized regions of the cochlea. The CM, being a summed potential, reflects activity across all active hair cells but is dominated at the electrode site by hair cell regions that are most phase-coherent in their response. This tends to occur at the basal end of the cochlea.

The mechanism(s) responsible for cochlear nerve deficiency in children who fail newborn hearing screening remains speculative. Presumably, developmental aplasia/agenesis could account for some of the cases associated with inner ear dysplasia. However, when obvious osseous labyrinthine or IAC

defects are lacking, isolated cochlear nerve agenesis or degeneration must be considered. In development cases, it is possible that a vascular insult during critical periods may result in neural loss. The fact that (1) the cochlear nerve and cochlear hair cells derive their blood supply from the internal auditory artery and (2) the CM, indicative of hair cell function, persists in the absence of a cochlear nerve, suggests that vascular insufficiency is less likely. Moreover, uncontrolled apoptosis regulation of auditory nerve remodeling could explain some cases. Acquired post-developmental degeneration of the cochlear nerve in response to some pathologic insult must also be considered. Perinatal, neurotrophic viral infection such as cytomegalovirus, herpes simplex virus, or other viruses should be closely investigated. Finally, long-term follow-up of these children to detect metabolic and neurologic diseases will also be needed.

CONCLUSIONS

Findings of the present study suggest that cochlear nerve deficiency may not be as uncommon as previously thought. Moreover, identification of this problem requires a detailed understanding of the clinical presentation, electrophysiologic findings, and proper interpretation of an MRI of the brain, IACs, and labyrinth. We believe that MRI should be performed in all children with sensorineural hearing loss, especially those with the clinical picture of AN. Confirmation of cochlear nerve deficiency provides powerful information for parents of these children. In unilateral cases, amplification of the affected ear may be unnecessary, whereas careful observation for the unaffected ear is indicated. In cases in which cochlear nerves are absent bilaterally, families can choose other forms of communication early on rather than embark on a drawn out trial with amplification, or, worse yet, cochlear implantation.

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