Clinical Findings for a Group of Children with Auditory Neuropathy

Gary Rance, David E. Beer, Barbara Cone-Wesson, Robert K. Shepherd, Richard C. Dowell, Alison M. King, Field W. Rickards, and Graeme M. Clark

Objective: **To examine the prevalence of auditory neuropathy in a group of infants at risk for hearing impairment and to present an overview of the clinical findings for affected children.**

Design: **Results for 20 subjects who showed repeatable cochlear microphonic potentials in the absence of click-evoked auditory brain stem responses are included in this study. Behavioral and steady state evoked potential thresholds were established in each case. Where possible, otoacoustic emission and speech perception results (unaided and aided) also were obtained.**

Results: **One in 433 (0.23%) of the children in our series had evidence of auditory neuropathy. The audiometric findings for these subjects varied significantly, with behavioral thresholds ranging from normal to profound levels. Discrimination skills were also variable. Approximately half of the subjects showed little understanding, or even awareness, of speech inputs in both the unaided and aided conditions. There were, however, a number of children who could score at significant levels on speech discrimination tasks and who benefited from the provision of amplification.**

Conclusion: **The results suggest that auditory neuropathy is more common in the infant population than previously suspected. The effects of neuropathy on auditory function appear to be idiosyncratic, producing significant variations in both the detection and discrimination of auditory signals. As such, the management of children with this disorder must allow for individual differences.**

(Ear & Hearing 1999;20;238–252)

The use of auditory evoked potential techniques such as the auditory brain stem response (ABR) for the assessment of hearing in young and difficult-to-test children is now well established. A number of studies have demonstrated a strong correlation between ABR threshold and hearing level in both normally hearing and hearing-impaired subjects (Gorga, Worthington, Reiland, Beauchaine, & Goldgar, 1985; Hyde, Riko, & Malizia, 1990; Kileny & Magathan, 1987; Picton, Durieux-Smith, & Moran, 1994; Sasama, 1990; Stapells, Gravel, & Martin, 1995; van der Drift, Brocaar, & van Zanten, 1987). As a result, reasonably accurate estimates of hearing level can be made for children who are too immature to cooperate for behavioral audiometry.

However, there have been reports in the literature of isolated cases in which evoked potential threshold levels have been significantly worse than would be expected from the subject's audiogram (Davis & Hirsh, 1979; Hildsheimer, Muchnik, & Rubenstein, 1993; Kraus, Ozdamar, Stein, & Reed, 1984; Lenhardt, 1981; Worthington & Peters, 1980). For example, Kraus and her colleagues identified seven cases in a group of 49 children with absent ABRs who had behavioral thresholds in the normal to moderate hearing loss range. These authors concluded that the inconsistency between behavioral and evoked potential findings in these children may have been the result of dual cochlear and auditory brain stem dysfunction.

The presence of preneural evoked responses such as the cochlear microphonic (CM) potential and otoacoustic emissions (OAEs) in a number of recently reported cases has indicated that ABRs may be absent in children and adults with outer hair cell (OHC) function and reasonable hearing thresholds (Deltenre, Mansbach, Bozet, Clercx, & Hecox, 1997; Sininger, Hood, Starr, Berlin, & Picton, 1995; Starr, Picton, Sininger, Hood, & Berlin, 1996).

Starr et al. (1996) used the presence of these cochlear responses (OAEs and CMs) and absent or abnormal ABRs in a group of 10 adults and children to identify a disorder that they called "auditory neuropathy" (AN). The term "neuropathy" is used to denote functional disturbances and/or pathologic changes in the peripheral nervous system, although the exact site(s) of lesion and pathologic processes that results in these findings has not been determined nor localized specifically to the VIIIth nerve. The Starr et al. (1996) series formed a fairly homogeneous group, with all but one of the subjects presenting with acquired hearing loss, all but one showing thresholds in the mild to moderate range,

Co-operative Centre for Cochlear Implant Speech and Hearing Research (G.R., R.C.D., G.M.C.), Royal Victorian Eye and Ear Hospital (G.R., R.C.D., G.M.C.), Department of Otolaryngology, University of Melbourne (G.R., R.C.D., B.C-W., G.M.C.), Department of Audiology, Monash Medical Centre (D.E.B.), Australian Hearing Services (A.K.), and Deafness Studies Unit, University of Melbourne (F.W.R.), Australia.

0196/0202/99/2003-0238/0 • Ear & Hearing • Copyright © 1999 by Williams & Wilkins • Printed in the U.S.A.

TABLE 1. Risk factors and percentages of children in each risk category for subjects referred through the Victorian Infant Hearing Screening Program.

Risk Factor	Percentage
Family history	38
Birthweight <1500 g	18
Parental concern	14
Hyperbilirubinemia (SBR >350 μmol/L)	9
Congenital malformation	9
Birth asphyxia	5
Other	7

and all but two subsequently developing signs of peripheral nerve neuropathies.

Evidence for the existence of AN in the infant population recently has begun to appear in the literature. Deltenre et al. (1997) described the findings for three infants who had suffered major neonatal illness and who showed electrophysiologic (ABR/CM) and OAE results fitting the AN profile within the first year of life. Similarly, Stein, Tremblay, Pasternak, Banerjee, Lindermann, and Kraus (1996) identified four children through a special care nursery screening program with normal OAEs and absent or abnormal ABRs in the neonatal period.

The present paper provides an overview and discussion of the clinical findings for a group of 20 young children whose electrophysiologic test results were consistent with the presence of AN.

METHODS

Subjects

Twenty infants and young children who showed repeatable click-evoked CM potentials but absent click-evoked ABRs were included in this retrospective study. Twelve of these subjects were identified from a group of 5199 children assessed between 1991 and 1996 at the Victorian Children's Hearing Centre (VCHC) and the Monash Medical Centre (MMC). This testing was carried out as part of an early hearing loss identification program that targeted children whose neonatal or family histories placed them at increased risk for hearing loss. The risk factors and percentages of children in each category are shown in Table 1. The remaining eight children were referred for testing following concerns regarding their hearing status or speech and language development.

The subjects were aged between 1 and 49 mo at the time of the initial evoked potential testing. For 14 infants tested at less than 9 mo of age, the assessments were repeated at 12 mo to rule out the possibility of transient neurologic abnormality (Edwards, Durieux-Smith, & Picton, 1985; Kileny & Robertson, 1985). In each of these 14 cases, the ABR was absent and the CM present when the child was retested.

TABLE 2. Hearing loss risk factors in subjects with auditory neuropathy.

Child	Risk Factor	Other Disabilities	Gestation
1	Jaundice (1010)		37
2	Jaundice (792)		36
3	Jaundice (467)		39
4	Jaundice (420)		40
5	Jaundice (380)		41
6	Jaundice (353)/hypoxia	Cerebral palsy	34
7	Hydrocephalus/hypoxia		33
8	LBW (900g)/hypoxia		25
9	Parental concern	Cerebral palsy	40
10	Unilateral ME malformation	Unilateral facial palsy	39
11	Neonatal meningitis		39
12	Parental concern		41
13	Jaundice (540)		40
14	Jaundice (470)/hypoxia		32
15	Jaundice (420)		41
16	Jaundice (390)/hypoxia		31
17	None	Cerebral palsy	40
18	None		39
19	None		39
20	None		39

Subjects 1 through 12 were identified through the "at-risk" screening program. Subjects 13 through 20 were referred following concerns regarding their auditory progress.
Bilirubin concentration levels (in parentheses) measured in μmol/L (μmol/L divided by 17 ≈ mg%).
Gestation = number of weeks at birth.
LBW = low birth weight; ME = middle ear.

Etiology

The risk criteria for which the 20 AN children were referred are summarized in Table 2. In some cases the child had multiple risk factors. In addition to auditory evoked potential test abnormalities, four of the children showed evidence of other disabilities relating to sensory motor deficits. Each of the subjects underwent a clinical neurologic assessment. In no child was there evidence of associated peripheral neuropathy. Cerebral MRI scans were carried out on six of the subjects. Normal findings were reported for each of these cases.

Test results were excluded if an air/bone gap was indicated (where bone conduction results were available) or if abnormal tympanometric results were observed. For children under the age of 6 mo, tympanograms were obtained using multiple probe frequencies to reduce the possibility of artifactual results (Marchant, McMillan, Shurin, Turczyk, Feinstein, & Panek, 1986).

APPARATUS AND PROCEDURES

Evoked Potential Assessment

Evoked potential tests were carried out in a sound-treated room with the child either in natural sleep (n = 17) or sedated with chloral hydrate (50 mg/kg) (n = 3). The EEG activity was measured using silver-silver chloride disk electrodes or disposable Nikomed neonatal electrodes. Differential recordings were made between the vertex or high forehead (noninverting input) and the mastoid or earlobe ipsilateral to the stimulated ear (inverting input). A third electrode on the contralateral earlobe or mastoid acted as a ground. Interelectrode impedance in all cases was less than 10 kΩ at 260 Hz.

Click-Evoked ABR Measurement

ABR testing was performed at the two centers (VCHC and MMC) using similar procedures and test facilities. Assessments at the VCHC were carried out using a system that was custom built in association with the University of Melbourne, whereas testing at the MMC was performed with the Biologic Navigator apparatus. The test parameters and procedures in the two clinics were identical in all respects, except for click presentation rate, which at the VCHC was 12 Hz and at the MMC was 30 Hz. Because the effects of higher click rates are uncertain in subjects with AN, testing was repeated at 12 Hz in all children initially assessed using the 30 Hz presentation rate. There were no instances in which the ABR was absent at 30 Hz and present at 12 Hz.

ABRs were sought to 100 μsec acoustic click stimuli presented monaurally via Etymotic Research ER-3A tubephones at maximum levels of 95 to 100 dB nHL. The stimuli were calibrated using a DB-0138 2-cc coupler with the sound tube connected via a dB-0138 nipple. Peak-equivalent methods were used (Glattke, 1983). A panel of 10 normal-hearing adults were tested to establish the nHL levels. The results showed that a 0 dB nHL stimulus had a peak equivalent SPL of 36 dB. As such, the maximum presentation level for the clicks was 136 dB SPL-(peak).

For recordings made before 1994 (14 children), the raw EEG was amplified and filtered using a band pass of 100 Hz to 3000 Hz (slope 12 dB/octave). The filter settings for testing carried out from 1994 onward were 30 Hz to 1500 Hz. Trials containing amplitudes in excess of 15 μV were automatically rejected. The poststimulus analysis time was typically 16 msec, and 2000 samples were included in each averaged response.

Of the 5199 children who underwent this screening ABR assessment, 37 failed to show repeatable waveforms when presented with two series of alternating polarity clicks at 100 dB nHL. CM potentials were sought in these cases.

CM Measurement

CM testing was carried out using series of unipolar acoustic clicks. Two runs with condensation clicks and two runs with rarefaction clicks were recorded at each presentation level. The CM was considered to be present if the response waveform showed a 180° phase shift with the change in stimulus polarity. Once a CM was obtained, a response threshold was sought by descending in 10 dB steps to a minimum level of 60 dB nHL.

The ER-3A tubephones used to present the stimuli introduced a delay of 0.9 msec between the electrical signal at the transducer and the presentation of the acoustic stimulus at the ear canal. This meant that the electromagnetic artifact was temporally separate from the cochlear potentials, allowing relatively easy identification of the response. The authenticity of the CM response also was confirmed through test runs in which the stimulus tube was clamped to prevent the acoustic signal from reaching the ear canal. Under these circumstances, genuine cochlear potentials were abolished while the stimulus artifact remained unaltered.

Steady State Evoked Potential (SSEP) Measurement

SSEP assessments were carried out at the VCHC using a custom built evoked potential system that employed an IBM-compatible XT-type microcomputer to generate stimuli and analyze responses in the manner described by Cohen, Rickards, and Clark (1991). The raw EEG signal was passed through a preamplifier and filtered using a band pass of 0.2 Hz to 10 kHz. The signal then underwent a Fourier analysis at the stimulus modulation frequency (90 Hz) using analogue multiplication followed by low-pass filtering (Regan, 1966). Two multipliers and two low-pass filters were employed to extract both response phase and response amplitude information. The presence or absence of a response then was determined automatically from these data using a detection criterion that looked for nonrandom phase behavior. The particulars of this analysis, which is equivalent to the phase coherence technique described by Jerger, Chmiel, Frost, and Coker (1986) and Stapells, Makeig, and Galambos (1987), are discussed in detail in Cohen et al. (1991) and Rance, Rickards, Cohen, De Vidi, and Clark (1995).

The test stimuli were 1000 Hz and 4000 Hz tones amplitude and frequency modulated at a rate of 90

Hz. A modulation rate of 90 Hz was used to avoid the problems associated with SSEP testing in sleeping subjects with stimuli presented at lower (<70 Hz) modulation frequencies. An amplitude modulation depth of 100% and a frequency modulation width of 10% were combined to maximize response amplitude (Cohen et al., 1991). The stimulus tones were presented monaurally via mu-metal shielded TDH-39 headphones that allowed maximum sound levels of 120 dB HL. Calibration was performed using pure tones as per the AS 1591.2 standard, a B & K artificial ear (6-cc coupler), a B & K 2613 amplifier, and a B & K 2120 frequency analyzer. The introduction of modulation caused a small increase in stimulus energy that was less than 2 dB (Cohen et al., 1991).

SSEP thresholds were obtained by increasing the presentation level in 10 dB steps from a starting level around 70 dB HL until a statistically significant coherent response was obtained. Stimulus level then was decreased in 5 dB steps until the distribution of phase angles became random. Threshold was defined as the minimum level at which the phase coherence was significant.

OAE Measurement

Transient OAE testing was carried out using an ILO-88 system. The presentation level of the click stimuli was 82 ± 5 dB SPL. An emission was considered to be present if, in the 20 msec post-stimulus period, a response signal to noise ratio of >3 dB and a waveform reproducibility >75% was obtained in at least three octave bands.

Behavioral Audiometric Testing

Behavioral audiometric testing was performed by experienced pediatric audiologists at a number of agencies including the VCHC, MMC, and the Australian Hearing services. As a result, the testing conditions varied by facility, but in all cases the assessments were carried out in sound-treated rooms using standard test protocols. Unaided results were obtained under headphones for all children, and, where appropriate, free field aided thresholds also were established.

Each child was assessed on at least two occasions using conditioned audiometric test techniques appropriate to his or her developmental age (VRA/play audiometry). In 14 of the 20 children, three or more audiograms were available for each ear. The variance of the behavioral thresholds was examined in these cases.

Assistive Devices

Fifteen of the 20 subjects were fitted binaurally with behind-the-ear hearing aids and, at the time of data collection, had been consistent users for a period of more than 1 yr. In three of the children, aiding was never attempted because behavioral thresholds were at normal or near normal levels; in two cases, aids were fitted initially but were removed when behavioral responses subsequently were obtained at levels precluding significant hearing loss.

The hearing aids were supplied and managed by the Australian Hearing Services. In some children conservative fittings were trialed initially, but in all cases the aid settings subsequently were increased to the levels prescribed for ears with sensorineural hearing loss by Byrne and Dillon (1986) and Byrne, Newall, and Parkinson (1990).

One child who had shown behavioral thresholds in the profound hearing loss range wore hearing aids for 2 yr before undergoing the cochlear implant procedure.

RESULTS

Incidence

Of the 5199 children assessed as part of the "at-risk" screening program, 109 "failed" their ABR assessment (see Table 3 for details). The criteria for failure in this test regime were elevated thresholds (>40 dB nHL) on repeated ABR measurements and normal immittance results. All of these subjects subsequently were found to have either a sensorineural hearing loss of greater than mild degree (n = 97) or evidence of AN (n = 12). The prevalence of children with AN within our at-risk population was therefore 1 in 433 (0.23%) and within our group of children with permanent hearing deficit was 1 in 9 (11.01%).

Thirty-seven of the children who failed the ABR at screening levels showed no repeatable ABR bilaterally to acoustic clicks at the maximum presenta-

TABLE 3. Summary of Victorian Infant Hearing Screening Program results.

	VCHC	MMC	Total	Incidence (%)
Number of children tested	2299	2900	5199	
Subjects with permanent hearing loss	48	61	109	2.09
Subjects with absent ABR	23	14	37	0.71
Subjects with absent ABR and CM present	5	7	12	0.23

VCHC = Victorian Children's Hearing Centre; MMC = Monash Medical Centre; ABR = auditory brain stem response; CM = cochlear microphonic.

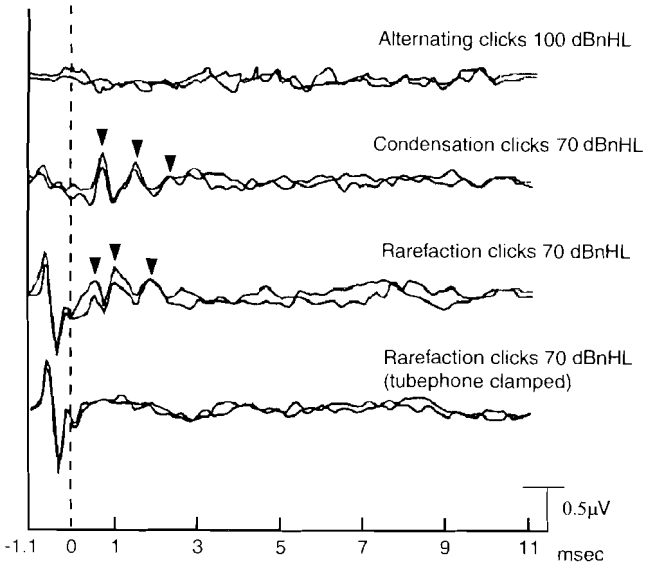

Figure 1. Averaged EEG findings for subject 14. The dotted line represents the point at which the stimulus reached the cochlea. The top tracings show no repeatable potentials to alternating clicks presented at 100 dB nHL. The middle tracing pairs show repeatable cochlear microphonic responses but absent auditory brain stem response waveforms to unipolar stimuli at 70 dB nHL. The triangles indicate the positive peaks in the cochlear microphonic waveform. The final tracings, in which only the stimulus artifact is evident, were obtained to rarefacting clicks presented with the tubephone clamped.

tion level (100 dB nHL). CM testing failed to show a response in either ear in 25 of these cases. Subsequent behavioral testing of these children revealed severe to profound sensorineural hearing loss on all occasions.

CM

All 12 subjects identified by the screening program and the additional eight subjects referred for specific assessment showed clear CM potentials at levels between 60 and 70 dB nHL. The peak to peak amplitudes of these responses when elicited by acoustic clicks at 70 dB nHL varied from 0.5 μV to 1.2 μV. An example of the results obtained in these cases can be seen in Figure 1. In 18 of the 20 subjects, the CM response was present bilaterally. One subject was tested unilaterally because a congenital malformation prevented access to the left ear. In another subject, the CM was present unilaterally. The microphonic in this case was absent in an ear that had undergone the cochlear implant procedure.

Behavioral Hearing Levels

Nine of the 14 subjects for whom three or more reliable audiograms were available showed hearing

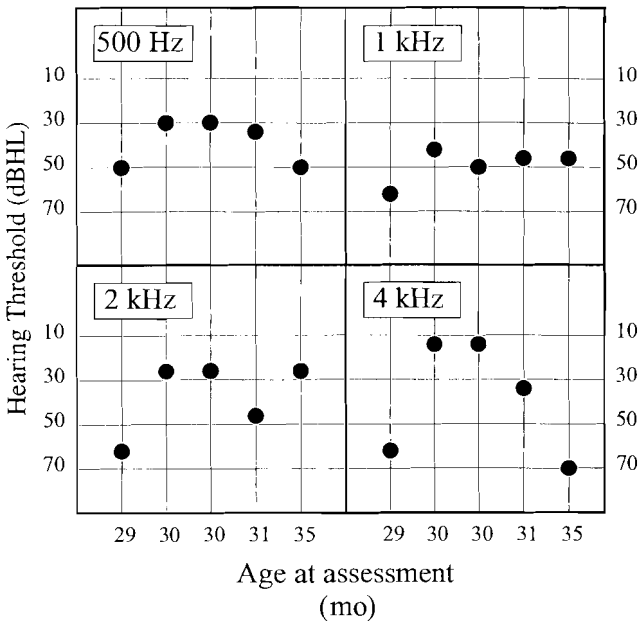

Figure 2. Audiometric results for child 16. The five assessments were carried out over a 6 mo period. Results obtained on each occasion were considered to be an accurate reflection of the child's acuity for that day.

thresholds that were stable over time. Threshold variance values for these children when averaged across the audiometric frequencies varied from 4.5 to 7.1 dB. The five remaining subjects, on the other hand, showed significant hearing level fluctuations. In these children, whose threshold variance values ranged from 10.4 to 32.6 dB, repeated tests (on different days) revealed air and bone conduction thresholds that fluctuated by as much as 45 dB. Figure 2, which shows the audiometric findings for child 16, is typical of the results obtained in these cases.

The behavioral hearing thresholds obtained from the children in our group also showed a great deal of intersubject variation. Figure 3 illustrates the distribution of 3-frequency average scores for each of the 38 ears tested. For the children with fluctuating

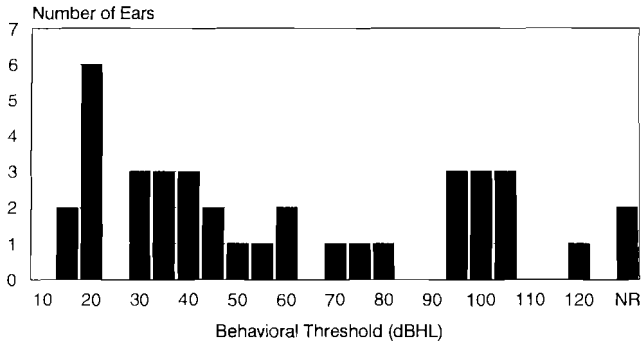

Figure 3. The distribution of behavioral hearing thresholds (3-frequency average) for 38 ears with auditory neuropathy.

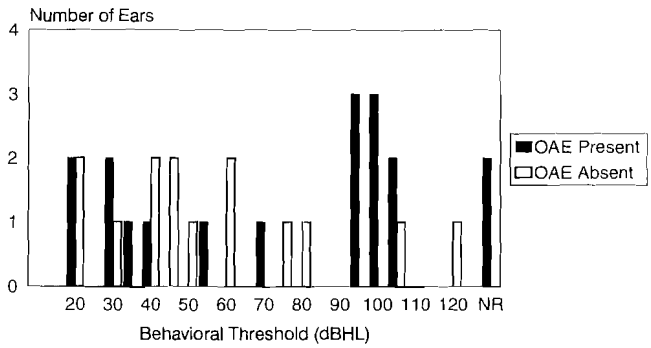

Figure 4. The distribution of behavioral hearing thresholds (3-frequency average) for ears with auditory neuropathy. Results for ears with repeatable otoacoustic emissions (OAEs) are represented by filled columns, and ears with no recordable emissions are represented by unfilled columns.

hearing, mean thresholds were used. Hearing levels in our group ranged from normal levels in some children to profound hearing loss. The hearing loss in each of the children with elevated thresholds was present bilaterally.

The configuration of the subjects' audiograms tended to vary with degree of hearing loss. The eight ears with normal or near normal hearing (≤20 dB HL) showed similar acuity at each of the test frequencies. Ears with thresholds in the mild to severe hearing loss range, on the other hand, were more likely to have audiograms that showed poorest hearing in the low to mid frequencies and better thresholds in the high frequencies. Eleven of the 18 ears followed this pattern. The remaining seven ears showed flat audiograms. For the 12 ears with profound hearing loss, either flat losses or corner audiograms were obtained.

Transient OAEs

Transient OAE testing was attempted in 17 of the 20 children. The response was present bilaterally in eight of these cases. In child 10, the OAE was absent in the malformed ear and was present in the anatomically normal ear. Overall response amplitudes were 11.04 dB ± 1.66 dB, and the average waveform reproducibility in the 1 to 4 kHz octave bands was approximately 85%. As such, the OAEs in these ears were similar to those reported for normal-hearing infants and children (Widen, 1997).

The remaining eight subjects with whom OAE testing was attempted showed no emission in either ear despite low subject noise levels, favorable recording conditions, and the presence of the CM.

The relationship between OAE test result and behavioral hearing level was examined. Figure 4 shows the distribution of 3-frequency average scores obtained for ears with (filled columns) and without (unfilled columns) a transient OAE. A nonparametric comparison (Mann-Whitney Test) of the distribution of these thresholds indicated that there was no significant difference between the hearing levels obtained for ears with or without an emission.

SSEPs

The relationship between behavioral and SSEP thresholds for each of the ears in this study at the 1 and 4 kHz test frequencies is shown in Figure 5A. A Pearson product-moment correlation analysis revealed coefficients of only 0.537 for the 1 kHz stimulus and 0.358 for the 4 kHz stimulus. These marginally significant results suggest that only a weak relationship between behavioral and SSEP thresholds existed for our subjects.

Speech Perception

Speech perception test results were available for 10 of the subjects in our group. Six of these children showed significant scores on open-set (PBK words) and/or closed-set (Picture Vocabulary Test) testing when assessed in their best listening condition (unaided or aided) (see Table 4 for details). The stimuli were presented live voice at levels around 70 dB SPL. Four of the subjects showed no measurable speech perception ability, scoring at chance levels only. They each, however, demonstrated an ability to complete the task with significant scores in the auditory/visual test condition (Table 4).

The relationship between speech perception ability and the findings of the other assessments in our test battery was examined in these 10 subjects. Linear regression analyses showed no significant correlation between closed-set speech perception score and behavioral threshold, behavioral threshold variance, and SSEP threshold (1 and 4 kHz). A two tailed *t*-test also failed to show a significant relationship between speech perception performance and the presence or absence of the OAE.

In each of the 15 consistent hearing aid users in our group, the amplified speech spectrum was tolerated using gain and frequency response settings that assumed that the hearing loss was of sensorineural origin. Eight of the 15 hearing aid users underwent speech perception testing in both the unaided and aided conditions (see Table 4 for details). Significant differences between unaided and aided scores were obtained for four of these subjects ($p < 0.01$). The other four children showed no amplification benefit, scoring equally poorly in both conditions.

Immaturity or generalized developmental problems prevented formal speech perception assessment in 7 of the 15 hearing aid users. Anecdotal

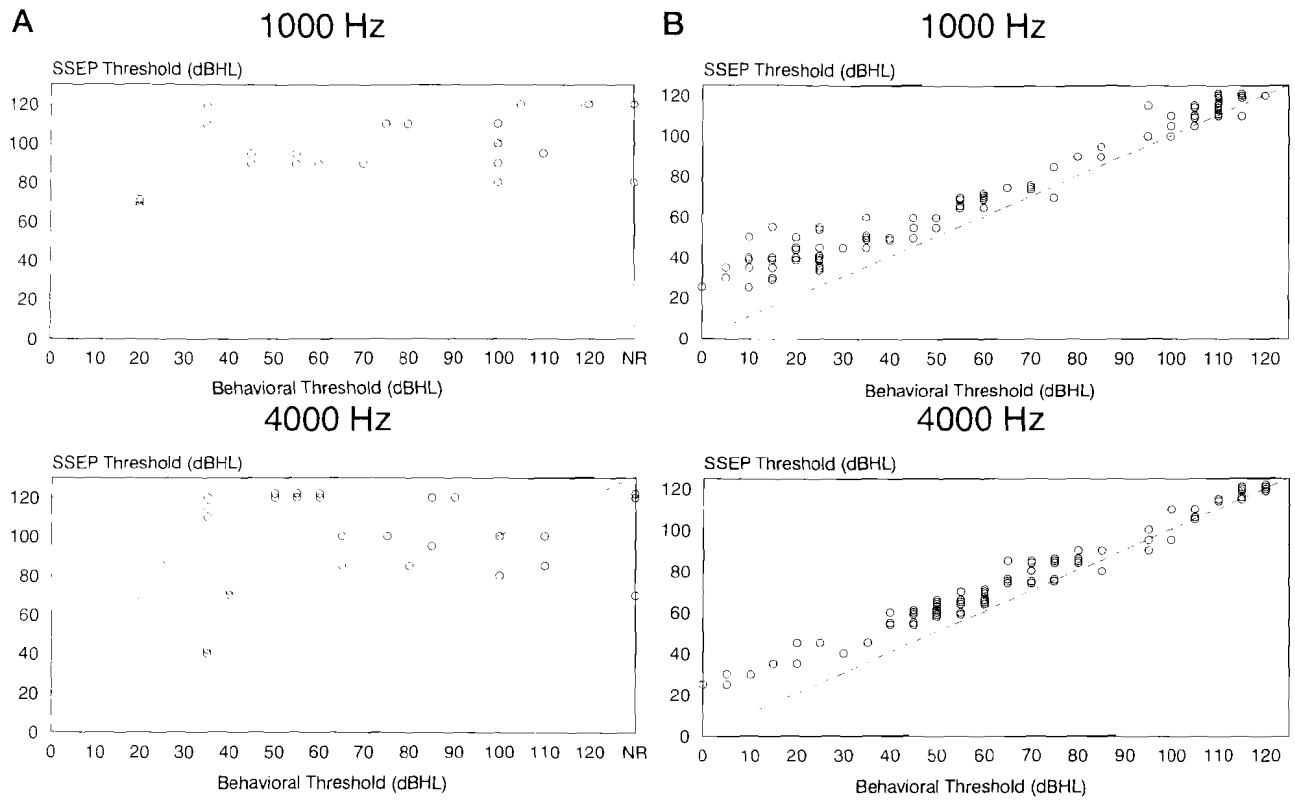

Figure 5. (A) The distribution of steady state evoked potential (SSEP)/behavioral threshold comparisons at 1 and 4 kHz for ears with auditory neuropathy. Points with multiple subjects have symbols offset (±1 dB). Clinical constraints prevented the recording of thresholds at both 1 and 4 kHz in some cases. (B) The distribution of SSEP/behavioral threshold comparisons at 1 and 4 kHz for 60 subjects with sensorineural hearing loss (Rance et al., 1995).

evidence provided by experienced clinicians (audiologists and teachers of the deaf) suggested that in four of these children, general communicative responsiveness was increased in the aided condition.

A nonparametric (Mann-Whitney) assessment of the relationship between unaided behavioral hearing threshold and aid usage showed no significant difference between those children who obtained benefit from their hearing aids and those who did not. This result suggests that behavioral hearing levels in children with AN cannot be used to predict the usefulness of amplification.

The effect of amplification on hearing thresholds may, however, provide some guide as to the child's likely aided speech perception abilities. The eight children who appeared to benefit from the hearing aids all showed aided thresholds at levels predicted by their aiding prescription (Byrne & Dillon, 1986), i.e., their aided hearing thresholds were significantly better than their unaided levels. In contrast,

TABLE 4. Speech discrimination test results for children with auditory neuropathy.

		PBK Words (Open Set)		Picture Vocabulary Test (Closed Set)		
Subject	3-Frequency Average (dB HL)	Unaided	Aided	Unaided	Aided	Aid/Visual
3	15			11/12		
4	20			12/12		
16	30	32%	88%		12/12	
17	35			3/12	2/12	9/12
8	45			3/12	3/12	10/12
13	55	8%	43%		12/12	
12	95			2/12	8/12	
15	105			1/12	8/12	
14	115			2/24	4/24	22/24
10	120+			1/12	1/12	11/12

PBK Words Phonetically Balanced Kindergarten Word test; Picture Vocabulary Test = Subtest 4 of the PLOTT test.

five of the seven children who demonstrated no obvious aided speech perception benefit showed no difference between their aided and unaided hearing thresholds.

CASE STUDY

Cochlear implantation is now a well-established management option for children with significant hearing loss. To date there have been no published results for AN patients who have received such a device. We present the findings for one of our subjects (child 14) who was implanted with the Nucleus-22 M system.

This 4-yr-old boy was born at 32 wk gestation weighing 2.2 kg. Despite his prematurity, he presented with no other neonatal risk factors apart from a high bilirubin level (SBR: 452 μmol/L). After his parents noticed a lack of auditory responsiveness, his hearing was assessed at the age of 9 mo. He subsequently was diagnosed with profound bilateral hearing loss and was fitted binaurally with high-powered hearing aids at the age of 13 mo.

After 2 yr of consistent aid use, this child had shown limited awareness of sound and had failed to develop oral language. It was considered that he would benefit from a cochlear implant, and he underwent the procedure in the left ear at the age of 3 yr 9 mo.

Despite the fact that this child showed significant improvements in his language ability and lipreading skills in the period after implantation, his performance with the cochlear implant was consistently poor. On speech perception testing carried out 1 yr postoperatively, his audition alone score on a 12 item closed-set task (Picture Vocabulary Test—PLOTT Test) was at a chance level (2/24). His auditory/visual result (22/24) indicated that he was able to understand and complete the task. This child also performed poorly on open-set testing (audition alone), obtaining only a marginally significant phoneme score (8%) on the PBK word test.

Evoked potential assessment was carried out as part of a battery of tests to investigate his unusually poor performance. ABR testing showed no repeatable waveforms to 100 dB nHL acoustic clicks presented to the right (nonimplanted) ear. CM responses were present to 70 dB nHL (see Fig. 1 for details). A similar assessment of the implanted ear showed no ABR or CM response at 100 dB nHL. The microphonic in this case is likely to have been disrupted by damage to the cochlea's OCHs or middle ear structures during implant surgery and/or by postoperative fibrous tissue growth dampening the displacement of the basilar membrane. Although there have been cases reported in the literature of unilateral abnormality (Konradsson, 1996), absent waveforms on an electrically evoked ABR (EABR) test suggested that this child's neuropathy was present on the implanted side as well.

DISCUSSION

One hundred nine of the 5199 babies (2.09%) in our screening program failed the ABR assessment and subsequently were found to have either sensorineural hearing loss of greater than mild degree or evidence of AN. This prevalence of hearing impairment is similar to that reported by the Joint Committee on Infant Hearing (US) (1991), which found that between 2.5% and 5.0% of neonates with similar risk factors show a deficit of mild degree or worse.

In 37 of the children, no repeatable ABRs could be identified with click stimuli presented in either ear at maximum levels (95 to 100 dB nHL). CM assessment in 25 of these cases showed no responses bilaterally. Subsequent behavioral testing revealed that all of these children had sensorineural hearing losses in the severe to profound range. As such, the absence of both the ABR and CM waveforms was a reliable indicator of significant hearing loss.

Twelve of the children in the screened group showed absent ABRs but present CM responses. This represents an incidence of 0.23% or 1 in every 433 of our at-risk infants. Of the 109 children with permanent hearing deficit, we therefore found evidence of AN in 11% or 1 in 9 cases. This figure is significantly higher than that obtained by Davis and Hirsh (1979), who considered that only 1 in 200 of their hearing-impaired subjects showed evidence of auditory pathway abnormality. The high prevalence of AN in our population may be a reflection of the manner in which they were referred for assessment. A large proportion of the screening group was born prematurely and required extended periods of intensive care. Although preterm birth in itself does not appear to impede neurologic development, the status of the child's organ systems can have an impact on neural integrity (Salamy, Eggermont, & Eldredge, 1994).

The most common risk factor among our subjects was neonatal hyperbilirubinemia. Six of the 12 children identified by the screening program and 10 of the 20 children in the broader AN group showed bilirubin concentrations of >350 μmol/L. Excessive amounts of bilirubin (a by-product of red blood cell metabolism), which often is associated with liver immaturity in the newborn, can be toxic to the central nervous system and can result in significant neurologic insult known as kernicterus. Although the majority of neonates (60%) experience some

"physiologic jaundice," which is not toxic, the problem of neurotoxicity is exacerbated in premature infants, those with a maternal-fetal blood group incompatibility (such as Rh-factor), those with congenital or perinatal infections, and those suffering from perinatal conditions such as hypoxia (Borg, 1997). Unconjugated bilirubin (bilirubin that is not bound to the albumin protein rendering it harmless) can cross the blood-brain barrier, causing icteric staining of the central nervous system. Even short-term episodes of hyperbilirubinemia have been shown to result in both temporary and permanent evoked potential abnormalities including elevated ABR thresholds (Hung, 1989) and prolonged ABR wave (I-V) latencies (Nakamura, Takada, Shimabuku, Matsuo, Matsuo, & Negishi, 1985; Tan, Skurr, & Yip, 1992), suggesting that both the peripheral and central auditory systems are vulnerable to bilirubin insult.

An animal model of bilirubin toxicity supports the notion that AN may be a sequelae of hyperbilirubinemia. Shapiro and Te-Selle (1994) demonstrated that in Gunn rats, acute bilirubin concentrations can result in abnormal ABRs in the presence of normal CMs. In another study, Conlee and Shapiro (1991) examined the brain stems of Gunn rats killed when bilirubin levels were at their highest. They found that the volume and cells of the cochlear nucleus and trapezoid body were smaller than those of control animals and that the most severely jaundiced animals in the experimental group also had kernicteric staining of the glia in these nuclei.

The recent reports of AN in young infants also point to jaundice as a factor. Stein et al. (1996) present four infants and Berlin, Bordelon, Hurley, Hood, and Parkins (1997) five infants, all with a history of hyperbilirubinemia. Interestingly, both of these studies describe improvements in evoked potential response that may have been associated with "reversible desynchronization of the ABR." In our series, the six jaundiced children who showed abnormal ABRs when tested before the age of 3 mo showed no improvement when reviewed at 12 mo of age.

In addition to the 10 patients with hyperbilirubinemia in our group, three others had a rocky perinatal course, including hydrocephalus with hypoxia, extreme low birthweight (900 grams) with hypoxia, and neonatal meningitis. These conditions all have been associated with neurologic sequelae at peripheral and central loci of the auditory system (Borg, 1997; Boynton, Boynton, Merritt, Vaucher, James, & Bejar, 1986; Edwards et al., 1985; Hecox, 1985; Kileny, Connelly, & Robertson, 1980; Kileny & Robertson, 1985; Leech & Alvord, 1977; Stockard & Stockard, 1981). The infants described by Deltenre et al. (1997) also had complicated neonatal courses with multiple factors that could cause central nervous system insult.

In summary, among our group of 20 subjects, there were in fact only three children who had no risk factors for central nervous system impairment. Thus, we may assume the same underlying pathophysiology for nervous system damage in AN as is recognized for the neurologic sequelae of hyperbilirubinemia, hypoxia, congenital infection, and prematurity—all conditions identified in our sample.

A number of authors have suggested that AN could be associated with a loss of myelin and could be localized to the Type 1 afferent auditory nerve fibers (Kraus, Ozdamar, Stein, & Reed, 1984; Starr et al., 1996). Partial or complete loss of myelin can have profound effects on the generation and propagation of action potentials within auditory nerve fibers. Demyelination results in an increased membrane capacitance and a decrease in membrane resistance, leading to a delayed excitation, a reduction in the velocity of action potential propagation, and an increase in conduction vulnerability (Cragg & Thomas, 1964; McDonald & Sears, 1970; Pender & Sears, 1984; Rasminsky & Sears, 1972; Tasaki, 1955). Although neurones that are not entirely myelinated are capable of conducting action potentials, they do so with prolonged refractory periods and an impaired ability to transmit high-frequency pulse trains (Cragg & Thomas, 1964; Koles & Rasminsky, 1972; McDonald & Sears, 1970; Pender & Sears, 1984 ; Rasminsky & Sears, 1972). Furthermore, repetitive activation of demyelinated fibers results in a progressive increase in the conduction time of the action potential and may lead to an intermittent or total block in their propagation ("conduction block") (Koles & Rasminsky, 1972; Rasminsky & Sears, 1972).

The pathophysiologic changes in neural conduction properties associated with demyelination are likely to have profound effects on ABRs, which are reliant on the relatively precise synchronous response of a population of auditory nerve fibers to a transient acoustic stimulus. Reductions in the temporal synchrony of demyelinized VIIIth nerve fibers is likely to lead to a significant reduction in the amplitude of the evoked response. Moreover, with more advanced lesions, the propagation of the action potential is likely to become increasingly vulnerable and the risk of depolarization block is increased—especially for the relatively repetitious stimuli used to generate ABRs.

Starr et al., 1996 suggested that in some of their adult subjects, the AN was likely to be the result of a demyelinating process. These investigators found evidence of peripheral neuropathy in 8 of their 10

patients. In two of these, the clinical findings were consistent with the hereditary sensory-motor neuropathy Charcot-Marie-Tooth (Type 1). Because demyelination is a feature of this disease, they concluded that, in these cases at least, the abnormal evoked potential findings were most likely the result of myelin damage.

There was no evidence of generalized neuropathic disorder in any of the children evaluated in this study. However, it is possible that the course of the pathology was not sufficiently advanced in these cases to manifest itself in clinical symptoms. In the patients identified by Starr and colleagues (1996), the peripheral neuropathies did not become obvious until at least the age of 10 yr. Moreover, it would appear from their longitudinal study that auditory dysfunction was typically among the earliest indicators of neuropathic disorder.

Another explanation that has been postulated for the pattern of findings seen in subjects with AN (i.e., significant decrement in the ABR with evidence of OHC function) suggests that the pathology may be restricted to the inner hair cell (IHC) or its synapse with the Type 1 auditory nerve fiber. This hypothesis cannot be ruled out at this stage because suitable diagnostic tests are not available. A similar electrophysiologic profile has in fact been produced in animals treated with carboplatin, an anti-cancer agent that induces selective IHC lesions (Takeno, Harrison, Ibrahim, Wake, & Mount, 1994, Wake, Anderson, Takeno, Mount, & Harrison, 1996). However, isolated IHC damage does not explain the inconsistency between audiometric and ABR findings because patients with IHC damage would be expected to show behavioral and electrophysiologic thresholds that are elevated by a similar degree. The behavioral audiograms of our series of AN children varied widely (Fig. 3) and included eight ears with thresholds in the normal hearing range. It seems very unlikely that in these ears there was sufficient IHC damage to completely disrupt the ABR while retaining normal acuity.

Evidence of OHC integrity in our 20 cases was obtained through CM testing. Other studies have used evoked OAEs to differentiate between preneural and more central pathologies (Deltenre et al., 1997; Starr et al., 1996; Stein et al., 1996). OAE testing in our population did, however, suggest that this technique may not be adequate to identify all cases of AN. Approximately one-half of our subjects had no OAEs and consequently would have gone undiagnosed had they not shown a CM response.

Despite the fact that CM potentials and OAEs appear to have a common generator (OHCs) (Norton, Ferguson, & Mascher, 1989), there are a number of circumstances in which an ear might show a microphonic and yet have no OAE. An emission may, for example, be produced by the OHCs but be impeded in its propagation through the middle ear system (Lonsbury-Martin, Whitehead, & Martin, 1991; Rossi, Solero, Rolando, & Olinda, 1988). Normal tympanograms were obtained from all of our subjects, making this scenario unlikely, but it is possible that in some cases subtle middle ear pathology prevented the recording of the response.

Another possibility is that the OHCs in these children were damaged to the extent that they could produce neither the CM nor OAE responses and that the observed microphonics were in fact IHC generated. Although it is well accepted that the CM, when recorded from extra-tympanic sites, is dominated by activity from OHCs (Dallos, 1973; Norton et al., 1989), there is some suggestion that IHCs also may be able to generate a CM (albeit of lower amplitude). Dallos and Cheatham (1976), for example, suggest that the IHCs produce a CM that is 19 dB less than that generated by the OHCs. That being the case, we consider it unlikely that the CM responses in our patients were produced by IHCs. Although the literature on the size of the scalp-recorded CM is limited, the data presented by Sohmer and Pratt (1976) and Pratt, Sohmer, and Barazani (1978) for normal-hearing subjects with brief tonal stimuli and by Chisin, Pearman, and Sohmer (1979) for acoustic clicks are of a similar order to those obtained in our subjects. Furthermore, the range of peak to peak amplitudes that we observed in our AN cases to clicks at 70 dB nHL (0.5 μV to 1.2 μV) was similar to that seen for normal-hearing subjects (assessed through the screening program) at the same presentation level.

Finally, it is possible that the OHCs of these children had undergone sufficient insult to disrupt the active process (and hence the OAE) but had not been damaged to the point where the CM was abolished. Numerous studies have found that OAEs are sensitive to even minor cochlear insults (Harris, 1990; Lichtenstein & Stapells, 1996; Lonsbury-Martin et al., 1991; Nelson & Kimberley, 1992; Stevens, 1988). Our results for children with sensorineural hearing loss (identified through the screening program) suggest that the CM response is more robust. We typically found that the microphonic could be recorded in ears with even moderate hearing loss and that the CM thresholds in these cases were usually similar to those of the ABR. Sohmer, Kinarti, and Gafni (1980) also demonstrated that the CM could be recorded in ears with significant sensorineural hearing loss. These findings suggest that the OHCs can, in some cases, retain their ability to produce a receptor potential despite the presence of

cochlear damage sufficient to disrupt the motile aspects of OHC function.

SSEPs are periodic scalp responses that can be recorded in subjects of all ages (Levi, Folson, & Dobie, 1993; Rance et al., 1995; Rance, Dowell, Rickards, Beer, & Clark, 1998; Rickards, Tan, Cohen, Wilson, Drew, & Clark, 1994). These continuous potentials, when elicited by tonal stimuli modulated at rates around 90 Hz, appear to have similar generators to the late components of the ABR (Cohen et al., 1991; Kuwada, Batra, & Maher, 1986; Rickards & Clark, 1984). Unlike the ABR, however, successful recording of the SSEP requires only that the auditory system produce a response that is phase locked to the modulation envelope of the stimulus. Because detection of the SSEP is based on analysis in the frequency domain (using Fourier transformation), rather than in the time domain (as is the case for transient responses), we were hopeful that the SSEP would be more resistant to the neural dyssynchrony that appears to arise in cases of AN.

Recently published findings for subjects with sensorineural hearing loss have suggested that the technique can provide accurate estimates of the behavioral audiogram (Lins et al., 1996; Rance et al., 1995; Rance et al., 1998). Figure 5B shows the close relationship between SSEP and behavioral thresholds obtained from a group of 60 child and adult subjects in one of our earlier studies (Rance et al., 1995). The correlation coefficients obtained in this investigation were 0.98 at 1 kHz and 0.99 at 4 kHz.

SSEP results obtained from our AN subjects under similar test conditions were significantly poorer than those seen for ears with sensorineural loss (Fig. 5A). Although the response was recordable at some level in each case, there was only a very weak relationship (r = 0.54 at 1 kHz; r = 0.36 at 4 kHz) between behavioral hearing level and SSEP threshold. Clearly, the abnormality that had disrupted the ABR in these children also was exerting an influence over the SSEP results. As such, the high rate SSEP appears to have little or no predictive value for hearing levels in children with AN.

An unusual aspect of the SSEP/behavioral threshold correlation for the AN group was the number of occasions in which an SSEP was obtained at levels below the behavioral threshold (n = 5 at 1 kHz; n = 6 at 4 kHz). SSEP thresholds for subjects with sensorineural hearing loss typically exceed the hearing threshold (Fig. 5B). This inconsistency raises questions about the manner in which children with AN perceive auditory stimuli. It is possible that in some cases distortion introduced in the auditory pathway by the neuropathic process could have made the warble tone stimuli used in the behavioral testing unrecognizable. The fact that SSEP responses in some cases were recorded at levels up to 40 dB lower than the child's behavioral threshold indicates that the auditory pathway in these instances was able to produce a phase locked response to stimuli at levels well below the point at which the child became aware of the signal.

SSEPs may be elicited more efficiently by stimuli modulated at slower rates (such as 40 Hz) in awake adult subjects with AN. The 40 Hz stimulus rate generates a response with a derived latency of approximately 30 msec and is thought to result from the superposition of transient middle latency responses (Galambos, Makeig, & Talmachoff, 1981). Late and middle latency responses are not as dependant on precise neural synchrony as the ABR and appear to be more robust in subjects with AN. Starr et al. (1996) were able to record these potentials in approximately half of the adult subjects that they tested, and Stein et al. showed middle latency responses in all four of their infants. The presence of the 40 Hz SSEP response was not investigated in our group. Interpretation of results obtained from sleeping infants and children with AN at this rate would be complicated by the fact that the response becomes unreliable in the normal-hearing population under these conditions (Aoyagi, Kiren, Fuse, Suzuki, Yokoto, & Koike, 1994; Levi et al., 1993; Maurizi, Amadori, Paludetti, Ottaviani, Rosignoli, & Luciano, 1990; Stapells, Galambos, & Costello, 1988).

Difficulty with the understanding of speech is a consistent finding in subjects with AN (Davis & Hirsh, 1979; Kraus et al., 1984, Starr et al., 1996). Starr and colleagues (1996) reported that in all of their adult subjects, scores on word intelligibility testing were poorer than expected given the level of their hearing thresholds and that general speech comprehension was a major problem. Because there is some evidence that temporal cues play a role in the encoding of human speech (e.g., Sachs, Voight, & Young, 1983), it is possible that the poor speech comprehension of these patients was associated with the reduced temporal synchrony of VIIIth nerve firing.

The loss of temporal synchrony may not, however, explain completely the poor speech perception seen in subjects with AN. Speech perception in cochlear implant patients can be excellent (up to 80% word scores for open-set monosyllables; Dowell, Blamey, & Clark, 1995, Hollow et al., 1997; Skinner et al., 1994) with speech coding schemes that, in general, do not reproduce the temporal patterns present in the normal cochlea. In addition, the discrimination of periodicity is poor for cochlear implant patients, with virtually no discrimination of pulse rates above 500 Hz and difference limens for lower frequencies

much poorer than for normal-hearing listeners (Shannon, 1983; Tong, Clark, Blamey, Busby, & Dowell, 1982). As such, it would appear that speech perception can be robust despite gross distortion of temporal aspects of the signal. It seems likely, therefore, that for patients with AN there is distortion of the tonotopicity of the neural signals reaching the higher centers of the central auditory system.

The speech perception abilities of our subjects were variable. Six of the 10 children who could provide reliable responses on speech perception testing were able to make use of their hearing, scoring at significant levels on open- and/or closed-set tasks. The remaining four children, however, showed no discrimination ability, scoring at chance levels only (Table 4).

Speech perception performance could not be predicted from the results of any of the other assessments in our test battery. Behavioral threshold level, for example, which in ears with sensorineural hearing loss is strongly correlated to speech perception ability (Boothroyd, 1984), was unrelated to closed-set speech perception score. Child 15, for instance, despite thresholds in the profound hearing loss range, showed significant speech discrimination ability (when aided), whereas child 17, who had thresholds in the mild range, could score only at chance levels.

Degree of behavioral threshold variability was also a poor predictor of speech perception performance. Five of the AN children showed significantly fluctuating audiograms. Intuitively, this finding, which has been reported previously (Sinninger et al., 1995) might be expected to correlate with poor discrimination, but this did not appear to be the case. Child 16, in fact, whose threshold variance was among the highest (32.6 dB), showed the best speech perception of all of our subjects.

Starr et al. (1996) reported that the provision of amplification in their group was of no benefit and in some cases lead to "detrimental effects." Our experience with hearing aid fitting has been rather more positive. Although seven of the 15 children with whom hearing aids were trialed showed no benefit after more than 1 yr of consistent use, eight children did show a significant aided advantage on speech perception testing or in general auditory responsiveness. Our results indicate that a diagnosis of AN in a young child does not preclude the possibility of significant speech perception skills and aided benefit. As such, we recommend that some form of amplification be attempted in all pediatric neuropathy cases in which the behavioral thresholds are abnormal.

A significant number of the ears in our sample (12) showed behavioral thresholds in the profound hearing loss range. Although there have been isolated cases of severe loss reported for ears with present OAEs (Konradsson, 1996; Prieve, Gorga, & Neely, 1991), almost all of the AN patients presented by Starr et al. (1996) and Deltenre et al. (1997) showed behavioral thresholds at mild to moderate levels. The findings in our subjects raise the question of cochlear implantation in children with AN. Cochlear implants have been shown to provide speech perception benefits for children with significant sensorineural hearing loss (Dowell, 1995; Osberger, 1995). However, the prognosis for candidates with AN is unclear and is likely to depend on the site(s) of lesion. If, for example, the damage is restricted to the IHC or the synapse to the auditory nerve fiber, cochlear implantation is likely to be successful because the electrical signal provided by the device bypasses this portion of the auditory pathway, stimulating the spiral ganglion cells directly. If, on the other hand, the damage is medial to these structures (as seems most likely), the propagation of the implant signal through the auditory system may be compromised.

The great majority of cochlear implant patients with profound sensorineural hearing loss also show partial degeneration of auditory nerve fibers secondary to the loss of hair cells (Shepherd & Javel, 1997). Associated with this neural loss is a partial loss of myelin; however, the central axons of these fibers projecting through the internal auditory meatus remain predominantly myelinated even in long-term profound deafness (Felix & Hoffmann, 1985; Spoendlin & Schrott, 1989). In subjects with AN associated with significant myelin deficiencies, electrical stimulation of the VIIIth nerve will generate and propagate action potentials, although significant increases in threshold and dynamic range are likely (Shepherd & Javel, 1997). Moreover, there is a reduction in the ability of these nerve fibers to respond to high stimulus rates as a result of depolarization block. Electrical stimulation of the auditory nerve in myelin-deficient mice evoked EABRs, although these responses showed elevated thresholds and prolonged latencies compared with EABRs evoked from control animals (Zhou, Abbas, & Assouline, 1995). Clearly, action potentials can be generated and propagated in relatively mild forms of this pathology. However, as the extent of the lesion progresses, neural activity generated via a cochlear implant will be equally susceptible to conduction block as activity generated via normal transduction mechanisms. Under these extreme circumstances, AN patients would not be expected to receive significant benefit from a cochlear implant.

The findings for our implanted subject were consistent with the results of these physiologic studies. In this child's case, the absence of waveforms on an electrically evoked ABR assessment suggested that the neuropathy was present at the level of the auditory brain stem. Auditory sensations could be elicited by the system, but only at very high presentation levels. Stimulation on approximately half of the electrodes was inaudible at maximal levels, and the remaining electrodes required levels of current far in excess of that expected for an average cochlear implant user. Not surprisingly, the auditory skills of this child were very poor. After 1 yr of continuous device use, his speech perception scores were at chance or near chance levels, placing him in the lowest 10% of the pediatric performance range.

Although the results for this one child do not mean that all candidates with AN should be precluded from cochlear implantation, they do point to potentially poorer than average performance. As such, we recommend that tests of preneural function be included in the preimplant assessment battery so that subjects with AN can be identified and families can make informed decisions based on appropriate expectations.

In conclusion, the results show that for our population of at-risk babies, the number of cases of AN was significantly higher than previous reports would have predicted. In the future, we consider that the incidence of pediatric AN is likely to increase even further as strategies for the care for premature and low birthweight babies improve. Findings to date have suggested that decreased mortality rates in these children lead to a proportional increase in adverse neurologic consequences in the survivors. We therefore recommend that tests of cochlear function (CM particularly) become part of the standard infant test routine and be undertaken for all children with absent or abnormal ABRs so that cases of AN can be identified and appropriate intervention strategies can be considered. What constitutes appropriate audiologic and educational intervention for these children is uncertain at this stage. The subjects described in this study varied significantly in both their audiometric findings and general response to sound. Whether or not this performance variability reflects the fact that they are suffering from different pathologies or different degrees of the same pathology cannot be determined. What is clear is that the effects of the neuropathy on auditory function are idiosyncratic and cannot be predicted from the tests that are currently available. As such, the management of children with AN must be flexible and take into account individual differences.

ACKNOWLEDGMENTS:

We gratefully acknowledge the contribution made by the audiologists of the Australian Hearing Services and Monash Medical Centre in data collection for this paper. Thanks also to Ms. Zeffie Poulakis for her input regarding the Victorian Infant Hearing Screening Program.

Address for correspondence: Gary Rance, University of Melbourne, School of Audiology, 172 Victoria Parade, East Melbourne, VIC. 3002, Australia.

Received August 28, 1998; accepted January 21, 1999

REFERENCES

Aoyagi, M., Kiren, T., Fuse, T., Suzuki, Y., Yokoto, M., & Koike, Y. (1994). Effects of ageing on amplitude-modulation following response. *Acta Otolaryngologica. Supplement (Stockholm), 511*, 15–22.

Berlin, C. I., Bordelon, M. C. D., Hurley, A., Hood, L. J., & Parkins, C. W. (1997). Autoimmune inner ear disease: basic science and audiological issues. In C.I. Berlin (Ed.), *Neurotransmission and hearing loss: Basic science, diagnosis and management* (pp. 137–146). San Diego: Singular Publishing Group.

Boothroyd, A. (1984). Perception of speech contrasts by subjects with sensorineural hearing loss. *Journal of Speech and Hearing Research, 27*, 134–144.

Borg, E. (1997). Perinatal asphyxia, hypoxia, ischemia and hearing loss. An overview. *Scandinavian Audiology, 26*, 77–91.

Boynton, B. R., Boynton, C. A., Merritt, T. A., Vaucher, Y. E., James, H. E., & Bejar, R. F. (1986). Ventriculoperitoneal shunts in low birth weight infants with intracranial haemorrhage: neurodevelopmental outcome. *Neurosurgery, 18*, 141–145.

Byrne, D., & Dillon, H. (1986). The National Acoustic Laboratories (NAL) new procedure for selecting the gain and frequency response of a hearing aid. *Ear and Hearing, 7*, 257–265.

Byrne, D., Newall, P., & Parkinson, A. (1990). Hearing aid gain and frequency response requirements for the severely/profoundly hearing impaired. *Ear and Hearing, 11*, 40–49.

Chisin, R., Pearman, M., & Sohmer, H. (1979). Cochlear and brain stem responses in hearing loss following neonatal hyperbilirubinemia. *Annals of Otology, Rhinology, & Laryngology, 88*, 352–357.

Cohen, L. T., Rickards, F. W., & Clark, G. M. (1991). A comparison of steady-state evoked potentials to modulated tones in awake and sleeping humans. *Journal of the Acoustical Society of America, 90*, 2467–2479.

Conlee, J. W., & Shapiro, S. M. (1991). Morphological changes in the cochlear nucleus and nucleus of the trapezoid body in Gunn rat pups. *Hearing Research, 57*(1), 23–30.

Cragg, B. G., & Thomas, P. K. (1964). Changes in nerve conduction in experimental allergic neuritis. *Journal of Neurology, Neurosurgery, and Psychiatry, 27*, 106–115.

Dallos, P., (1973). *The auditory periphery: Biophysics and physiology*. New York: Academic Press.

Dallos, P., & Cheatham, M. A., (1976). Production of cochlear potentials by inner and outer hair cells. *Journal of the Acoustical Society of America, 60*, 510–512.

Davis, H., & Hirsh, S. K. (1979). The audiometric utility of the brain stem response to low frequency sounds. *Audiology, 15*, 181–195.

Deltenre, P., Mansbach, A. L., Bozet, C., Clercx, A., & Hecox, K. E. (1997). Auditory neuropathy: A report on three cases with

early onsets and major neonatal illnesses. *Electroencephalography and Clinical Neurophysiology, 104*, 17–22.

Dowell, R. C. (1995). Speech perception in adult cochlear implant users. In G. Plant & K.E Spers (Eds.), *Profound deafness and speech communication* (pp. 262–284). London: Whurr.

Dowell, R. C., Blamey, P. J., & Clark, G. M. (1995). Potential and limitations of cochlear implantation in children. *Annals of Otology, Rhinology, and Laryngology, 104*(Suppl. 166), 324–327.

Edwards, C. G., Durieux-Smith, A., Picton, T. W. (1985). Auditory brainstem response audiometry in neonatal hydrocephalus. *Journal of Otolaryngology, 14*, 40–46.

Felix, H., & Hoffmann, V. (1985). Light and electron microscopic investigation of cochlear nerve specimens from profoundly deaf patients. *Acta Otolaryngologica. Supplement (Stockholm), 423*, 67–72.

Galambos, R., Makeig, S., & Talmachoff, P. J. (1981). A 40 Hz auditory potential recorded from the human scalp. *Proceedings of the National Academy of Science USA, 78*, 2643–2647.

Glattke, T. J. (1983). *Short latency auditory evoked potentials*. Baltimore: University Park Press.

Gorga, M. P., Worthington, D. W., Reiland, J. K., Beauchaine, K. A., & Goldgar, D. E. (1985). Some comparisons between auditory brainstem response threshold, latencies, and the pure-tone audiogram. *Ear and Hearing, 6*, 105–112.

Harris, F. P. (1990). Distortion product otoacoustic emissions in humans with high frequency hearing loss. *Journal of Speech and Hearing Research, 33*, 594–600.

Hecox, K. (1985). Neurological applications of the auditory brainstem response to the paediatric age group. In J.T. Jacobsen (Ed.), *The auditory brainstem response* (pp. 287–295). London: Taylor and Francis.

Hildsheimer, M., Muchnik, C., & Rubenstein, M. (1993). Problems in interpretation of brainstem-evoked response audiometry results. *Audiology, 24*, 374–379.

Hollow, R. D., Plant, K., Larratt, M., Skok, M., Whitford, L., Dowell, R. C., & Clark, G. M. (1997). Current speech perception benefits for adults using the Nucleus-22 channel cochlear implant. In G.M. Clark (Ed.), *Cochlear implants* (pp. 249–254). Bologna: Monduzzi Editore.

Hung, K. L. (1989). Auditory brainstem responses in patients with neonatal hyperbilirubinemia and bilirubin encephalopathy. *Brain and Development, 11*, 297–301.

Hyde, M. L., Riko, K., & Malizia, K. (1990). Audiometric accuracy of the click ABR in infants at risk for hearing loss. *Journal of the American Academy of Audiology, 1*, 59–74.

Jerger, J. F., Chmiel, R., Frost, J. D., & Coker, N. (1986). The effect of sleep on the auditory steady-state evoked potential. *Ear and Hearing, 7*, 240–245.

Joint Committee on Infant Hearing (1991). 1990 position statement. *Audiology Today, 3*(4), 9–14.

Kileny, P. R., Connelly, C., & Robertson, C. M. T. (1980). Auditory brainstem responses in perinatal asphyxia. *International Journal of Paediatric Otorhinolaryngology, 2*, 147–159.

Kileny, P. R., & Magathan, M. G. (1987). Predictive value of ABR in infants and children with moderate to profound hearing impairments. *Ear and Hearing, 8*, 217–221.

Kileny, P. R., & Robertson, C. M. T. (1985). Neurological aspects of infant hearing assessment. *Journal of Otolaryngology, 14*, 34–39.

Koles, Z. J., & Rasminsky, M. (1972). A computer simulation of conduction in demyelinated nerve fibres. *Journal of Physiology, 227*, 351–364.

Konradsson, K. S. (1996). Bilaterally presented otoacoustic emissions in four children with profound idiopathic unilateral hearing loss. *Audiology, 35*, 217–227.

Kraus, N. A., Ozdamar, O., Stein, L., & Reed, N. (1984). Absent auditory brain stem response: Peripheral hearing loss or brainstem dysfunction? *Laryngoscope, 94*, 400–406.

Kuwada, S., Batra, R., & Maher, V. L. (1986). Scalp potentials of normal and hearing impaired subjects in response to sinusoidally amplitude modulated tones. *Hearing Research, 21*, 179–192.

Leech, R. W., & Alvord, E. C. (1977). Anoxic ischemic encephalopathy in the human neonatal period. The significance of brainstem involvement. *Archives of Neurology, 34*, 109–113.

Lenhardt, M. L. (1981). Childhood auditory processing disorder with brainstem evoked response verification. *Archives of Otolaryngology, 107*, 623–625.

Levi, E. C., Folsom, R. C., & Dobie, R. A. (1993). Amplitude modulation following response (AMFR): Effects of modulation rate, carrier frequency, age and state. *Hearing Research, 5*, 366–370.

Lichtenstein, V., & Stapells, D. R. (1996). Frequency specific identification of hearing loss using transient-evoked otoacoustic emissions to clicks and tones. *Hearing Research, 98*, 125–136.

Lins, O. G., Picton, T. W., Boucher, B. L., Durieux-Smith, A., Champagne, S. C., Moran, L. M., & Savio, G. (1996). Frequency-specific audiometry using steady-state responses. *Ear and Hearing, 17*, 81–96.

Lonsbury-Martin, B. L., Whitehead, M. L., & Martin, G. K. (1991). Clinical applications of otoacoustic emissions. *Journal of Speech and Hearing Research, 34*, 964–981.

Marchant, C. D., McMillan, P. M., Shurin, P. A., Turczyk, V. A., Feinstein, J. C., & Panek, D. M. (1986). Objective diagnosis of otitis media in early infancy by tympanometry and ipsilateral acoustic reflex thresholds. *Journal of Pediatrics, 109*, 590–595.

Maurizi, M., Amadori, G., Paludetti, G., Ottaviani, F., Rosignoli, M., & Luciano, R. (1990). 40 Hz steady-state responses in newborns and children. *Audiology, 29*, 322–328.

McDonald, W. I., & Sears, T. A. (1970). The effects of experimental demyelination on conduction in the central nervous system. *Brain, 93*, 583–598.

Nakamura, H., Takada, S., Shimabuku, R., Matsuo, M., Matsuo, T., & Negishi, H. (1985). Auditory nerve and brainstem responses in new-born infants with hyperbilirubinemia. *Pediatrics, 75*, 703–708.

Nelson, D. A., & Kimberley, B. P. (1992). Distortion product emissions and auditory sensitivity in human ears with normal hearing and cochlear loss. *Journal of Speech and Hearing Research, 35*, 1142–1159.

Norton, S. J., Ferguson, R., & Mascher, K. (1989). Evoked otoacoustic emissions and extratympanic cochlear microphonics recorded from human ears. *Abstracts of the Twelfth Midwinter Research Meeting of the Association for Research in Otolaryngology, 227*(A).

Osberger, M. J. (1995). Speech perception and production skills in children with cochlear implants. In G. Plant & K.E. Spens (Eds.), *Profound deafness and speech communication* (pp. 231–261). London: Whurr.

Pender, M. P., & Sears, T. A. (1984). The pathophysiology of acute experimental allergic encephalomyelitis in the rabbit. *Brain, 107*, 699–726.

Picton, T. W., Durieux-Smith, A., & Moran, L. (1994). Recording auditory brainstem responses from infants. *International Journal of Paediatric Otorhinolaryngology, 28*, 93–110.

Pratt, H., Sohmer, H., & Barazani, N. (1978). Surface-recorded cochlear microphonic potentials during temporary threshold shifts in man. *Audiology, 17*, 204–212.

Prieve, B. A., Gorga, M. P., & Neely, S. T. (1991). Otoacoustic emissions in an adult with severe hearing loss. *Journal of Speech and Hearing Research, 34*, 379–385.

Rance, G., Dowell, R. C., Rickards, F. W., Beer, D. E., & Clark, G. M. (1998). Steady-state evoked potential and behavioral hearing thresholds in a group of children with absent click-evoked auditory brainstem response. *Ear and Hearing, 19*, 48–61.

Rance, G., Rickards, F. W., Cohen, L. T., De Vidi, S., & Clark, G. M. (1995). The automated prediction of hearing thresholds in sleeping subjects using auditory steady-state evoked potentials. *Ear and Hearing, 16*, 499–507.

Rasminsky, M., & Sears, T. A. (1972). Internodal conduction in undissected demyelinated nerve fibres. *Journal of Physiology, 227*, 323–350.

Regan, D. (1966). Some characteristics of average steady-state and transient responses evoked by modulated light. *Electroencephalography and Clinical Neurophysiology, 20*, 238–248.

Rickards, F. W., & Clark, G. M. (1984). Steady-state evoked potentials to amplitude modulated tones. In R.H. Nodar, C. Barber (Eds.), *Evoked potentials II* (pp.163–168). Boston: Butterworth.

Rickards, F. W., Tan, L. E., Cohen, L. T., Wilson, O. J., Drew, J. H., & Clark, G. M. (1994). Auditory steady-state evoked potentials in newborns. *British Journal of Audiology, 28*, 327–337.

Rossi, G., Solero, P., Rolando, M., & Olinda, M. (1988). Delayed otoacoustic emissions evoked by bone-conduction stimulation: Experimental data on their origin, characteristics and transfer to the external ear in man. *Scandinavian Audiology, 17*(Suppl. 29), 1–24.

Sachs, M. B., Voight, H. F., & Young, E. D. (1983). Auditory nerve representation of vowels in background noise. *Journal of Neurophysiology, 50*, 27–45.

Salamy, A., Eggermont, J., Eldredge, L. (1994). Neurodevelopment and auditory function in pre-term infants. In J.T. Jacobsen (Ed.), *Principles and applications in auditory evoked potentials* (pp. 287–312). Needham Heights, MA: Allyn & Bacon.

Sasama, R. (1990). Hearing threshold investigations in infants and children. *Audiology, 29*, 76–84.

Shannon, R. V. (1983). Multichannel electrical stimulation of the auditory nerve in man: I. Basic psychophysics. *Hearing Research, 11*, 157–189.

Shapiro, S. M., & Te-Selle, M. E. (1994). Cochlear microphonics in the jaundiced Gunn rat. *American journal of Otolaryngology, 15*, 129–137.

Shepherd, R. K., & Javel, E. (1997). Electrical simulation of the auditory nerve. I Correlation of physiological responses with cochlear status. *Hearing Research, 108*, 112–144.

Sininger, Y. S., Hood, L. J., Starr, A., Berlin, C. I., & Picton, T. W. (1995). Hearing loss due to auditory neuropathy. *Audiology Today, 7*, 10–13.

Skinner, M. W., Clark, G. M., Whitford, L. A., Seligman, P. M., Staller, S. J., Shipp, D. P., Shallop, J. K., Everingham, C., Menapace, C. M., Arndt, P. L., Antognelli, B. A., Brimacomb, J. A., Pijl, S., Daniels, P., George, C. R., McDermott, H. J., & Beiter, A. L. (1994). Evaluation of a new spectral coding strategy for the Nucleus-22 channel cochlear implant system. *American Journal of Otology, 15*(2), 15–27.

Sohmer, H., Kinarti, R., & Gafni, M. (1980). The source along the basilar membrane of the cochlear microphonic potential recorded by surface electrodes in man. *Electroencephalography and Clinical Neurophysiology, 49*, 506–514.

Sohmer, H., & Pratt, H. (1976). Recording of the cochlear microphonic potential with surface electrodes. *Electroencephalography and Clinical Neurophysiology, 40*, 253–260.

Spoendlin, H., & Schrott, A. (1989). Analysis of the human auditory nerve. *Hearing Research, 43*, 25–38.

Stapells, D. R., Galambos, R., & Costello, J. (1988). Inconsistency of auditory middle latency and steady-state responses in infants. *Electroencephalography and Clinical Neurophysiology, 71*, 289–295.

Stapells, D. R., Gravel, J. S., & Martin, B. A. (1995). Thresholds for auditory brainstem responses to tones in notched noise from infants and young children with normal hearing or sensorineural hearing loss. *Ear and Hearing, 16*, 361–371.

Stapells, D. R., Makeig, G., Galambos, R. (1987). Auditory steady-state response threshold prediction using phase coherence. *Electroencephalography and Clinical Neurophysiology, 67*, 260–270.

Starr, A., Picton, T. W., Sininger, Y. S., Hood, L. J., & Berlin, C. I. (1996). Auditory neuropathy. *Brain, 119*, 741–753.

Stein, L., Tremblay, K., Pasternak, J., Banerjee, S., Lindermann, K., & Kraus, N. (1996). Brainstem abnormalities in neonates with normal otoacoustic emissions. *Seminars in Hearing, 17*, 197–213.

Stevens, J. C. (1988). Click-evoked otoacoustic emissions in normal and hearing impaired adults. *British Journal of Audiology, 22*, 45–49.

Stockard, J. E., & Stockard, J. J. (1981). Brainstem auditory evoked potentials in normal and otoneurologically impaired newborns and infants. In C.E. Henry (Ed.), *Current clinical neurophysiology: EEG and evoked potentials* (pp. 421–466). Miami, FL: Elsevier-North Publishing.

Takeno, S., Harrison, R. V., Ibrahim, D., Wake, M., & Mount, R. J. (1994). Cochlear function after selective inner hair cell degeneration induced by carboplatin. *Hearing Research, 75*, 93–102.

Tan, K. L., Skurr, B. A., & Yip, Y. Y. (1992). Phototherapy and the brainstem auditory evoked response in neonatal hyperbilirubinemia. *Journal of Pediatrics, 120*, 306–308.

Tasaki, I. (1955). New measurements of the capacity and resistance of the myelinated sheath and the nodal membrane of the isolated frog nerve fiber. *American Journal of Physiology, 188*, 639–650.

Tong, Y. C., Clark, G. M., Blamey, P. J., Busby, P. A., & Dowell, R. C. (1982). Psychophysical studies for two multiple-channel cochlear implant patients. *Journal of the Acoustical Society of America, 71*, 153–160.

Van der Drift, J. F. C., Brocaar, M. P., & van Zanten, G. A. (1987). The relation between the pure-tone audiogram and the click auditory brainstem response threshold in cochlear hearing loss. *Audiology, 26*, 1–10.

Wake, M., Anderson, J., Takeno, S., Mount, R. J., & Harrison, R. V. (1996). Otoacoustic emission amplification after inner hair cell damage. *Acta Otolaryngologica (Stockholm), 116*, 374–381.

Widen, J. E. (1997). Evoked otoacoustic emissions in evaluating children. In M.S. Robinette & T.J. Glattke (Eds.), *Otoacoustic emissions: Clinical applications* (pp. 271–306). New York: Theime.

Worthington, D. W., & Peters, J. (1980). Quantifiable hearing and no ABR: Paradox or error? *Ear and Hearing, 1*, 281–285.

Zhou, R., Abbas, P. J., & Assouline, J. G. (1995). Electrically evoked auditory brainstem responses in peripheral myelin-deficient mice. *Hearing Research, 88*, 98–106.

Author/s:
RANCE, GARY;Beer, David E.;Cone-Wesson, Barbara;Shepherd, Robert K.;Dowell, Richard C.;King, Alison M.;Rickards, Field W.;Clark, Graeme M.

Title:
Clinical findings for a group of infants and young children with auditory neuropathy

Date:
1999

Citation:
Rance, G., Beer, D. E., Cone-Wesson, B., Shepherd, R. K., Dowell, R. C., King, A. M., et al. (1999). Clinical findings for a group of infants and young children with auditory neuropathy. Ear and Hearing, 20, 238-252.

Persistent Link:
http://hdl.handle.net/11343/27535