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Transient Deafness Due To Temperature-Sensitive Auditory Neuropathy

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▼ Abstract

Objective: To define mechanisms accounting for transient deafness in three children (two siblings, ages 3 and 6, and an unrelated child, age 15) when they become febrile.

Design: Audiometric tests (pure-tone audiometry, speech and sentence comprehension), tympanometry, middle ear muscle reflex thresholds, otoacoustic emissions (OAEs), and electrophysiological methods (auditory brain stem responses [ABRs], sensory evoked potentials, peripheral nerve conduction velocities) were used to test the children when they were afebrile and febrile.

Results: ABRs, when afebrile, were abnormal with a profound delay of the IV-V and absence of waves I-III. The ABR in one of the children, tested when febrile, showed no ABR components. Measures of cochlear receptor function using OAEs were normal in both febrile and afebrile states. Cochlear microphonic potentials were present in the three children, and a summing potential was likely present in two. When afebrile, there was a mild threshold elevation for all frequencies in the 15-yr-old and a mild elevation of thresholds for just low frequencies in the two siblings. Speech comprehension in quiet was normal but impaired in noise. One of the siblings tested when febrile had a profound elevation (>80 dB) of pure-tone thresholds and speech comprehension was absent. Acoustic reflexes subserving middle ear muscles and olivocochlear bundle were absent when febrile and when afebrile. No other peripheral or cranial nerve abnormalities were found in any of the children. Sensory nerve action potentials from median nerve in one of the children showed no abnormalities on warming of the hand to 39°C.

Conclusion: These children have an auditory neuropathy manifested by a disorder of auditory nerve function in the presence of normal cochlear outer hair cell functions. They develop a conduction block of the auditory nerves when their core body temperature rises due, most likely, to a demyelinating disorder of the auditory nerve. The auditory neuropathy in the two affected siblings is likely to be inherited as a recessive disorder.

Criteria for defining that a hearing loss is due to a disorder of auditory nerve (Starr et al., 1991; Starr, Picton, Sininger, Hood, & Berlin, 1996) are based on results from physiological tests: patients with auditory neuropathy have normal cochlear outer hair cell function (normal otoacoustic emissions [OAEs] and/or cochlear microphonic) but abnormal auditory nerve function (absent or abnormal auditory brain stem potentials beginning with wave I). Wave I of the auditory brain stem potentials is the component generated by activity of the peripheral portion of the auditory nerve (Achor & Starr, 1980; Moller, Jenetta, & Sekhar, 1988; Starr & Zaaroor, 1990). Auditory nerve disorders have been identified in patients varying in age from newborns to adults. The etiologies have been diverse and include neonatal hyperbilirubinemia (Stein, Tremblay, Pasternak, Banerjee, Lindemann, & Kraus, 1996), severe illness during the neonatal period (Deltenre, Mansbach, Bozet, Clercx, & Hecox, 1997a), part of a generalized hereditary, metabolic, toxic, or inflammatory neuropathy (Alexander, Thomas, Mohan, & Narendranathan, 1995; Berlin, Hood, Cecola, Jackson, & Szabo, 1993; Hardin, 1995; Jabbari, Coats, Salazar, Martin, Scherokman, & Laws, 1993; Kalaydjieva et al., 1996; Nicholson & Corbett, 1996; Pareyson, Scaioli, Berta, & Sghirlanzoni, 1995; Quattrone et al., 1996; Raglan, Prasher, Trinder, & Rudge, 1987; Ragno, Curatola, Rossi, & Salvolini, 1992; Scaioli, Pareyson, Avanzini, & Sghirlanzoni, 1992; Starr et al., 1996), and an isolated neuropathy of the VIIIth nerve (Kaga, Nakamura, Shinogami, Tsuzuku, Yamada, & Sindo, 1996; Sakaguchi, 1994; Sawada, 1979; Starr et al., 1996). In those children and young adults with auditory neuropathy whose hearing functions have been studied carefully, the loss is typically of insidious onset, initially affects a moderate elevation of puretone threshold, particularly of low and middle frequencies, impairs speech comprehension out of proportion to the pure-tone threshold loss, impairs auditory perceptions dependent on temporal cues of the auditory signals, and can be slowly progressive (Starr et al., 1991, 1996). We have identified three children with a temperature-dependent disorder of auditory nerve function who become transiently deaf when their core body temperature is raised by as little as one degree Celsius. Their hearing sensitivity returns promptly when body temperature becomes normal again. They have no evidence of a generalized neuropathic disorder nor of any systemic illness. An analysis of their clinical course and the results of auditory function tests performed when afebrile and when febrile provide insights into the neurophysiological mechanisms that may be accounting for the expression of auditory nerve dysfunction. Gorga and colleagues report their observations in another child with a quite similar episodic hearing loss accompanying febrile episodes (Gorga, Stelmachowicz, Barlow, & Brookhouser, 1995).

Method

Audiometric Tests

Pure-tone audiometry (250 Hz to 8000 Hz) was performed with air- and bone-conducted signals. Speech tests included the definition of reception thresholds and monosyllabic intelligibility tested at 30 dB SL or maximum limits of the audiometer. Sentence comprehension in quiet and with noise at 90 and 270 degrees azimuth was evaluated using the Hearing in Noise Test for Children (HINT-C) (Gellnet, Sumida, Nilsson, & Soli, Reference Note 1; Gellnet, Nilsson, Soli, & Sumida, Reference Note 2).

Standard measures of tympanic membrane mobility (tympanometry) were made along with acoustic reflex thresholds for pure-tone stimuli from 500 to 4000 Hz. Tympanograms were considered normal if middle ear pressure was >-150 mm H₂O and compliance was >0.3 cc. Pure-tone acoustic reflex thresholds were measured both ipsilateral and contralateral to the stimulated ear. The reflex was considered absent when there was no response with stimulus levels at 110 dB HL. Nonacoustic activation of middle ear muscles was measured in one of the children by stroking the face and as an associated muscle activity accompanying swallowing, speaking, and closing the eyes (Salomon & Starr, 1964).

Auditory Physiological Tests

OAEs • Click-evoked OAEs were measured with an ILO-92 OAE system. Nonlinear click levels ranged from 80 to 86 dB peak SPL. Responses to as many as 260 stimuli were averaged over a 20 msec window. The presence of normal OAEs in the 2.5 to 20 msec poststimulus period was determined by overall response amplitude signal to noise ratio of at least 4 dB and waveform reproducibility in at least three octave bands of $>75\%$.

The presence of contralateral noise-induced suppression of transient-evoked emissions (olivocochlear reflex) was tested using a white noise at 60 dB SPL and linear click stimuli (Collet, Kemp, Veuillet, Ducleaux, Moulin, & Moron, 1990). Three trials each with and without contralateral noise were interleaved, and amplitude changes and time delays were analyzed for transient-evoked otoacoustic emission (TEOAE) suppression as a function of poststimulus time. The presence of normal contralateral suppression was defined by an average noise-induced reduction of the TEOAEs of >1 dB with an intertrial variance of OAEs without noise of <0.5 dB.

Evoked Potentials

Auditory brain stem evoked potentials were recorded in two electrode configurations: 1) a vertical channel, vertex (Cz) to seventh cervical vertebra (C_{VII}) to optimize detection of the IV-V complex, and 2) vertex to the ipsilateral mastoid (Cz-ipsi) to enhance VIIIth nerve and cochlear potentials. Amplifier band pass was 100 to 3000 Hz for all subjects, with additional testing at 30 to 3000 Hz for Subject 3. Rarefaction or condensation click stimuli (100 μ sec) were presented monaurally at 25/sec for all subject, with additional testing at other stimulus rates for Subjects 1 and 3. Intensities from threshold to 85 dB nHL were used. Acoustic stimuli were applied through insert transducers (Etymotic model ER-2) coupled to the ear canal by a short tube and foam tip. The resulting delay between transducer activation and the appearance of the sound in the ear canal was taken into account in calculating the latency of the auditory brain stem response (ABR) components. On one test occasion, TDH-49 earphone transducers were employed. The presence of reproducible components was defined using either visual estimations of the evoked potential waveforms or a mathematical estimate of the signal to noise ratio (Don & Elberling, 1996). The auditory brain stem potentials evoked to condensation and to rarefaction stimuli subsequently were processed to enhance particular types of potentials. Subtraction of potentials to condensation from rarefaction stimuli results in the enhancement of cochlear microphonics and the attenuation of neural components. Summing of potentials to condensation and rarefaction stimuli results in the attenuation of cochlear microphonics and the enhancement of neural potentials and summing potentials (SP). In one of the patients, middle- and long-latency auditory potentials, pattern-reversal visual potentials, and median and posterior tibial nerve somatosensory evoked potentials were recorded (Starr, 1978).

Nerve Conduction Studies

Peripheral nerve conduction studies using surface electrodes were made in one subject. Nerve conduction velocities were measured for sural, peroneal, and median nerves on one side. The effect of raising hand temperature to 39°C on distal median sensory nerve conduction was examined. The hand was warmed to 39°C by a small heating pad, and palmar skin surface temperature was recorded every few minutes. The hand then was allowed to cool while both skin temperature and nerve potentials were recorded.

Case Reports and Results

Three children, two siblings, a girl age 6 (date of birth: 5/90, Subject 1) and a boy age 2 (date of birth: 10/94, Subject 2), and an unrelated girl, age 15 (date of birth: 12/81, Subject 3) become transiently deaf when febrile. Within an hour after treatment with antipyretic agents (acetaminophen, ibuprofen), the children regain their ability to respond to sounds and to speak. The children's speech and auditory behavior otherwise have been entirely normal except that two of the children (Subjects 1 and 3) have difficulty understanding speech in noisy environments. The two related children (Subjects 1 and 2) have two older siblings (girls, ages 9 and 10) who do not have hearing or communication problems when either febrile or afebrile. Subject 3 has two siblings who have normal hearing and are unaffected by fever. The family histories are negative for other members having hearing or neurological problems. We have studied the children when afebrile and one of the affected siblings (Subject 1) when febrile. Details of their development, examination, and audiological and medical tests follow.

Subject 1

The affected girl, whom we will refer to as "Sister," was born by vaginal delivery without complications after a normal gestation. The developmental highlights were normal for motor and social functions. However, speech and language functions were slightly delayed. She talked at 2 yr and initially made articulation errors. These speech and language problems are not evident now, and she attends regular classes and school performance is normal. When Sister was 3 yr and 1 mo of age, she had the first episode of transient deafness in association with an upper respiratory infection and a low-grade fever; she was unresponsive to sounds and would not speak. She resumed talking and responding to sounds within a few hours after treatment with acetaminophen. The following day, when afebrile, pure-tone audiometry showed a mild low-frequency loss with normal tympanograms and an absence of acoustic middle ear muscle reflexes bilaterally.

Afebrile Test Results • Sister had 13 separate audiological examinations between 1995 and 1997 when she was afebrile. On every occasion, a puretone audiogram and speech audiometry were performed. Physiological testing was performed for OAEs (three times), ABRs (three times), and middle ear muscle reflexes (seven times). The results are shown in [Table 1](#) and [Figures 1, 2, and 3](#).

Subject Number	Date	Temperature	Discr (%) [*]	Discr in Noise (%) [†]	Tymp	MEM	OCB
1	1995-1997	Normal	88-100 (n = 13)	<10	Normal	abs × 6 (n = 7)	abs × 3 (n = 3)
1	5/26/95	38.1°C	0	nt	Normal	abs	abs
1	9/5/96	37.8°C	0	nt	Normal	abs	abs
2	1996	Normal	nt	nt	Normal	abs	abs
3	1997	Normal	100	<10	Normal	abs	abs

^{*} Discrimination PBK words.
[†] Discrimination of Sentences in Noise (Hnt-CI).
 TYMP = tympanogram; MEM = middle ear muscle acoustic reflexes measuring both ipsilateral and contralateral to the stimulated ear; OCB = olivocochlear bundle acoustic reflexes measuring OAEs with contralateral stimulation; nt = not tested; abs = absent.

TABLE 1. Audiological test results

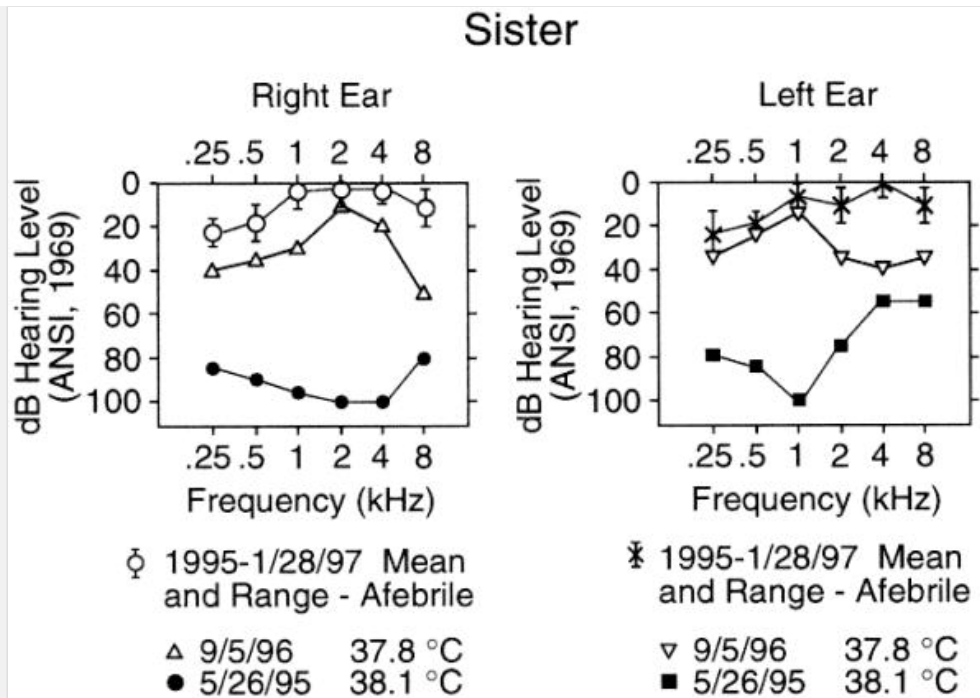


Figure 1. Pure-tone audiogram and speech comprehension from Subject 1 (Sister) when afebrile and on two occasions when febrile. The afebrile values are the mean and range of 13 separate tests over a 2 yr period. The febrile values were obtained when core temperatures were 38.1°C and 37.8°C. Note the mild elevation of low-frequency thresholds with normal word comprehension when afebrile. When the temperature was 37.8°C, pure-tone thresholds were elevated approximately 30 dB at all frequencies, whereas word comprehension (see Table 1) was severely compromised (0%). When febrile at 38.1°C, pure-tone thresholds were elevated approximately 60 to 80 dB and word comprehension (see Table 1) was again markedly compromised (0%). Results of acoustic middle ear muscle reflexes and tympanograms are shown in Table 1.

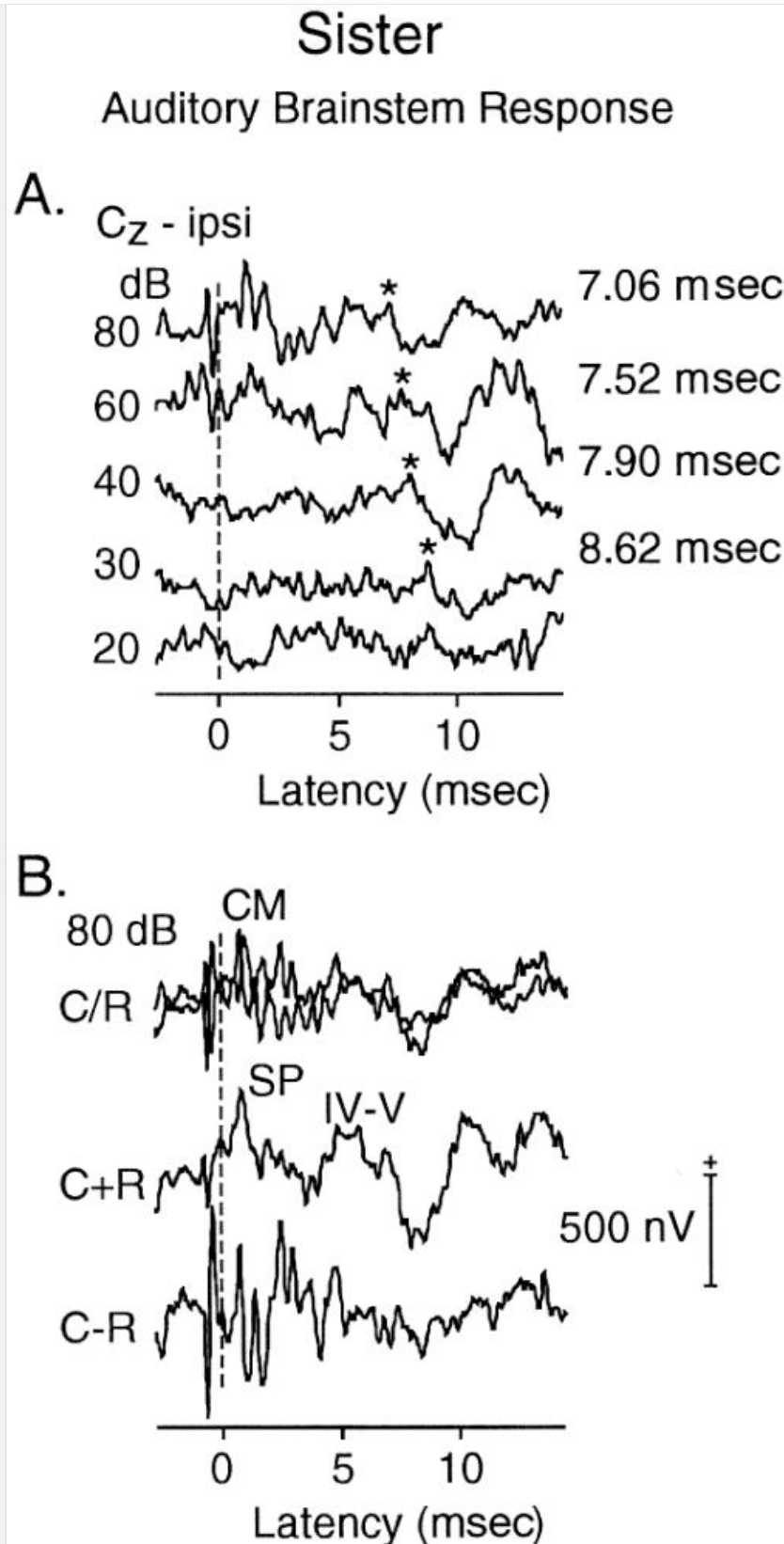


Figure 2. Auditory brain stem responses from stimulation of the left ear when Sister was afebrile. The top panel (A) contains ABRs in response to condensation stimuli (Cz-ipsi). The acoustic transducer was connected to the ear canal by a length of tubing, causing a delay between activation of the transducer and arrival of the acoustic stimulus in the ear canal. Note the presence of an electrical stimulus artifact present at high signal intensities (80, 60 dB) that precedes the onset of acoustic stimulation indicated by the interrupted vertical line at 0 msec. The IV-V complex (*) was present and of prolonged latency and can be traced to threshold at 30 dB nHL. The lower panel (B) contains superimposed recordings to condensation and rarefaction stimuli (C/R) from Cz-ipsi mastoid to 80 dB nHL clicks. Note in the top traces (C/R) the 180 degree phase shift between the recorded potentials until approximately 5 msec, indicating their origin as cochlear microphonics. The second tracing is the sum of the C and R responses (C + R), and the third tracing is the difference between the C and R responses (C - R). Summing the potentials results in an attenuation of cochlear microphonics and an enhancement of a transient early component (labeled as a summing potential, SP) and a broad neural responses (IV-V complex); subtracting the potentials (C - R) attenuates the IV-V complex and the summing potential is obscured by the cochlear microphonics.

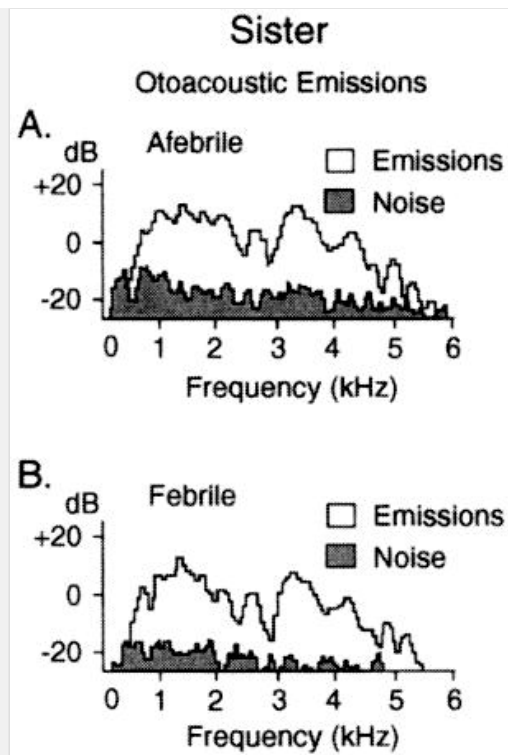


Figure 3. Transient otoacoustic emissions from the left ear of Sister when afebrile (A) and when febrile (B) at 38.1°C. The emissions were comparable and of large amplitude in both instances.

1. Pure-tone thresholds showed a mild low-frequency loss (Fig. 1).
2. Speech perception was normal using PBK word lists (Table 1). Sentence comprehension was below the 10th percentile for her age in both quiet and noise (HINT-C).
3. Tympanometry was normal (Table 1).
4. Acoustic middle ear reflexes were absent on six of seven test occasions. The one instance in which acoustic middle ear muscle reflexes were detected was both ipsilateral and contralateral to left ear stimulation at the highest intensity employed, 110 dB, and only to 500 Hz stimuli.
5. ABRs were assessed on two occasions (6/95 and 1/97). On 6/95, the IV-V complex to 80 dB nHL clicks was delayed in latency for both AS (6.1 msec) and AD (7.2 msec). Waves I-III could not be defined because of the presence of cochlear microphonic potentials. ABR testing could not be completed, and thresholds were not determined. On 12/96, ABRs were tested from threshold to 80 dB nHL for AS (Fig. 2). The IV-V complex could be detected to 30 dB nHL. The threshold value is 20 dB higher than found in our young, healthy controls. The slope of the IV-V complex latency as a function of intensity was normal at 32 $\mu\text{sec}/\text{dB}$. Waves I-III were not identified because of the large amplitude cochlear microphonics extending for almost 5 msec after stimulus presentation. These early potentials reversed polarity to condensation and to rarefaction clicks (C/R traces in lower panel, Fig. 2). When the potentials to the two click polarities were summed (C + R in Fig. 2), microphonic potentials were attenuated, leaving a broad IV-V complex peaking at approximately 7.1 msec. Another component, peaking at 0.9 msec, also was revealed. Its latency was too early for wave I but was appropriate for an SP, and we will provisionally use this designation. Alternatively, this component could reflect a nonlinearity of amplitude of cochlear microphonics to condensation and to rarefaction clicks. Note that in the subtracted recordings of ABRs to condensation and rarefaction clicks (C - R), cochlear microphonics were enhanced, obscuring the SP, and the IV-V complex was attenuated.
6. TEOAEs (Fig. 3A) were normal and of robust amplitude (18.4 dB AS; 22.0 dB AD). There was no suppression of OAE amplitudes by contralateral noise.

Febrile Test Results • During this same 2 yr period, Sister had at least six episodes of transient deafness accompanying low-grade fevers. On two of these occasions, she was examined at the Children's Auditory Research and Evaluation Center of the House Ear Institute before receiving antipyretic agents. Core body temperature had been defined approximately 2 hr earlier using a temperature sensor in the ear canal at 37.8°C (5/95) and at 38.1°C (9/96).

The physical examination on 5/95 revealed an inflamed pharynx and normal tympanic membranes. She was evaluated for immune disorders, with normal laboratory findings including complete blood counts, FTA, rheumatoid factor, quantitative immunoglobulins G and A, and total IgE. Antigen-specific IgE, as measured by ELISA, showed moderate reaction to several regionally important aeroallergens, including several weed grass and tree pollens, as well as to several mold spores and cat dander. The antinuclear antibody (ANA) level was abnormal at 1:160 with a speckled pattern. Urinalysis was normal. An anticochlear antibody (Heat Shock Protein 70) was normal. She also was seen by a rheumatologist who felt the elevated ANA titer was nonspecific and not diagnostic of lupus erythematosus. Specific viral titers including IgG and IgM (acute and convalescent) for herpes and cytomegalic virus were negative.

Audiological evaluations when Sister was febrile on 5/95 at 38.1°C (see also [Figs. 1, 3, and 4](#); [Table 1](#)) showed the following:

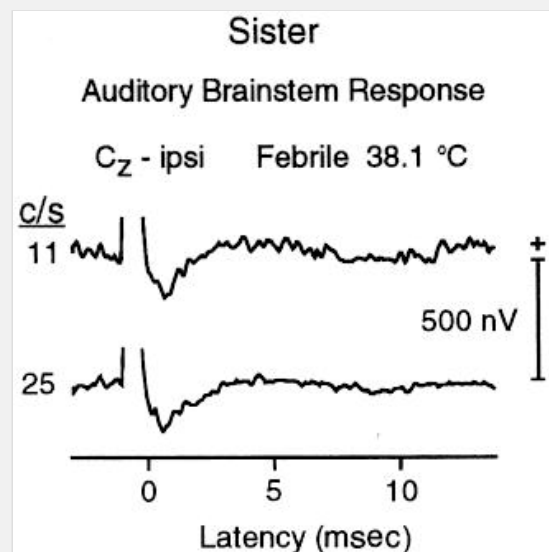


Figure 4. Auditory brain stem potentials recorded from Czipsi in Sister when febrile at 38.1°C. Stimulus intensities were 90 dB nHL and stimulus rates were 11/sec and 25/sec. A large stimulus artifact was present in the recordings, reflecting the proximity of the TDH-49 earphones to the recording electrode (ipsilateral mastoid). Note that all components were absent.

1. Pure-tone thresholds were severely impaired, with a loss of 80 to 100 dB HL in the right ear and 55 to 100 dB HL in the left ear. The hearing loss was relatively flat in the right ear and affected low frequencies to a greater extent than high frequencies in the left ear ([Fig. 1](#)).
2. Speech awareness threshold was at 80 dB nHL, but she was unable to repeat any of the test spondee words.
3. Tympanometry was normal.
4. Acoustic middle ear muscle reflexes were absent.
5. ABRs ([Fig. 4](#)) were absent bilaterally to monaural stimulation with clicks or 500 Hz tone bursts at 90 dB nHL using TDH-49 transducers placed on the ears. Circumaural transducers were used to obtain higher output levels than is possible with insert transducers. Stimulus rates at both 25/sec and 11/sec were tested. The tracings to 25/sec stimulus rates in [Figure 4](#) do not contain neural components, and a large stimulus artifact was present that would have masked cochlear microphonic potentials.
6. TEOAEs ([Fig. 3B](#)) were normal, with amplitudes of 18.4 (AS) and 22 dB (AD).

The following day the fever had resolved, and the mother reported that the child's hearing had returned. A high resolution computed tomography scan showed an opaque left maxillary sinus with normal temporal bone and cochlear structures. The vestibular aqueducts were identified and were not enlarged.

In 1996, Sister was again tested when febrile with a temperature of 37.8°C (see [Fig. 1](#)). She showed a mild to moderate elevation of pure-tone thresholds (average loss of 30.1 dB AD, 29.2 dB AS) and marked impairment of speech comprehension (0%). Auditory evoked potentials and OAEs were not tested. The following day her fever had abated and her auditory functions had returned to "normal." Her parents observed that there was an invariable hearing loss whenever there was a fever. Sister described to her parents that her hearing becomes affected "suddenly" when she is febrile.

A neurological examination, performed when she was 6 yr of age, was normal, without evidence of involvement of cranial or peripheral nerves. An MRI of the brain in 1995, with and without gadolinium, was normal, without evidence of tumor or abnormal myelin. Middle- and long-latency auditory evoked potentials were tested when she was asleep, and a reproducible P100 component was identified. Pattern reversal visual potentials and median nerve somatosensory evoked potentials also were normal. Nerve conduction velocities fell within normal ranges with the following values:

1. Median motor (elbow to wrist), 45.6 m/sec and 15 mV.
2. Median sensory (wrist to second digit), 48.2 m/sec and 25 μ V.
3. Sural nerve (mid-calf to ankle), 47.1 m/sec and 10 μ V.

Median sensory nerve action potentials recorded during warming of the hand to 39°C showed an increase both of amplitude and conduction velocity without the development of conduction block (Fig. 5). The increase in conduction velocity with temperature was approximately 2.14 m/sec per °C (linear trend; $p < 0.01$; $r^2 = 0.86$) and was within normal values. The increase in amplitude of the sensory nerve potentials with temperature was not significant for linear or quadratic trends.

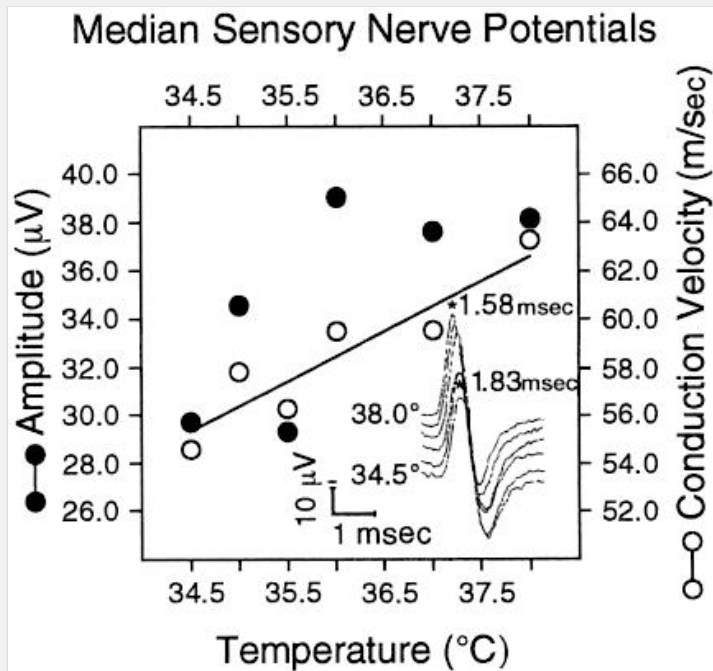


Figure 5. Median sensory nerve potentials from Sister recorded from the index finger to stimulation at the wrist as a function of palmar skin temperature. The graph plots a normal increase of conduction velocity with hand temperature. A linear function relating temperature and conduction velocity is plotted with a slope of 2.14 m/sec per °C. The amplitude of the nerve action potentials also increased with temperature, but the function relating amplitude and temperature did not reach significant levels for linear or quadratic fits. The nerve action potentials are shown (insert) in the lower right side of the figure; stimulation onset is not shown in the waveform traces. The peak latencies of the sensory nerve action potential at 38°C and 34.5°C are noted.

Subject 2

The affected "Brother" was examined when he was 24 mo and again when he was 33 mo of age. He was afebrile and responsive to sounds. He was the product of a normal pregnancy and delivery. He had developed normally, walked at 1 yr of age, and currently speaks two- and three-word phrases. Results of a speech and language evaluation were appropriate for his age. He has had at least two episodes of deafness accompanying mild elevations of body temperature since becoming 2 yr of age.

Afebrile Test Results • The neurological exam when afebrile showed no abnormalities and no evidence of cranial or peripheral neuropathy. Audiological results are in [Table 1](#) and [Figure 6](#) and showed the following:

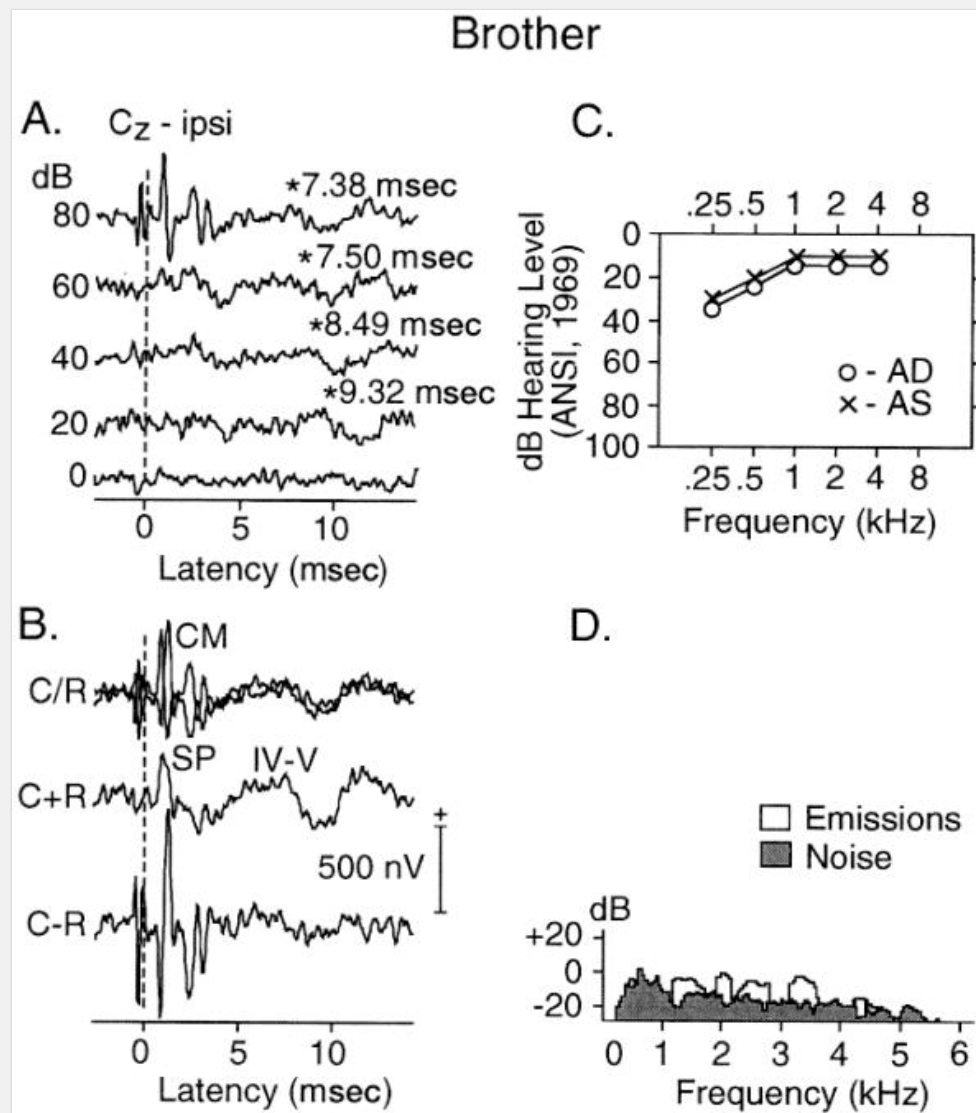


Figure 6. Results from Brother (Subject 2). Pure-tone audiogram (C), auditory brain stem potentials (A,B), and otoacoustic emissions (D) were recorded when afebrile. The ABRs and OAEs are from stimulating the left ear and are essentially identical to those from the right ear. The parameters of recording and stimulation were the same as in [Figure 2](#). In A, note the delayed latency of the IV-V complex (7.38 msec at 80 dB nHL) without early neural components (waves I-III). Cochlear microphonics were present at 80 dB nHL. In B, ABRs to condensation and rarefaction clicks are superimposed (C/R), summed (C + R), and subtracted (C - R) as in [Figure 2](#). Note the presence of a transient summing potential (SP) and the IV-V complex in the summed record.

1. Audiogram showed a mild (30 dB) low-frequency hearing loss ([Fig. 6C](#)).
2. Speech awareness thresholds were normal.
3. Tympanograms were normal.
4. Acoustic middle ear muscle reflexes were absent bilaterally to ipsilateral and contralateral stimulation.
5. ABRs ([Fig. 6A](#)) to left ear stimulation showed a delayed IV-V complex (7.38 msec) to 80 dB nHL clicks. There were early deflections that were cochlear microphonics, and waves I-III could not be identified. The threshold intensity for defining the IV-V complex was 20 dB nHL. Stimulating AD showed a IV-V complex at 80 dB nHL at a delayed latency of 7.0 msec and a threshold of detection at 30 dB. The latency/intensity function for the IV-V complex was normal at 32 μ sec/dB AD and 37 μ sec/dB AS. ABRs evoked by condensation and by rarefaction clicks at 80 dB nHL also are shown in [Figure 6B](#) (C/R). Summing these ABRs (C + R) cancels cochlear microphonics, revealing a presumed SP at 0.9 msec and a broad IV-V complex peaking at approximately 7.0 msec. Subtracting these ABRs (C - R, [Fig. 6B](#)) enhances the cochlear microphonics, obscures the SP, and attenuates the IV-V complex.
6. TEOAEs ([Fig. 6D](#)) were of normal amplitude (20.9 dB AD, 17.7 dB AS) bilaterally. There was no suppression of OAEs with contralateral noise stimulation.
7. Long- and middle-latency auditory evoked potentials were tested when Brother was asleep, and no reproducible components were identified.

Subject 3

This 15-yr-old girl's first episode of deafness accompanied a high fever after a DPT inoculation when she was 4 yr of age. She presently continues to experience an impairment of hearing whenever she is febrile and takes antipyretic agents immediately when she experiences hearing loss. She also has noted difficulty in understanding speech in noisy environments. Her development otherwise has been normal. She is an excellent student in regular school. She is an excellent athlete. She has no symptoms suggestive of other cranial or peripheral neuropathies.

Afebrile Test Results • The neurological examination was normal, without evidence of cranial or peripheral neuropathy. In particular, cranial nerve examination, motor strength and coordination, deep tendon reflexes, and sensory thresholds to touch and vibration all were normal. This subject was unable to tolerate electrical stimulation of the peripheral nerves for the assessment of nerve conduction velocities. The audiological results are in [Figure 7](#) and [Table 1](#).

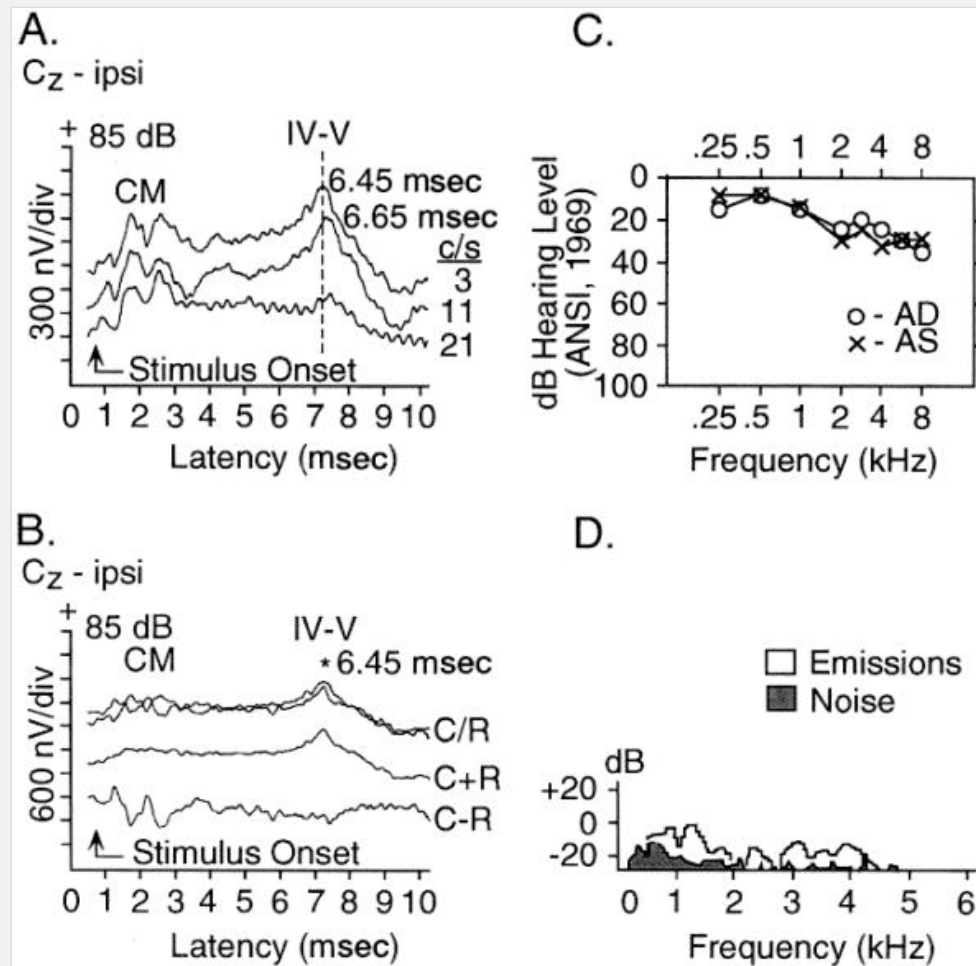


Figure 7. Auditory brain stem potentials (A and B), pure-tone audiogram (C), and otoacoustic emissions (D) from Subject 3 when afebrile. The ABRs and OAEs are only shown from stimulating the right ear. For the ABR in A and B, the parameters of recording (30-3000 Hz) and stimulation rates (from 3/sec to 21/sec) differed slightly from those used in the other figures (see Method). In A, the IV-V complex was present at slow stimulus rates (3/sec and 11/sec) but became markedly attenuated at fast rates (21/sec). Note that the latency of the IV-V complex was delayed even at slow stimulus rates and that early neural components (waves I-III) either were not present or were obscured by cochlear microphonics. In B, ABRs to condensation and rarefaction clicks are superimposed (C/R), summed (C + R), and subtracted (C - R). Note the presence of a IV-V complex without waves I-III in the summed record and the absence of neural components in the subtracted record. The cochlear microphonic was attenuated in the summed record and enhanced in the subtracted record. An SP cannot be identified securely in the summed record.

1. Audiogram showed normal pure-tone thresholds ([Fig. 7C](#)).
2. Speech perception was normal (100%) using NU-6 word lists. Sentence comprehension was below the 10th percentile for her age in both quiet and noise (HINT-C).
3. Tympanograms were normal.
4. Acoustic middle ear muscle reflexes were absent bilaterally to ipsi- and contralateral stimulation.
5. ABRs to 85 dB nHL clicks showed cochlear microphonics and a delayed IV-V complex (AS 6.45 msec, AD 6.70 msec) without waves I-III ([Fig. 7, A and B](#), for ABRs from AS). The threshold intensity for defining the IV-V complex was 50 dB nHL. The detection of the IV-V complex was particularly sensitive to the stimulus rate and clearly was present at rates of 3.4/sec and 11.3/sec but became markedly attenuated at 21.1/sec ([Fig. 7A](#)). Our experience in healthy subjects is that the amplitude of the IV-V complex is not significantly attenuated with stimulus rates below 30/sec. Summing ABRs to condensation and rarefaction clicks (C + R, [Fig. 7B](#)) canceled microphonics, leaving a broad IV-V complex. An SP was not clearly evident. Subtracting these ABRs (C - R, [Fig. 7B](#)) enhanced the cochlear microphonics and attenuated the IV-V complex.

6. TEOAEs (Fig. 7D) were of normal amplitude (8.8 dB AD, 6.3 dB AS) bilaterally. There was no suppression of OAEs with contralateral noise stimulation.

7. Long- and middle-latency auditory evoked potentials were present.

Discussion

We have identified three children who show severe to profound hearing loss with mild elevation (approximately 1°C) of core body temperature. The results in these children can be divided into three categories. First are those tests that are normal when febrile and when afebrile. This category includes tests of cochlear (OAEs, cochlear microphonics) and middle ear functions (tympanometry). Second are those tests that are mildly abnormal when afebrile and markedly abnormal when febrile. This category includes tests of auditory neural function (ABR) as well as hearing thresholds. Third are those tests that are markedly abnormal and do not change with body temperature, including brain stem reflexes to acoustic stimulation involving middle ear muscles and olivocochlear projections.

This pattern of physiological test results is compatible with a disorder of auditory nerve function that we have termed "auditory neuropathy" (Starr et al., 1996). All of the patients reported with auditory neuropathy (Berlin et al., 1993; Deltenre et al., 1997a; Kaga et al., 1996; Starr et al., 1991, 1996; Stein et al., 1996) have a disorder of auditory nerve function in the presence of normal cochlear outer hair cell function evidenced by 1) an absence or severe abnormality of the ABR beginning with wave I, the component reflecting activity of VIIIth nerve within the cochlea; and 2) preserved OAEs and/or cochlear microphonics reflecting the integrity of function of the outer hair cells in the cochlea. Some of these patients also have an accompanying generalized neuropathy affecting other cranial and/or peripheral nerves (Starr et al., 1996). The patients reported in this paper fulfill these criteria for auditory nerve disorder by having preserved OAEs (both febrile and afebrile) and absent ABRs beginning with wave I when febrile, or abnormal ABRs with absence of waves I-III and a delayed IV-V complex when afebrile. There was no evidence that these three patients also have a generalized peripheral or cranial neuropathy.

In one of the patients of this report, the identification of a IV-V complex when afebrile required testing at relatively slow click rates (3/sec and 11/sec) because the IV-V complex was markedly attenuated with stimulation at relatively fast rates (21/sec and 25/sec). Our clinical experience in healthy subjects has been that the IV-V complex is not greatly attenuated at 25/sec rates. Moreover, stimulus rates close to 25/sec typically are used in the clinic to define the latency of the IV-V complex when testing cochlear and auditory brain stem functions. The bases for the loss of the IV-V complex in this one patient with stimulus rates as low as 21/sec may represent an inability of the affected auditory nerves to effectively transmit repetitive neural impulses.

There were large amplitude cochlear microphonic potentials present in the three children of this report, as has been noted in other children with auditory neuropathy (Deltenre, Mansbach, Bozet, Clercx, & Hecox, 1997b; Starr et al., 1991). Additional studies are needed to determine whether the microphonics are actually larger than normal or whether their prominence is due to the absence of the short latency neural components of the ABRs. Processing the ABRs evoked by separate presentations of condensation and rarefaction clicks revealed the presence of a short latency component, presumed to be an SP in two of the children. If additional studies verify the classification of this early potential as an SP, it would provide additional evidence of normal cochlear receptor function in these children.

In patients with an auditory nerve disorder, the development of deafness with slight elevation of body temperature is most consistent with a demyelinating neuropathy of the auditory nerve. In myelinated mammalian nerves, the ionic processes accounting for the generation of the action potential are restricted to the nodes of Ranvier, the junction points between adjacent myelin glial cells (oligodendroglia for central pathways and Schwann cells for peripheral nerves). The nodal membrane is rich in Na⁺ channels essential for the generation of the nerve action potential, whereas paranodal and internodal membrane sites have few Na⁺ channels but are rich in K⁺ channels. Thus, the generation of Na⁺ current contributing to the development of the action potential in myelinated nerve is not continuous along the nerve but is restricted to the nodes of Ranvier. The restriction of the action potential to the nodes of Ranvier results in a discontinuity of conduction from node to node known as saltatory conduction and accounts in part for the rapid conduction velocity of myelinated fibers.

Internodal conduction velocity in a segmentally demyelinated axon is slowed and varies with the extent of demyelination (Razminsky, 1973). When the nerve impulse passes a demyelinated region and encounters a normally myelinated segment, conduction velocity resumes normal speeds. If the length of the demyelinated zones in these axons differs, conduction speeds of demyelinated axons of comparable size will vary and affect the degree of synchrony of discharge between adjacent axons. We have proposed that dysynchrony of conduction in VIIIth nerve fibers is one of the mechanisms that may account for the failure to average auditory brain stem potentials in patients with auditory neuropathy (Starr et al., 1991, 1996). Dysynchrony of auditory nerve fiber discharges also could account for the difficulties these patients have in making perceptual judgments dependent on temporal information contained in auditory signals such as in gap detection, masking level differences, and lateralization of binaural signals (Starr et al., 1991, 1996).

The maintenance of nerve transmission in the paranodal region of demyelinated axons is temperature dependent. With slight elevations of temperature, the voltage-dependent Na⁺ channels become inactivated more rapidly than at normal temperatures, resulting in a failure of impulse generation, and a conduction block can develop (Razminsky, 1973). The appearance of conduction block in certain demyelinated axons in experimental conditions can occur with temperature elevations of as little as 0.5°C. It is relevant that one of our patients (Subject 1) noted that hearing was affected "suddenly" as temperature increased. An increase of core body temperature of approximately 1°C was accompanied by a profound hearing loss. Conduction block accompanying slight increases of body temperature also has been suggested as accounting for the transient reappearance of neurological deficits in patients with multiple sclerosis when they experience fevers (Saul, Hayat, & Selhorst, 1995). It is particularly relevant that the oldest child (Subject 3) uses the change in hearing as the first indication of the development of a fever and treats herself with antipyretic agents.

It is likely that the children of this report have a demyelinating disorder of the auditory nerve and experience both a conduction block of the auditory nerve and deafness when their body temperatures become elevated. The site of demyelination is not known but could be in the "peripheral" or Schwann cell myelinated portion of auditory nerve distal to the dura mater and/or in its "central" portion proximal to the dura mater where the axons are myelinated by oligodendroglial cells. All of the other patients with auditory neuropathy who we have encountered (now numbering approximately 50 instances) have not reported aggravation of their hearing impairment with febrile episodes. It may be that the pathology in most patients with auditory neuropathy differed from that present in the three patients of this report. Other possible sites of damage in the auditory periphery that could lead to impaired auditory nerve function include the generation of receptor potentials by the inner hair cells, inner hair transmitter release, nerve impulse generation in VIIIth nerve dendrites, and VIIIth nerve ganglion cell function. There either are few data on temperature dependence of these physiological processes, or they appear to be relatively insensitive to temperature effects when compared with disruption of conduction along demyelinated axons. A transient worsening of neurological function accompanying fevers is not a regular feature of patients with abnormal myelin development, known collectively as the leukodystrophies.

There now are a number of etiologies related to the occurrence of auditory neuropathies. These include 1) genetic factors as in hereditary sensory motor neuropathy (Hardin, 1995; Kalaydjieva et al., 1996) and Freidreich's ataxia (Cassandro, Mosca, Sequino, De Falco, & Campanella, 1986); 2) immune disorders as in Guillain-Barre syndrome (Nelson, Gilmore, & Massey, 1988); 3) infectious processes such as mumps (Sawada, 1979); and 4) toxic-metabolic disorders during the neonatal period as in hyperbilirubinemia (Stein et al., 1996) and anoxia (Deltenre et al., 1997a). A genetic factor likely is contributing to the auditory neuropathy in the two siblings of this report. Both parents and two other siblings are unaffected, compatible with a recessive mode in the two affected siblings. The neuropathy in at least one of the affected siblings (Sister) appears to be restricted to the VIIIth nerve at this time because tests of other cranial and peripheral nerve functions (visual evoked potentials, somatosensory evoked potentials, clinical neurological evaluation, peripheral nerve conduction studies) were normal. The sensitivity of function of the auditory nerve to slight elevations of core temperature was not observed for the median nerve of Sister. When the median nerve was warmed to 39°C, the patient did not report a loss of sensation nor did she develop a conduction block of median sensory nerve potentials. Although conduction block is a feature of demyelinating peripheral neuropathies, it appears to be selective for motor rather than sensory axons (Kiernan, Mogyoros, & Burke, 1996). There is one reported instance of a child with a demyelinating peripheral neuropathy in whom febrile episodes were associated with transient worsening of motor function (Chaudhry, Crawford, & DeRossett, 1993).

The children have relatively normal speech and language functions in the presence of abnormal function of the auditory periphery beginning at the auditory nerve as revealed by ABRs. Psychoacoustic tests that define temporal processing of auditory signals have revealed profound deficits in patients with auditory neuropathy (Starr et al., 1991, 1996). A disorder of temporal processing could account for the particular difficulties in understanding speech in noisy but not in quiet environments of these patients.

Acoustic middle ear reflexes are regularly absent in patients with auditory nerve disorders (Starr et al., 1996), even when pure-tone thresholds are relatively normal as in the patients of this report. It is unlikely that efferent motor processes controlling stapedius muscle are abnormal because nonacoustic middle ear muscle reflexes were preserved (see also Gorga et al., 1995). Typically, acoustic middle ear reflexes are elicited with sounds of relatively high intensity beginning at about 85 dB HL above threshold, suggesting that the encoding of high intensity signals may be disrupted by an auditory nerve disorder.

The demonstration in these children of an episodic hearing deficit compatible with a demyelinating disorder of auditory nerve in the presence of normal cochlear outer hair cell functions emphasizes the importance of establishing criteria to distinguish among the varieties of hearing loss, including auditory nerve dysfunction (neural deafness), sensory receptor disorders (sensory deafness), and mixed impairments of both nerve and receptors (sensorineural deafness). The results from ABRs and OAEs appear to be important for distinguishing among the various hearing disorders.

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References

Achor, J., & Starr, A. (1980). Auditory brain stem responses in the cat I. Intracranial and extracranial recordings. *Electroencephalography and Clinical Neurophysiology*, 48, 154-173. [[Context Link](#)]

- Alexander, M., Thomas, S. V., Mohan, P. K., & Narendranathan, M. (1995). Prolonged brainstem auditory evoked potential latencies in tropical pancreatic diabetics with normal hearing. *Electroencephalography and Clinical Neurophysiology*, 35, 95-98. [\[Context Link\]](#)
- Berlin, C. I., Hood, L. J., Cecola, P., Jackson, D. F., & Szabo, P. (1993). Does type I afferent neuron dysfunction reveal itself through lack of efferent suppression? *Hearing Research*, 65, 40-50. [Bibliographic Links](#) | [\[Context Link\]](#)
- Cassandro, E., Mosca, F., Sequino, L., De Falco, F. A., & Campanella, G. (1986). Otoneurological findings in Friedreich's ataxia and other inherited neuropathies. *Audiology*, 24, 84-91. [Bibliographic Links](#) | [\[Context Link\]](#)
- Chaudhry, V., Crawford, T. O., & DeRossett, S. E. (1993). Thermal sensitivity in demyelinating neuropathy. *Muscle and Nerve*, 16, 301-306. [\[Context Link\]](#)
- Collet, L., Kemp, D. T., Veuillet, E., Duceaux, R., Moulin, A., & Moron, A. (1990). Effect of contralateral auditory stimuli on active cochlear micro-mechanical properties in human subjects. *Hearing Research*, 43, 251-261. [\[Context Link\]](#)
- Deltenre, P., Mansbach, A. L., Bozet, A., Clercx, A., & Hecox, K. E. (1997a). Auditory neuropathy: A report on three cases with early onsets and major neonatal illnesses. *Electroencephalography and Clinical Neurophysiology*, 104, 17-22. [\[Context Link\]](#)
- Deltenre, P., Mansbach, A. L., Bozet, A., Clercx, A., & Hecox, K. E. (1997b). Temporal distortion products (kernal slices) evoked by maximal-length-sequences in auditory neuropathy: Evidence for a cochlear pre-synaptic origin. *Electroencephalography and Clinical Neurophysiology*, 104, 14-21. [\[Context Link\]](#)
- Don, M., & Elberling, C. (1996). Use of quantitative measures of auditory brain-stem response peak amplitude and residual background noise in the decision to stop averaging. *Journal of the Acoustical Society of America*, 99, 491-499. [\[Context Link\]](#)
- Gorga, M., Stelmachowicz, P. G., Barlow, S. M., & Brookhouser, P. E. (1995). Case of recurrent reversible, sensorineural hearing loss in a child. *Journal of the American Academy of Audiology*, 6, 163-171. [\[Context Link\]](#)
- Hardin, A. (1995). From the syndrome of Charcot, Marie and Tooth to disorders of peripheral myelin proteins. *Brain*, 118, 809-818. [\[Context Link\]](#)
- Jabbari, B., Coats, M., Salazar, A., Martin, A., Scherokman, B., & Laws, W. A. (1993). Longitudinal study of EEG and evoked potentials in neurologically asymptomatic HIV infected subjects. *Electroencephalography and Clinical Neurophysiology*, 86, 145-151. [\[Context Link\]](#)
- Kaga, K., Nakumura, M., Shinogami, M., Tsuzuku, T., Yamada, K., & Sindo, M. (1996). Auditory nerve disease of both ears revealed by auditory brainstem responses, electrochleography and otoacoustic emissions. *Scandinavian Audiology*, 25, 233-238. [\[Context Link\]](#)
- Kalaydjieva, L., Hallmayer, J., Chandler, D., Savov, A., Nikolova, A., Angelicheva, D., King, R. H., Ishpekova, B., Honeyman, K., Calafell, F., & others. (1996). Gene mapping in Gypsies identifies a novel demyelinating neuropathy on chromosome 8q24. *Nature Genetics*, 14, 214-217. [\[Context Link\]](#)
- Kiernan, M. C., Mogyoros, I., & Burke, D. (1996). Differences in the recovery of excitability in sensory and motor axons of human median nerve. *Brain*, 119, 1099-1105. [Bibliographic Links](#) | [\[Context Link\]](#)
- Moller, A. R., Jennetta, P. J., Sekhar, L. N. (1988). Contributions from the auditory nerve to the brainstem auditory evoked potentials (BAEP's): Results of intracranial recordings in man. *Electroencephalography and Clinical Neurophysiology*, 48, 151-160. [\[Context Link\]](#)
- Nelson, K. R., Gilmore, R. L., & Massey, A. (1988). Acoustic nerve-conduction abnormalities in Guillain-Barre syndrome. *Neurology*, 38, 1263-1266. [Bibliographic Links](#) | [\[Context Link\]](#)
- Nicholson, G., & Corbett, A. (1996). Slowing of central conduction in X-linked Charcot-Marie-Tooth neuropathy shown by brain stem auditory evoked responses. *Journal of Neurology, Neurosurgery and Psychiatry*, 61, 43-46. [\[Context Link\]](#)
- Pareyson, D., Scaioli, V., Berta, E., & Sghirlanzoni, A. (1995). Acoustic nerve in peripheral neuropathy: A BAEP study. Brainstem auditory evoked potentials. *Electromyography and Clinical Neurophysiology*, 35, 359-364. [\[Context Link\]](#)
- Quattrone, A., Gambardella, A., Bono, F., Aguglia, U., Bolino, A., Bruni, A. C., Montesi, M. P., Oliveri, R. L., Sabetelli, M., Tamburrini, O., & others. (1996). Autosomal recessive hereditary motor and sensory neuropathy with focally folded myelin sheaths: Clinical, electrophysiologic, and genetic aspects of a large family. *Neurology*, 46, 1318-1324. [\[Context Link\]](#)

Raglan, E., Prasher, D. K., Trinder, E., & Rudge, P.(1987). Auditory function in hereditary motor and sensory neuropathy(Charcot-Marie-Tooth Disease) *Acta Otolaryngology (Stockholm)*, 103, 50-55. [\[Context Link\]](#)

Ragno, M., Curatola, L., Rossi, R., & Salvolini, U.(1992). Clinical multimodal electrophysiological study of a family with progressive cerebellar ataxia and late deafness and an autosomal recessive inheritance. *Acta Neurologica*, 14, 431-439. [Bibliographic Links](#) | [\[Context Link\]](#)

Razminsky, M. (1973). The effect of temperature on conduction in demyelinated single nerve fibers. *Archives of Neurology*, 28, 287-292. [\[Context Link\]](#)

Sakaguchi, H. (1994). Electrocochleography in deaf subjects. *Journal of Oto-Rhino-Laryngology*, 56, 133-136. [\[Context Link\]](#)

Salomon, G., & Starr, A. (1964). Electromyography of middle ear muscles in man during motor activities. *Acta Neurologica Scandinavia*, 39, 161-168. [\[Context Link\]](#)

Saul, R. F., Hayat, G., & Selhorst, J. B. (1995). Visual evoked potentials during hyperthermia. *Journal of Neuro-Ophthalmology*, 15, 70-78. [Ovid Full Text](#) | [Bibliographic Links](#) | [\[Context Link\]](#)

Sawada, M. (1979). Electrocochleography of ears with mumps deafness. *Archives of Otolaryngology*, 105, 475-478. [\[Context Link\]](#)

Scaioli, V., Pareyson, D., Avanzini, G., & Sghirlanzoni, A.(1992). F response and somatosensory and brainstem auditory evoked potential studies in HMSN type I and II. *Journal of Neurology, Neurosurgery and Psychiatry*, 55, 1027-1031. [\[Context Link\]](#)

Starr, A. (1978). Sensory-evoked potentials in clinical disorders of the nervous system. *Annual Review of Neurosciences*, 1, 103-127. [\[Context Link\]](#)

Starr A., McPherson, D., Patterson, J., Don, M., Luxford W., Shannon, R., Sininger, Y., Tonakawa, L., & Waring, M. (1991). Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. *Brain*, 114, 1157-1180. [Bibliographic Links](#) | [\[Context Link\]](#)

Starr, A., Picton, T. W., Sininger, Y., Hood, L. J., & Berlin, C. I. (1996). Auditory neuropathy. *Brain*, 119, 741-753. [Bibliographic Links](#) | [\[Context Link\]](#)

Starr, A., & Zaaroor, M. (1990). Eighth nerve contributions to cat auditory brainstem responses (ABR). *Hearing Research*, 48, 151-160. [Bibliographic Links](#) | [\[Context Link\]](#)

Stein, L., Tremblay, K., Pasternak, J., Banerjee, S., Lindemann, M. A., & Kraus, N. (1996). Brainstem abnormalities in neonates with normal otoacoustic emissions. *Seminars in Hearing*, 17, 197-212. [Bibliographic Links](#) | [\[Context Link\]](#)

Reference Notes

1 Gellnet, D., Sumida, A., Nilsson, M., Soli, S. D. (1994). *Development of the hearing in noise test for children (HINT-C)*. Presented at the 6th annual American Academy of Audiology convention, Richmond, VA. [\[Context Link\]](#)

2 Gellnet, D., Nilsson, M., Soli, S. D., & Sumida, A.(1996). *Development of the hearing in noise test for children(HINT-C)*, Technical Report, House Ear Institute, Los Angeles, CA. [\[Context Link\]](#)

IMAGE GALLERY

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Table 1

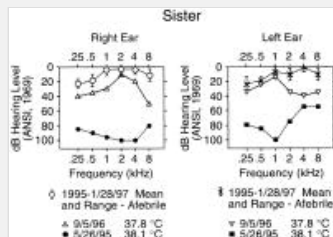


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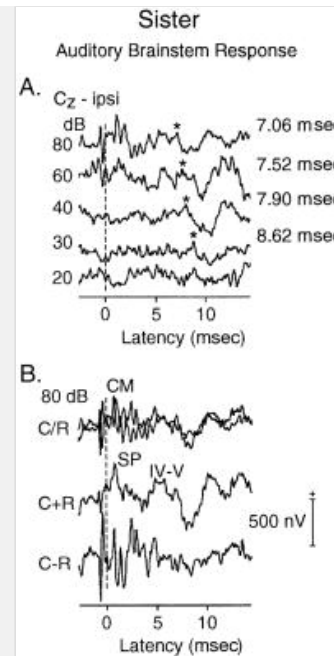


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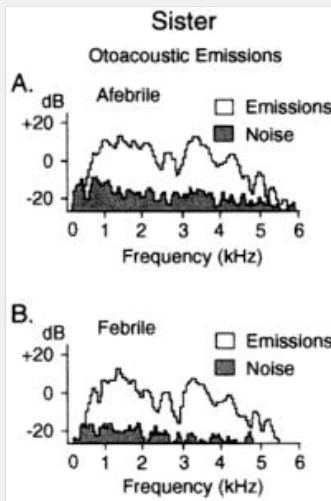


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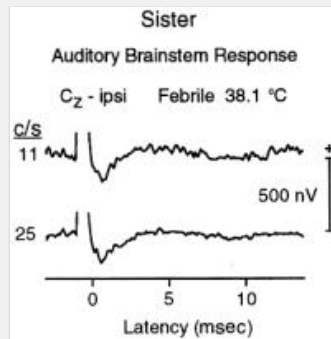


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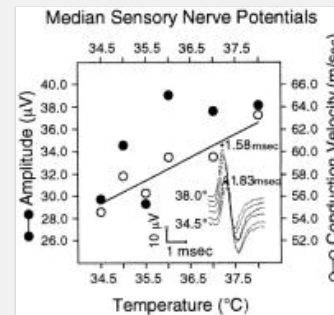


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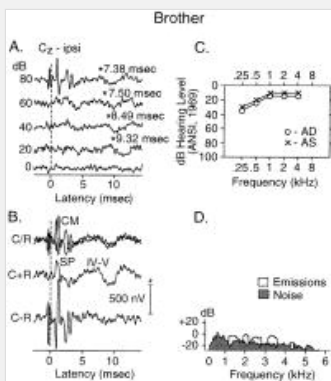


Figure 6

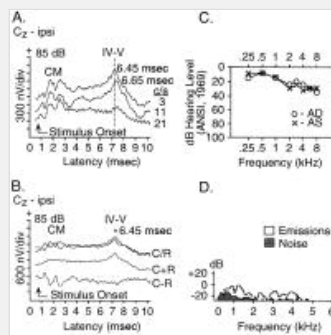


Figure 7

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