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Auditory neuropathy

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Summary

Ten patients presented as children or young adults with hearing impairments that, by behavioural and physiological testing, were compatible with a disorder of the auditory portion of the VIII cranial nerve. Evidence of normal cochlear outer hair cell function was provided by preservation of otoacoustic emissions and cochlear microphonics in all of the patients. Auditory brainstem potentials showed evidence of abnormal auditory pathway function beginning with the VIII nerve: the potentials were absent in nine patients and severely distorted in one patient. Auditory brainstem reflexes (middle ear muscles; crossed suppression of otoacoustic emissions) were absent in all of the tested patients. Behavioural audiometric testing showed a mild to moderate elevation of pure tone threshold in nine patients. The extent of the hearing loss, if due to cochlear receptor damage, should not have resulted in the loss of auditory brainstem potentials. The shape of the pure tone loss varied, being predominantly low frequency in five patients, flat across all frequencies in three patients and predominantly high frequency in two patients. Speech intelligibility was tested in eight patients, and in six was affected out of proportion to what would have been expected if the pure tone loss were of cochlear origin. The patients were otherwise neurologically normal when the hearing impairment was first manifest. Subsequently, eight of these patients developed evidence for a peripheral neuropathy. The neuropathy was hereditary in three and sporadic in five. We suggest that this type of hearing impairment is due to a disorder of auditory nerve function and may have, as one of its causes, a neuropathy of the auditory nerve, occurring either in isolation or as part of a generalized neuropathic process.

Keywords: neural hearing loss; auditory neuropathy

Abbreviations: ABR = auditory brainstem responses; HL = hearing level; nHL = normal hearing level

Introduction

We have identified a group of patients with hearing deficits who have preserved otoacoustic emissions and absent or severely abnormal auditory brainstem responses (ABRs). Most of the patients complain of difficulty understanding speech, particularly in the presence of noise. Using two particular tests of auditory function, otoacoustic emissions and auditory brainstem potentials, we were able to identify that the function of the VIII nerve was disordered, whereas the function of cochlear outer hair cells was normal.

Otoacoustic emissions, originally described by Kemp (1978), are faint sounds emitted by the cochlea, either spontaneously or in response to an acoustic signal (for review, *see* Probst *et al.*, 1991). These emissions are thought to be generated by active movements of the outer hair cells and are left intact after severance of the auditory nerve (Siegel and Kim, 1982). Otoacoustic emissions can be detected by a sensitive microphone placed within the external ear canal. Stimulation with transients, such as clicks, evokes emissions in the form of a brief acoustic echo lasting ~20 ms. Specific testing of a restricted region of hair cells can be carried out by stimulation with two continuous tones of different frequencies (F1 and F2) to evoke distortion-product otoacoustic emissions which are largest at the 2F1–F2 frequency. Criteria for normal otoacoustic emissions have been established allowing a test of outer hair cell function in patients with hearing loss in the clinic (Kemp *et al.*, 1990; Nelson and Kimberly, 1992; Smurzynski and Kim, 1992; Gorga *et al.*, 1993; Prieve *et al.*, 1993). Otoacoustic emissions are also being used as an objective test of the integrity of

the cochlea in patients unable to make behavioural responses for an audiogram (e.g. infants). Prior to the recognition of otoacoustic emissions, hair cell function was assessed by recording cochlear microphonic potentials generated in response to acoustic signals (Aran and Charlet de Sauvage, 1976; Coats, 1986). The cochlear microphonic is difficult to record in human subjects because of its small size and its susceptibility to contamination by electroacoustic artifacts and has, therefore, not been widely used in clinical testing (Eggermont, 1976).

Auditory brainstem potentials are the far-field reflection of electrical activity of the VIII nerve and auditory brainstem pathway that can be detected with scalp electrodes (Jewett and Williston, 1971). Clinical and experimental experience have established that waves I and II reflect activity of the distal and proximal portions of the VIII nerve, respectively, while waves III, IV and V reflect activity in central portions of the brainstem auditory pathway (Moller, 1994; Martin *et al.*, 1996). Judicious use of auditory brainstem potentials can assist in localizing lesions to particular portions of the auditory pathway (Starr and Hamilton, 1976).

In earlier publications (Starr *et al.*, 1991; Berlin *et al.*, 1993), we defined clinical, psychoacoustic and electrophysiological characteristics of three of these patients. We suggested that there was an abnormality of the auditory system localized either to the inner hair cells, to the synapse between inner hair cells and VIII nerve, or to the VIII nerve itself, since a disorder at any of these sites could account for the findings of normal otoacoustic emissions, loss of auditory brainstem potentials and disordered speech perception in the presence of relatively preserved pure tone thresholds. These patients were probably similar to those previously described with a paradoxical absence of auditory brainstem evoked potentials and only a slight impairment of hearing but in whom cochlear microphonic or otoacoustic emissions had not been recorded (Davis and Hirsh, 1979; Worthington and Peters, 1980; Lenhardt, 1981; Hildesheimer *et al.*, 1985). Kraus *et al.* (1984) found seven such examples among their 49 cases with absent auditory brainstem potentials. Davis and Hirsh (1979) estimated that one in 200 hearing impaired subjects are of this category.

In this report, we describe new observations on 10 patients (the three original patients and seven new patients) with a clinical syndrome compatible with a disorder of function of the auditory nerve. Eight of the patients have clinical and/or electrophysiological evidence of a peripheral neuropathy suggesting that the auditory nerves may be similarly affected. While hearing impairments have been reported in patients with hereditary and other peripheral neuropathies (Denny-Brown, 1951; Hallpike *et al.*, 1980; Musiek *et al.*, 1982; Raglan *et al.*, 1987; Perez *et al.*, 1988; Wright and Dyck, 1995) the differentiation of the hearing problem as cochlear or retrocohlear in origin has been hampered by the lack of objective evidence of receptor cochlear function. We have been able to document in this paper that cochlear outer hair cell function is, indeed, normal in these patients and that VIII nerve function is abnormal.

Methods

Audiometric tests

Patients were tested with standard clinical procedures at the three participating medical centres. The local University and/or Hospital review committees gave ethical approval to the procedures and, when required, patients gave their informed consent.

Pure-tone audiometry (250–8000 Hz) was performed by air and bone conducted signals. Speech intelligibility assessment was made in all but two patients: number 8, the 4-year-old with retardation of language and speech, and number 10, a Vietnamese-speaking patient for whom word lists in Vietnamese were not available. Speech tests administered to the other eight patients included the definition of reception thresholds and intelligibility tested at maximum comfort level. Speech intelligibility scores are not significantly affected by conductive hearing impairment, are reduced proportionally to the extent of pure tone hearing impairment in cochlear disorders, but in retrocohlear disorders, are reduced beyond what would be expected for the loss of sensitivity. Normative data exist that provide lower limit of speech intelligibility seen in hearing loss of cochlear origin based on the degree of loss (Yellin *et al.*, 1989). The expected speech intelligibility scores based on the average of pure tone thresholds at 1, 2 and 4 kHz were calculated. Scores lower than the predicted values in at least one ear were considered a sign of a retrocochlear loss. Expected sentence recognition scores were defined (Hood *et al.*, 1991), using the pure tone audiogram to find the number of audible cues available for that patient and dividing by the total number of audible cues in the speech spectrum.

Standard measures of tympanic membrane mobility (tympanometry) were made along with acoustic reflex thresholds for pure tone stimuli from 500 to 4000 Hz. Acoustic reflexes, measured ipsilateral and/or contralateral to the stimulated ear were considered absent when there was no response to test intensities up to and including 110 dB hearing level (HL).

Psychoacoustic evaluations

Extensive psychoacoustic testing was performed in two of the patients. The methods and results for Patient 7 have been presented in a previous paper (Starr *et al.*, 1991) and some of those data will be included in Table 1. For the second patient (number 2) discrimination limens for frequency, intensity, duration and gap detection were obtained by having the patient choose which of three stimuli was different from the other two. The standard stimulus (the one presented twice) was a 60 dB HL 1000 Hz tone lasting 750 ms. The changes in frequency, intensity and duration were all positive.

The gap occurred in the centre of the tone with fall–rise times of 5 ms. The difference between the target and the stimulus was automatically adjusted on the basis of the patient's response until a discrimination threshold was consistently bracketed. Masking level difference is the difference in threshold (Schoeny and Talbott, 1994) for a monaural tone (Sm) when presented in monaural noise (Nm) and when presented in binaural correlated noise (No) of the same intensity (NmSm versus NoSm comparison).

Auditory physiological tests

Otoacoustic emissions: click evoked otoacoustic emissions were measured with an ILO-88 OAE system. Click level ranged from 80 to 86 dB peak sound pressure. Responses to as many as 260 stimuli were averaged over a 20 ms window and stored in two separate buffers. The presence of normal transient evoked otoacoustic emissions in the 2.5–20 ms post-stimulus period was determined by response amplitude (noise subtracted) of at least 4 dB and waveform reproducibility in at least three octave bands of >75%.

The presence of contralateral noise induced reflex suppression of the transient evoked emissions was tested by presenting a white noise at 5 dB above the level of the click as monitored by an ER10C probe microphone. Three trials each with and without contralateral noise were interleaved and amplitude changes and time delays analysed for transient-evoked otoacoustic emission suppression as a function of post-stimulus time. The presence of normal contralateral suppression was defined by a reduction of the transient evoked otoacoustic emissions of >1 dB.

Evoked potentials

Auditory brainstem evoked potentials were recorded in two electrode configurations: in a vertical channel, vertex to seventh cervical vertebra to optimize detection of wave V and vertex to the ipsilateral ear using band-pass between 30 and 100–3000 Hz. Click stimuli were rarefaction clicks presented monaurally at rates from 5–25 s^{-1} and at intensities of 65, 75 and when necessary at 85 dB normal hearing level (nHL). Two averages were made at each test signal and the presence of reproducible components defined. Middle and long-latency auditory and pattern-reversal visual and median and posterior tibial nerve somatosensory evoked potentials were recorded in some patients using standard clinical protocols.

Peripheral nerve tests

Nerve conduction studies were performed on sural and peroneal nerve in eight out of the 11 patients. Nerve potentials were recorded from surface electrodes in response to cutaneously applied electrical stimuli while insuring that limb temperature was above 30°C. Abnormality was defined according to established criteria (Kimura, 1989). We also used clinical measures of peripheral nerve function (absence of deep tendon reflexes at the ankles, diminished vibratory sensibility in the feet to a 128 Hz tuning fork) as indices of a peripheral neuropathy.

Results

Over the past 7 years we have examined 10 patients who presented with hearing impairment, preserved otoacoustic emission and absent or severely distorted auditory brainstem potentials. Their characteristics (age, gender, etc.), test results for hearing (audiogram, speech intelligibility scores, auditory evoked potentials, otoacoustic emissions, middle ear muscle reflexes and psychoacoustic tests) are summarized in Table 1. The patients were of both genders and were children or young adults when they were first seen because of difficulty with understanding speech. Their audiograms showed a low frequency loss (a rising slope in Table 1) in five patients, a flat frequency loss in three patients and a high frequency loss (a falling slope in Table 1) in two patients. Word recognition scores were tested in eight patients and were impaired bilaterally out of proportion to what would been expected if the hearing loss were of cochlear origin in four (Yellin *et al.*, 1989). Among the five patients who did not have this finding, two (numbers 3 and 6) had an impairment greater than would have been expected in only one of the ears; one (number 9) had word intelligibility scores just beyond the conservative 2% cut-off point used by Yellin *et al.* (1989); one (number 4) had a severe hearing loss (pure tone averaged threshold loss of ~90 dB) with a predicted and actual intelligibility score of 0%. Using a measure of expected speech comprehension for sentences rather than individual words (Hood *et al.*, 1991), all of these patients, except number 4, should have had sentence comprehension above 95% in everyday one-on-one communication. In contrast, all of these patients (except the young child) reported that speech comprehension was a major problem. Masking level differences were absent in the six patients tested. However, in two of these patients (numbers 4 and 5), the absence of the masking level difference is of uncertain significance because of the severity or the asymmetry of the pure tone hearing loss (Schoeny and Talbott, 1994). In the other four patients, however, the failure to demonstrate any improvement of monaural masked thresholds for low frequency tones by the addition of correlated contralateral noise distinguishes them from patients with a cochlear or conductive hearing loss in whom masking level differences are present though reduced in magnitude compared with normal subjects (Hall and Harvey, 1985; Staffel *et al.*, 1990). All patients had an absence of acoustic reflex middle ear muscle contractions and an absence of noise-induced contralateral suppression of otoacoustic emissions.

Auditory brainstem potentials were bilaterally absent in nine out of the 10 patients. There were a number of patients with cochlear microphonic components that reversed polarity with reversal of the click phase from condensation to

Table 1 *Clinical, audiological and neurological characteristics of patients with auditory neuropathy*

	Case no.									
	1	2	3	4	5	6	7	8	9	10
Features										
Age now	49	32	19	34	40	15	17	4	16	35
Age onset hearing	<10	15	6	16	20	5	9	2	8	30
Age onset nerve	10	30	12	23	26	12	15	norm	norm	34
Gender	F	F	M	F	M	M	F	M	M	M
Neurol diagnosis	none	none	cmtII	cmtI	cmtI	none	none	none	none	none
Audiogram*										
Degree of loss	mod	mod	mild	sev	mod	mod	mod	mod	mild	mod
Slope	rise	rise	fall	flat	fall	rise	flat	flat	rise	rise
PTA thresholds†	33/40	41/33	20/27	85/92	73/37	40/30	36/20	36/36	18/10	47/42
Speech‡										
Intelligibility (%) ad/as	12/20	12/8	84/48	0/0	0/0	32/64	20/40	cnt	76/92	cnt
Expected intelligibility§	55/48	45/55	69/61	2/0	14/51	45/58	52/69	36/36	71/79	41/46
OAE										
Click (dB) ad/as¶	18/14	15/14	12/13	14/12	15/16	14/8	13/9	11/9	16/16	10/11
Distortion product	norm	abn	norm	norm	norm	nt	abn	norm	abn	norm
Crossed suppress#	0	0	0	0	0	nt	0	nt	0	0
Aud reflexes										
Stapedius	0	0	0	0	0	0	0	0	0	0
Aud EPs										
Brainstem	0	0	0	0	0	0	0	0	abn	0
Middle latency	nt	abn	0	nt	nt	0	0	nt	norm	0
Long latency	nt	abn	nt	nt	nt	0	abn	nt	norm	0
Aud discrim.										
MLD	0	0	0	0	0	0	nt	cnt	nt	nt
Gap detection (ms)	nt	12	nt	nt	nt	nt	80	cnt	nt	nt
Tone decay	nt	norm	nt	nt	nt	nt	norm	cnt	nt	nt
Neurol exam										
Ankle jerks	0	0	0	0	0	0	0	1+	1+	2+
Vibration	abn	abn	norm	abn	abn	norm	norm	cnt	norm	abn
Motor	norm	norm	atrophy	weak	weak	chorea	norm	norm	norm	atrophy
Gait	atax	atax	atax	atax	atax	atax	norm	norm	norm	atax
Nystagmus	yes	no	yes	no	no	yes	no	no	no	no
NCV**										
Velocity (m s^{-1})	nt	norm	norm	0	0	nt	norm	norm	nt	0
Amplitude (μV)	nt	2.3	1.3	0	0	nt	8	norm	nt	0
H reflex	nt	0	nt	nt	nt	nt	0	nt	nt	nt
EPs										
Visual	nt	norm	nt	nt	nt	abn	norm	norm	norm	abn
Somatosensory	nt	norm	nt	nt	nt	abn	norm	norm	norm	nt
P300	nt	norm	nt	nt	nt	nt	norm	nt	norm	nt
Other tests										
Vestibular	nt	norm	nt	nt	nt	nt	abn	cnt	norm	abn
MRI	abn	norm	norm	norm	norm	norm	norm	nt	norm	norm

OAE = otoacoustic emissions; Aud = auditory; Neurol = neurological; EPs = evoked potentials; NCV= nerve conduction velocity; Discrim = discrimination; PTA = pure tone average threshold loss in dB at 1, 2 and 4 kHz; ad/as = right ear/left ear; mod = moderate; sev = severe; MLD = masking level differences; vib = vibratory sense; vest = vestibular function; norm = normal; abn = abnormal; 0 = absent; nt = not tested; cnt = could not test; cmt = Charcot–Marie–Tooth; M = male; F = female. *Most recent audiological test; †average pure tone threshold in dB at 1, 2 and 4 kHz; ‡speech intelligibility tested at comfortable hearing level; §expected speech intelligibility in cochlear type hearing loss based on pure tone thresholds (1, 2 and 4 kHz) from Yellin *et al.* (1989); ¶test click of 80 dB peak SPL (Case 3, 65 dB SPL) elicits in normals OAEs of >4 dB; #contralateral acoustic stimulation produces attenuation in normals of OAE of >1 dB; **test of sural nerve. In those patients with absent sural nerve potentials, testing other nerves documented a demyelinating disorder for Patients 4 and 5 and an axonal disorder for Patient 10.

rarefaction. There was only one patient (number 9) who showed wave V to be present. In this patient, in response to clicks presented at intensities of 80–90 dB nHL and rates of between 11 and 28 s^{-1} (multiple recording sessions) wave V occurred with a peak latency of between 6.2 and 6.8 ms, an amplitude (measured to the succeeding negative wave) of

between 0.1 and 0.5 μV. There were low-amplitude reproducible components with latencies between 1 and 2 ms which reversed in polarity when the click was changed from condensation to rarefaction, compatible with cochlear microphonics. In recordings with ear-canal electrodes to 80–90 dB nHL clicks, there was a very small (<0.1 μV) component with a peak latency of 2.3 ms that did not change with click polarity suggesting it to be a wave I. Given the patient's relatively normal pure-tone thresholds at the high frequencies, wave I was significantly smaller and delayed in latency compared with a wave I recorded from ear canal electrodes in normals (amplitude >0.5 μV, latency <1.8 ms).

It was still possible to detect other types of auditory evoked potentials in some of these patients even though their brainstem potentials were absent. Middle-latency auditory evoked potentials were detected in one (number 2) out of five patients with absent brainstem potentials; long-latency components (N100, P200) were detected in three of four patients with absent auditory brainstem potentials. Both sustained DC potentials to long-lasting tones and cognitive potentials (P300) evoked in an auditory discrimination target-detection task were also present in the two patients (numbers 2 and 7) tested with these methods.

The results of the neurological examination, nerve-conduction velocity studies, sensory evoked potentials, vestibular tests and other laboratory procedures are in Table 1. Seven patients (numbers 1–7) showed clinical evidence of a peripheral neuropathy by absence of deep-tendon ankle reflexes and/or elevated thresholds to vibration of the toes. Seven patients (numbers 1–6 and 11) had a gait ataxia and one patient (number 6) had chorea. Vestibular function was impaired in several patients. Caloric testing of vestibular function elicited normal horizontal nystagmus and vertigo in two patients (numbers 2 and 9) but was ineffective in evoking these responses in two other patients (numbers 7 and 10). Three patients (numbers 1, 3 and 6) demonstrated horizontal nystagmus on lateral gaze. No further tests were performed on these patients to distinguish whether the site of the vestibular dysfunction was peripheral or central. Other sensory evoked potential tests (visual and somatosensory) were abnormal in three of the five patients. The MRI of the brain was normal in all but one patient (number 1), the latter showing small punctate lesions at the grey–white matter interface in both cerebral hemispheres, but not in the brainstem or cerebellum.

The hearing disorder preceded the definition of a peripheral neuropathy by several years in the eight patients with both deficits. The patients considered the hearing impairments to be their most severe deficit. Eight of these patients had clinical evidence of a peripheral neuropathy (absence of deep tendon reflexes in the ankles and/or elevated vibration thresholds in the feet to a 128 Hz tuning fork) and seven of them had nerve conduction studies performed which demonstrated abnormalities of either absence or slowing of nerve conduction velocities, diminished amplitude of the compound nerve action potential of the surface recorded nerve or muscle potentials, or absence of H-reflexes. The peripheral neuropathy was first recognized by clinical examination in five out of these eight patients. None of the patients had an enlargement of the nerves to palpation. Three of the patients' findings were consistent with a diagnosis of Charcot–Marie–Tooth [two of them hereditary motor sensory neuropathy (HMSN) Type I, and one HMSN Type II]. The diagnosis of the neuropathy in the other five patients has not been established. A biopsy of the affected nerves has not been performed in any of the patients.

To illustrate the disorder, we provide details from one of the patients (number 2).

Clinical history

This 32-year-old female patient presented with difficulty hearing which had begun at the age of 15 years and had been progressive. The hearing difficulties were experienced as being worse in the left ear than in the right, and worse with speech than with simple environmental sounds. The patient recognized speech sounds, could identify which language was being used, but had great difficulty understanding the actual words. She was able to understand speech using visual cues from lip and facial movements. She was unable to communicate on the telephone. The patient was bothered by loud sounds. The past history was remarkable for recurrent episodes of tonsillitis and conductive hearing loss in childhood, and two episodes of Bell's palsy at the ages of 11 and 12 years, both involving the left face followed by full recovery.

Audiometric evaluation

Pure tone audiometry at the age of 19 years showed a mild low-frequency hearing loss in the left ear and severely reduced speech perception in both ears (Fig. 1). Stapedius reflexes were present at high intensity and showed abnormally rapid decay at low frequencies. Audiometry at age 32 years showed a decrease in hearing sensitivity with a mild to moderate hearing loss in both ears, a much greater problem with speech perception and absence of stapedius middle ear muscle reflexes (Fig. 1). Psychoacoustic testing showed severely abnormal discrimination for frequency, intensity and duration, abnormal gap-detection and great difficulty in localizing sound on the basis of either time or intensity cues (Table 2). These results are similar to those of patient 7 reported by Starr *et al.* (1991).

Neurological evaluation

At age 32 years the patient was clinically evaluated by us. Mental status was quite normal other than for the great difficulty in perceiving speech using only acoustic cues. Cranial nerves were normal. Facial movements were complete and strong and the corneal reflexes were brisk. There was no nystagmus. Examination of the motor system showed normal

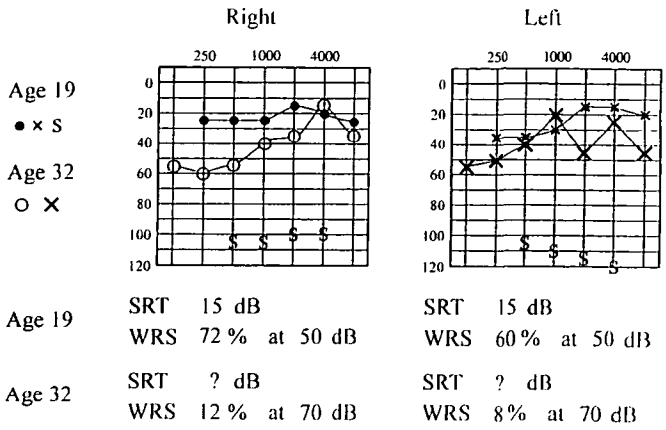

Fig. 1 Audiometric information. The graphs show the pure tone thresholds for the patient at ages 19 years (small symbols) and 32 years (large symbols). Also shown are the stapedius reflex thresholds (S) at age 19 years. These thresholds were obtained using contralateral stimulation and are plotted with the ear of stimulation rather than response. No stapedius reflexes were observed at age 32 years. Below the audiogram the results of speech audiometry are shown. The speech reception threshold (SRT) was obtained using spondaic words. The word recognition score (WRS) was the percentage of phonetically balanced words correctly identified at the intensity at which maximum discrimination occurred. The patient's speech threshold was not defined at age 32 years, but would have been ~41 dB in the right ear and ~33 db in the left ear based on pure tone averaged thresholds at 1, 2 and 4 kHz. Maximum word recognition score (WRS) at age 32 was considerably decreased compared with WRS at age 19 years and was also less than would be expected with a cochlear type hearing loss (*see* Table 1).

Table 2 *Auditory discriminations of Patient 2*

Test	L. ear	R. ear	Norms
Frequency (Hz)	235	172	2–17
Duration (ms)	145	118	25–50
Intensity (dB)	6	3	<1
Gap detection (ms)	12	6	1–5

All discriminations were carried out using 60 dB HL 1 kHz tone lasting 750 ms as the standard stimulus. The gap occurred in the centre of the tone with fall–rise times of 5 ms.

muscle strength, tone and rapid-alternating-movements. There were no deep-tendon reflexes, even with facilitation. Reflexes had also been noted to be absent by another neurologist 2 years earlier. Sensory examination was remarkable for an elevation of threshold for vibration and impaired position sense in the toes. There was unsteadiness when standing heel-to-toe with the eyes closed and slight gait ataxia on tandem walking.

Clinical investigations

Electronystagmography was within normal limits. The MRI (with gadolinium enhancement) showed no cerebral or brainstem abnormality. Neuropsychological examination showed some mild difficulty with attention. Language

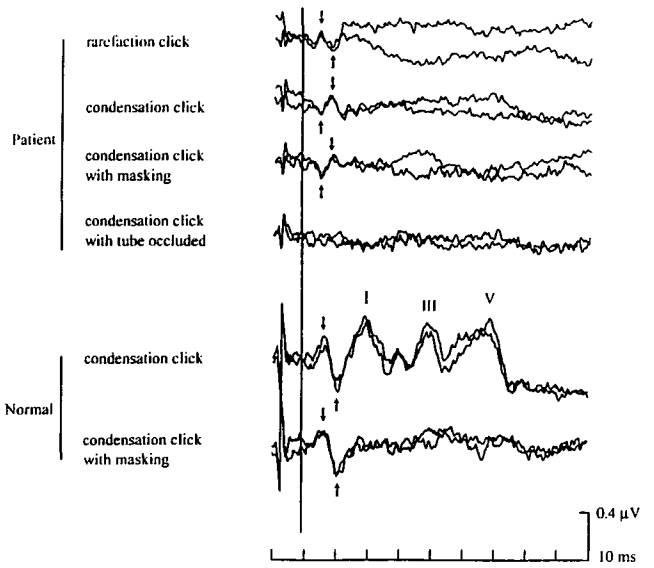

Fig. 2 Cochlear microphonics and auditory brainstem responses. The stimulus was a 75 dB nHL click presented at a rate of 10 s^{-1}. The stimuli were presented using insert earphones with a 0.9-ms delay from the microphone to the stimulus arriving at the tympanic membrane. Recordings were obtained between the vertex and an electrode in the external auditory meatus. Each tracing represents the average of 2000 recordings for the normal subject and 8000 recordings for the patient. The filter bandpass was 20–10 000 kHz. Only the results for the right ear are shown. The waveforms in the upper part of this figure were recorded from the patient and the waveforms in the lower part were recorded from a normal subject. The recordings from the patient show no recognizable ABRs. The arrows point to deflections which represent the cochlear microphonic. The deflections reverse in polarity when the click is changed from rarefaction to condensation. When sufficient masking noise is added to prevent perception of the clicks, the cochlear microphonic remains, whereas any ABR is cancelled. Closing off the tube from the microphone to the ear-insert shows that the recorded deflections are not delayed electrical artifacts from the microphone.

function was normal other than speech intelligibility. Blink reflexes were normal. Sensory-nerve conduction velocities of the sural nerve showed normal velocities but reduced amplitudes for the nerve action potential. Motor-nerve conduction and F-waves from stimulating the peroneal nerves were normal.

Evoked potential studies

The ABRs were recorded with an electrode inserted in the external auditory meatus to enhance the detection of microphonic and neural potentials originating in the cochlea. The recordings (Fig. 2) showed no recognizable components other than some small deflections beginning at a latency of 0.3 ms and lasting for ~2 ms (with major peaks at 0.5 and 1.0 ms). Experiments using condensation and rarefaction stimuli and masking noise demonstrated that these deflections were cochlear microphonics. The middle-latency potentials revealed a small positive wave with a latency of ~30 ms in response to clicks presented to the right ear or binaurally but

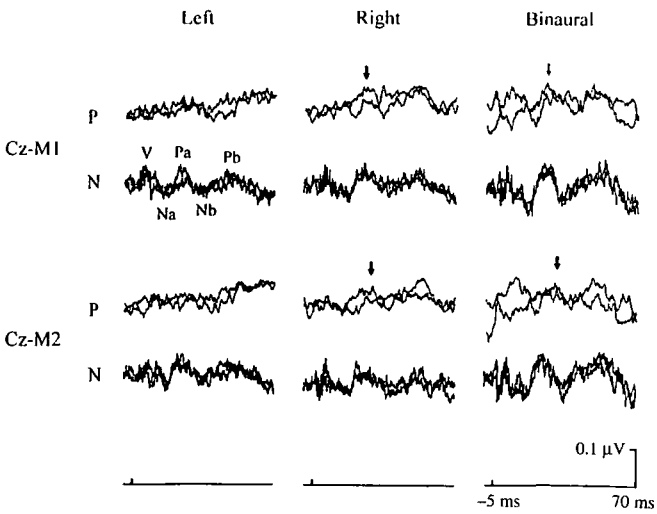

Fig. 3 Middle latency responses. These wave forms were recorded in response to rarefaction clicks presented at a rate of 10 s^{-1} to the left ear, to the right ear or binaurally with an intensity of 70 dB nHL. Recordings were obtained between the vertex and the left and right mastoids (M1, M2) with a frequency bandpass of 20–2000 Hz. Separate replicate responses are shown for the patient (P) and a normal subject (N). The tracings for the patient show no recognizable ABRs but a low amplitude wave Pa (identified with an arrow) in response to right ear or binaural stimulation but not to left ear stimulation. Each tracing for the normal subject represents the average of 1000 responses and for the patient the average of 2000 responses.

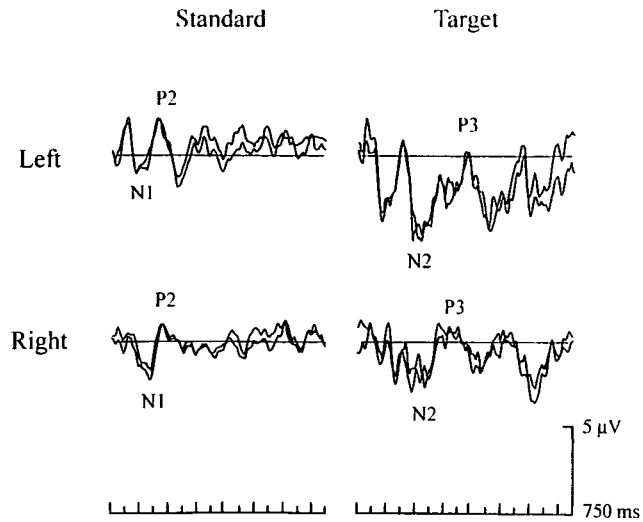

Fig. 4 Long-latency auditory evoked potentials. This figure shows the evoked potentials recorded from the vertex using a linked-mastoid reference during an odd-ball paradigm. The standard stimuli were tones of 1 kHz lasting 30 ms presented at a rate of once in every 1.1 s and an intensity of 70 dB nHL. Twenty percent of the stimuli were changed in frequency to 2 kHz and the patient was asked to detect and keep a running mental count of these targets. For the standard stimuli each tracing represents the average of ~240 stimuli and the target responses represent the average of ~60 stimuli. The subject shows small but reliable N1–P2 responses to the standard stimuli and an identifiable N2–P3 response to the target stimuli.

not to the left ear (Fig. 3). When the patient was retested 6 months later, middle latency components could not be identified from stimulation of either or both ears. The late auditory evoked potentials showed recognizable N1 and P2 components. These were small and often slightly later than normal. There was also a recognizable P300 wave (or P3 wave) in response to a detected target stimulus (Fig. 4). Somatosensory (median nerves) and visual pattern-reversal evoked potentials were normal.

Otoacoustic emissions

The transient otoacoustic emissions (Fig. 5) showed clearly recognizable waveforms that were within normal limits. The otoacoustic emissions were not significantly affected by contralateral noise stimulation (Berlin *et al.*, 1993). Distortion-product otoacoustic emissions showed decreased responsiveness at narrow frequency regions in the high frequencies (4 kHz in the right ear and 3–5 kHz in the left ear) and decreased levels of responsiveness at frequencies below 1 kHz in both ears. At the other frequencies the emission levels were well within normal limits.

Discussion

The patients of this study are strikingly similar in their auditory physiological measures that localize the disorder to the VIII nerve (absent or severely abnormal ABRs beginning with the VIII nerve component of wave I and preservation of the otoacoustic emissions). The type of VIII nerve abnormality present in these patients is not known. The disorder could be at the level of the inner hair cells, the synapse between inner hair cells and VIII nerve fibres, the ganglion neurons, the nerve fibres or any combination of the above. The outer hair cells in the cochlea are presumed to be normal, based on the finding of normal otoacoustic emissions. The status of the inner hair cells cannot be assessed as there are no procedures currently available for this purpose. Prieve *et al.* (1991) have suggested the possibility of a specific disturbance of inner hair cells in a patient with a severe hearing loss and preserved otoacoustic emissions. The patient differs from ours in that the hearing loss was severe (in our patients the loss was mild or moderate in most instances) and the transient otoacoustic emissions were of abnormally low amplitude, whereas in our patients the emissions were of normal amplitude in all but one. The possibility of a disorder of the synapse between inner hair cells and VIII nerve fibres also cannot be evaluated. Many of the patients demonstrated indications of a peripheral neuropathy, raising the possibility that their auditory nerves may also be affected by a neuropathic process to account for the hearing disorder. A resolution as to the site and mechanism(s) of the VIII nerve disorder is not possible at this time as the patients are alive so the cochlea and VIII nerve are not available for histological examination.

The patients were heterogeneous in the expression of the

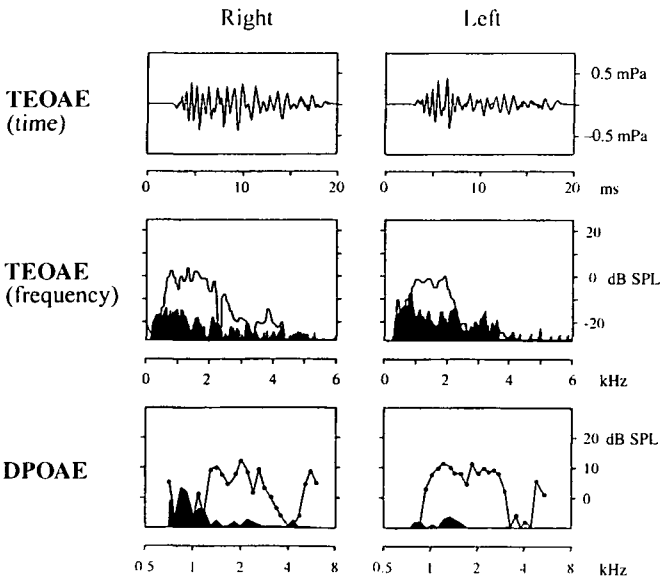

Fig. 5 Otoacoustic emissions. The tracings at the top of this figure show the transient-evoked otoacoustic emissions (TEOAE) recorded in response to an 80 dB peak SPL click presented at a rate of 20 s^{-1}. The response level was 15.4 dB SPL for the right ear and 14.0 dB for the left ear with noise levels of 1.0 and 2.8 dB. The frequency-spectrum of these responses is shown below the time wave forms. These spectra were replotted on a logarithmic frequency axis to make them comparable with the plots for the distortion-product emissions. In the lower part of the figure are shown the distortion-product otoacoustic emissions (DPOAE). These were recorded (at a separate time from the transient-evoked emissions) with an F2/F1 ratio of 1.22 and with both tones presented at an intensity level of 70 dB SPL. Responses are plotted at the F2 frequency. The residual noise levels are shown by the shaded areas.

peripheral neuropathy and in symptoms other than those affecting hearing. For instance, the neuropathy ranged from clearly apparent (three patients) as a manifestation of a hereditary sensory-motor neuropathy (Charcot–Marie–Tooth), to slight (five patients), evident only on clinical examination or nerve conduction studies. There were no signs of a neuropathy in two young patients (ages 4 and 16 years), who were perhaps too early in the course of the disorder to demonstrate signs of a peripheral neuropathy. There was evidence of involvement of other cranial nerves in some of the patients. Two of the patients had disordered vestibular caloric tests in the absence of any clinical signs or symptoms of vestibular dysfunction. Two of these patients (numbers 6 and 10) had impaired visual function classified as an optic neuropathy by visual evoked potential tests.

The hearing disorder was disabling for all patients and word intelligibility scores were, in general, poorer than scores achieved by patients with comparable pure tone losses due to cochlear damage (Yellin *et al.*, 1989). Another measure of expected speech comprehension (Hood *et al.*, 1991) showed that all of these patients, except number 4, should have had sentence comprehension >95% in everyday one-to-one communication. In contrast, all of these patients (except the young child) reported that speech comprehension was their major problem.

The hearing disorder was present for several years before the peripheral neuropathy was recognized. The identification of the neuropathy was only first appreciated following a neurological examination (loss of deep tendon reflexes in the lower extremities and/or elevated thresholds for vibration sensation). Moreover, in the one patient (number 7) followed for 7 years with repeated neurological examinations, the peripheral neuropathy has only become apparent in this past year. Even in the three patients with the hereditary neuropathy of the Charcot–Marie–Tooth type, the hearing impairment was their earliest and major complaint and disability. Our experience has been that the hearing loss is slowly progressive and does not benefit by amplification from hearing aids. Some of the patients and their audiologists have even felt the hearing aids to have detrimental effects. We are in the process of evaluating lip reading training and low-gain frequency modulated and vibro-tactile systems to augment communication.

In cochlear hearing loss there is a systematic relationship between the threshold for detecting an ABR and hearing threshold (Picton, 1990). In contrast, the correlation between auditory evoked potentials and hearing loss is complex in patients with retrocochlear lesions. In all but one of the patients of this study, auditory brainstem potentials were absent regardless of the extent of the hearing loss. Moreover, several of these patients had other types of auditory evoked potentials present. Similar observations have been made in acoustic neuromas and in demyelinating lesions of the brainstem (Picton, 1990).

In the patient we have used to illustrate this disorder (number 2) the distortion-product otoacoustic emissions showed an attenuation of emissions originating from the low frequencies and from small regions in the high-frequency range. Two other patients (numbers 7 and 9) also had small regions of abnormal distortion-product emissions. These focal abnormalities of emissions signify restricted regions of altered outer hair cell function and can be seen in otherwise normal individuals (Lasky *et al.*, 1992). We cannot exclude the possibility that these patches of hair cell abnormality may be a consequence of the auditory nerve disorder, either afferent or efferent, due to a lack of trophic factors on the outer or even the inner hair cells. Distortion product emissions were normal in the six other patients tested in this way (numbers 1, 3, 4, 5 and 8)

We originally suggested (Starr *et al.*, 1991) that the hearing deficits in these patients reflected altered temporal synchrony of auditory nerve afferent discharges. With a neuropathy and, in particular, a demyelinating neuropathy, nerve impulses slow when a demyelinated segment of the axon is encountered and then regain normal speed when that segment is passed (McDonald, 1980). This type of conduction change results in a slowing of nerve conduction velocity and, when a number of axons are similarly affected, a broadening of the whole-nerve action potential and the evoked compound motor

action potential. Demyelinated axons are impaired in their ability to transmit trains of impulses which, in the case of the VIII nerve, would interfere with the neural inputs to brainstem centres and may account for the absence of acoustically activated brainstem reflexes regulating middle ear muscles and the lack of crossed suppression of otoacoustic emissions found in all of these patients. The early clinical signs of a demyelinating neuropathy include a loss of deep-tendon reflexes and elevated vibratory threshold as were evident in many of our patients. Muscle bulk is usually affected late in a demyelinating neuropathy. The classical signs of axonal neuropathy are a decrease in the size of the whole-nerve action potential but not of any change in conduction velocity or width of the whole-nerve action potential. Theoretically an axonal neuropathy should not alter neural synchrony but only the number of conducting fibres. However, the finding that the auditory functions of the patient with Charcot–Marie–Tooth Type II, an axonal neuropathy, were similar to those of the patients with clinical and laboratory evidence of a demyelinating neuropathy, suggests that temporal synchrony may be affected to varying extents in all neuropathological processes. We suggest that the failure to detect an averaged auditory brainstem potential in these patients reflects altered temporal synchrony of auditory brainstem pathway activity due to the auditory nerve disorder. In these patients, auditory nerve and brainstem discharges are not precisely time-locked to the acoustic signal so that the short duration components (~1 ms in duration) are cancelled in the averaging process, rendering them indistinguishable from the background electrical events. The extent of the temporal dys-synchrony was insufficient in some of these patients to block the detection of the relatively long-duration (20–100 ms) components of middle and long-latency potentials.

Patients with acoustic neuroma that compress the VIII nerve without compromise of cochlear blood flow demonstrate many of the same auditory test results as the patients of this study. They can have normal otoacoustic emissions (Bonfils and Uziel, 1988) absent acoustic middle ear muscle reflexes, absent contralateral suppression of otoacoustic emissions, and disordered temporal processing manifested by a disproportionate loss of speech intelligibility relative to threshold change. The most common audiometric pattern in patients with an acoustic neuroma is a high-frequency loss (Johnson, 1977) due, perhaps, to the peripheral position of fibres from the basilar end of the cochlea in the auditory nerve rendering them particularly susceptible to the pressure effects from the tumour.

In contrast to acoustic neuromas, a high frequency hearing loss was not the dominant pattern in our patients: five of the patients (numbers 1, 2, 6, 9 and 10) had a low-frequency loss, three (numbers 4, 7 and 8) had a flat frequency loss, and two (numbers 3 and 5) had a high-frequency loss. The finding of a low-frequency hearing loss in many of these patients may be due to their impaired auditory processing of temporal information since the timing of auditory nerve discharges play a role, particularly, in the encoding of low spectral acoustic signals. Pitch is thought to be processed by two mechanisms. The first is by the place of activation along the cochlear partition with low frequencies causing maximal displacement of the apical portion of the basilar membrane and high frequencies exciting the basal end of the basilar membrane. Thus, the distribution of active fibres as a function of their sites of origin from the basilar membrane provides a code for defining the pitch of the acoustic stimulus. A second method of encoding pitch is specific for low frequencies (<2000 Hz) and employs a temporal code with nerve fibre discharges being time-locked to a particular portion or phase of the acoustic wave form. This time-locking can occur in fibres originating from the low-frequency portion of the basilar membrane and, if the intensity is high, from fibres originating from the basilar or high-frequency portions of the basilar membrane providing a temporal code for pitch. Such time-locking in VIII nerve fibres is clearly evident for acoustic signals up to ~2000 Hz and can also be detected in the periodicity of discharge pattern from brainstem portions of the auditory pathway (Starr and Hellerstein, 1971). Alternatively, it may be that the auditory nerve fibres encoding low-frequency information that come from the apex may be particularly affected by the neuropathological process since apical fibres have a longer course outside of the cochlear nucleus and have a greater axonal diameter than do basal fibres (Arnesen and Osen, 1978; Ryugo, 1992).

The ABR findings distinguish between the patients of this study with a presumed neuropathy of the VIII nerve and those with an acoustic neuroma. The most common ABR finding of an acoustic neuroma is a preservation of wave I with a delay or attenuation of later waves (Eggermont *et al.*, 1980; Picton, 1990). The tumour can also compress the vascular supply to the cochlea causing ischaemia. In these instances, wave I can be absent and the later waves (II–V) are delayed signifying damage to the high-frequency regions of the cochlea. Some patients with an acoustic neuroma may have an absence of all waves in the ABR accompanied by profound hearing loss reflecting widespread ischaemic damage to the cochlea. In contrast, the patients of this study (except number 9) showed all waves of the ABR to be absent when hearing thresholds were only moderately impaired. Other clinical features that distinguish patients of the present study and those with acoustic neuroma are that the latter commonly have tinnitus and dysequilibrium in association with their hearing loss. These symptoms were notably absent in the patients of the present study. Finally, tone decay, a prominent characteristic of patients with an acoustic neuroma, was absent in the two patients (numbers 2 and 7) of the present study tested with this procedure. Finally all but one of our patients had normal MRIs and none showed evidence of lesions of the VIII nerve and brainstem. The patient with the abnormal MRI was aged 44 years, when imaged, and the lesions were in the white matter of the cerebral hemispheres compatible with small vessel disease.

Patients with a disorder of the brainstem portions of the

auditory pathway sparing the VIII nerve could demonstrate most of the audiological features present by our patients. Speech perception could be impaired out-of-proportion to the pure tone hearing loss. Since the cochlea would not be involved, otoacoustic emissions would be normal. Brainstem centres regulating middle ear muscles and crossed otoacoustic emission suppression could be affected leading to abnormalities of these two measures. Auditory brainstem potentials could be absent or severely abnormal. However, the feature that would distinguish such patients with a brainstem disorder from those with an auditory nerve disorder would be the preservation in the former of wave I in the auditory brainstem potentials, which is generated by the extracranial portion of the VIII nerve in its course to the cochlea. The present methods of testing do not allow the definition of a brainstem auditory pathway disorder in the presence of profound involvement of the peripheral portions of the auditory pathway (cochlea and/or VIII nerve). The methods used in this study can identify a cochlear disorder and distinguish an VIII nerve disorder in the presence of preserved cochlear function.

Knowledge of the generator sites for the various ABR components can be used to localize the auditory neuropathy to particular portions of the nerve (Martin *et al.*, 1996). Wave I is generated in the distal portion of the nerve within the cochlea; wave II is generated in the proximal portion of the nerve, most likely at the junction between the nerve and the brainstem; wave III is generated within the cochlear nucleus, either from neuronal elements or from VIII nerve fibres within the structure (Moller, 1994). The measure of the time interval between waves I and III has been used as an index of the conduction time between the distal portion of the VIII nerve within the cochlea and the central portion of the VIII nerve within the cochlear nucleus. Wave I of the ABR is preserved in patients with an acoustic neuroma whereas subsequent waves may be lost reflecting a compression of the VIII nerve within the porous acousticus, proximal to the site of generation of wave I but distal to the site of generation of wave II. The absence or abnormality of all neural components of the ABR in the patients of this report is evidence that the distal portions of the auditory nerve are affected.

There have been frequent reports of bilateral sensorineural hearing loss in patients with various types of peripheral neuropathies including hereditary motor and sensory neuropathy (Musiek *et al.*, 1982; Raglan *et al.*, 1987; Perez *et al.*, 1988), hereditary sensory and autonomic neuropathy (Denny-Brown, 1951; Hallpike *et al.*, 1980; Wright and Dyck, 1995), and the neuropathy accompanying Friedreich's ataxia (Cassandro *et al.*, 1986). The incidence of hearing impairments in these patients can be significant, amounting to ~30% in published series (Raglan *et al.*, 1987; Perez *et al.*, 1988). In addition, there are numerous reports of abnormalities of auditory brainstem potentials in such patients including absence of wave I or prolongation of the I–III and/or I–V intervals (Satya-Murti *et al.*, 1979, 1980; Garg *et al.*, 1982; Taylor *et al.*, 1982; Rossini and Cracco, 1987; De Pablos *et al.*, 1991; Gadoth *et al.*, 1991; Kowalski *et al.*, 1991; Caruso *et al.*, 1992; Scaioli *et al.*, 1992). The demyelinating neuropathy of the Guillain–Barré syndrome may at times involve the auditory nerve. Patients with Guillain–Barré syndrome may show delays of the I–III interval although the incidence of this varies between reported series (Schiff *et al.*, 1985; Ropper and Chiappa, 1986). Nelson *et al.* (1988) reported two patients with Guillain–Barré syndrome with severe hearing impairment and abnormal brainstem auditory evoked potentials. One of these patients had no recognizable brainstem potentials at disease onset with the potentials reappearing as hearing recovered. Kernicterus may affect the auditory nerve (as well as other regions of the auditory system). Some of the patients with kernicterus reported by Kaga *et al.* (1979) showed relative preservation of pure tone thresholds with severely abnormal auditory brainstem potentials and may possibly have been similar to our patients. Patients with peripheral neuropathies accompanying uraemia (Antonelli *et al.*, 1990), diabetes (Parving *et al.*, 1990; Donald *et al.*, 1981), and exposure to toxins such as cisplatin (Hansen, 1992) have been reported as having hearing impairments and abnormalities of the absolute latency of wave I and/or prolongation of the I–III interval. If all of these patients were also to have normal otoacoustic emissions on testing, the designation of the hearing impairment and ABR abnormalities as due to an auditory neuropathy would seem appropriate.

Hearing disorders are not a regular feature of hereditary neuropathies reflecting, perhaps, that the phenotypic expression of genetic disorders varies depending on the influence of other genes or unknown factors (Wright and Dyck, 1995). Alternatively, the auditory nerves may actually be more widely involved in neuropathic disorders than is commonly known. Certainly, our ability to document such an involvement is recent and this paper demonstrates that the combination of physiological tests of hair cell function (otoacoustic emissions, cochlear microphonics) and auditory pathway function (auditory brainstem potentials) with audiological tests (speech intelligibility and pure tone audiograms) can provide evidence of a disorder of auditory nerve. The application of such tests to patients with hereditary and other neuropathies may provide new insights into the incidence of auditory nerve deficits in these patients.

Pathological descriptions of the cochlea and VIII nerve in these examples of possible neuropathy are rare. A case of deafness with Charcot–Marie–Tooth disease was reported to include changes in both the cochlear receptor elements and the spiral ganglion and acoustic nerve (Horoupian, 1989). In patients with Friedreich's degenerative disorder pallor of the vestibular and cochlear root has been noted (Bogaert and Martin, 1974). Spoendlin (1974) described damage to spiral ganglion but normal cochlea structures including preserved outer spiral fibres to outer hair cells. Hallpike *et al.* (1980) detailed the clinical and post-mortem results of a patient with an hereditary hearing disorder who later developed a peripheral neuropathy before expiring. The hearing loss was

characterized by a moderate flat pure tone loss with a disproportionately greater loss of speech comprehension. The patient had absence of deep tendon reflexes, sensory loss and ataxia. Pathological examination of the cochlea showed the hair cells to be preserved but the VIII nerve and cochlear ganglion cells to be degenerated. The peripheral nerves also showed a loss of nerve fibres but the neurons of the dorsal ganglion were preserved. These reports reveal differing extents of pathology in the auditory nerve and cochlea in patients with hereditary neuropathy. The patients in our study were selected by physiological tests to have a disorder localized primarily to the auditory nerve with relatively normal cochlear outer hair cell function. These patients would have to be studied over time to define whether cochlear hair cell loss will occur and contribute to the hearing deficit.

We consider that the electrophysiological and clinical evidence presented in this paper provides support for the hypothesis that the auditory nerve is the site of pathology in these patients with hearing impairment. Several of the patients clearly have a genetic basis for the neuropathy and have been clinically and electrophysiologically identified as belonging to the category of HSMN Types I and II. The other patients are sporadic and the basis of the neuropathy has not yet been defined. All of these patients can be identified by auditory physiological tests (auditory brainstem potentials, otoacoustic emissions, acoustic reflexes) to be distinct from patients with a cochlear hearing loss.

Auditory neuropathy could be one aetiology for some cases with the disorder known as central auditory dysfunction or 'central auditory processing disorder', especially those in whom pure tone thresholds were elevated (Jerger *et al.*, 1988; Musiek *et al.*, 1990; Gravel and Stapells, 1993; Widen *et al.*, 1995). Several other causes for central auditory dysfunction have been classified by results of auditory evoked potentials. Some patients may have abnormalities of the brainstem auditory pathways with preservation of the early brainstem components but abnormalities of the later waves (Lenhardt, 1981; Blegvad and Hvidegaard, 1983; Jerger *et al.*, 1992). If such patients also had cochlear receptor deficits, wave I might also be absent, complicating the identification of the brain site of their pathology. Other patients may have bilateral cortical damage (Ozdamar *et al.*, 1982; Woods *et al.*, 1987; Hood *et al.*, 1994). The physiological tests described in this paper can supplement behavioural testing in the differential diagnosis of central auditory processing disorders. The major requirements for diagnosing an auditory neuropathy include absent or severely abnormal auditory brainstem potentials beginning at wave I in the presence of preserved otoacoustic emissions.

Addendum

Several recently completed studies document absence of auditory brainstem potentials and preserved cochlear microphonic or otoacoustic emissions in neonates with hyperbiliruninaemia (Stein *et al.*, 1996), metabolic abnormalities (Deltendre *et al.*, 1996) and adults with unspecified degenerative disorders (Kaga *et al.*, 1996)

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