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Familial temperature-sensitive auditory neuropathy/auditory dyssynchrony

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Auditory neuropathy/auditory dyssynchrony is a hearing disorder characterized by impairment of neural synchrony in the presence of a normal cochlear outer hair cell function. Clinical findings are normal hearing or sensorineural hearing loss, absent/abnormal auditory brainstem response, normal otoacoustic emissions, normal cochlear microphonics, and poor speech perception abilities that are disproportionate to the hearing sensitivity.

We identified 5 patients, all related, with auditory neuropathy. Pure-tone audiometry, acoustic immittancemetry, evoked potentials, otoacoustic emission tests, and magnetic resonance imaging were performed on all of them. We followed the patients for 5 years.

We determined that their audiologic findings showed variations when they had influenza, due to high body temperature.

Auditory neuropathy/auditory dyssynchrony (AN/AD) is a hearing disorder characterized by an impairment of neural synchrony, in the presence of a normal cochlear outer hair cell function.[1] Clinical findings are normal hearing or sensorineural hearing loss, absent/abnormal auditory brainstem response (ABR), normal otoacoustic emissions, normal cochlear microphonics, and poor speech perception abilities that are disproportionate to the hearing sensitivity.[2]

Possible sites of auditory neuropathy include the inner hair cells, tectorial membrane, and synaptic juncture of the inner hair cells, auditory neurons in the spiral ganglion, and the VIIIth nerve fibers, or a combination of the three[3,4]. Neural problems may involve axonal or demyelization pathologies. Afferent and efferent pathways may be involved. Audiometric and electrophysiologic findings are consistent with retro outer hair cell dysfunction, though the exact site of the pathology is unknown.[5]

Age range of patients with AN varies from newborn to adult. Hereditary, metabolic, toxic, or neonatal problems-hyperbilirubinemia, asphyxia, and intracranial hemorrhage-are etiologies of AN reported in the literature.[6,7]

The prevalence of AN/AD is not known, but diagnosis rate has increased significantly since the routine use of otoacoustic emissions (OAE) testing.

AN/AD presents as heterogeneous hearing loss clinically and genetically. The case we are presenting is an example of hereditary AN/AD. Five members of the same family were examined in our clinic and diagnosed with AN/AD susceptible to temperature.

Initially, a 29-year-old woman presented with auditory neuropathy. She complained of hearing difficulty and poor speech discrimination. Family history revealed relatives with similar complaints. We eventually saw these relatives for audiologic evaluation.

Four relatives were also diagnosed with AN/AD. We followed all 5 patients for 5 years. We noted that their audiologic findings varied when their body temperature was high due to influenza.

The aim of the study is to present a case report of 5 patients with AN/AD and fluctuating hearing thresholds due to high fever.

MATERIALS AND METHODS

Pure-tone audiometry: Air- and bone-conducted pure-tone audiometry was performed in the range of 250 to 8000 Hz and 500 to 4000 Hz, respectively. Speech tests included speech reception threshold and monosyllabic speech discrimination and were applied at 40 dB SL or maximum levels of audiometer due to the patient's hearing thresholds. Marmara University Monosyllabic Word Lists in Turkish were used for evaluating speech discrimination. Speech discrimination tests were repeated with a speech to noise ratio of 10 dB.

Acoustic immitancemetry: Tympanometry and acoustic reflex measurements were performed. Tympanograms were considered normal when middle ear pressure was ≥75 mm H2O. Pure-tone stimuli at 500 to 4000 Hz were used for measurement of acoustic reflexes. The reflexes were measured in both ipsilateral and contralateral conditions. Maximum stimulus level was 110 dB.

Evoked responses: Standard clinical ABR audiometry and middle latency response (MLR) audiometry were recorded using Intelligent Hearing Systems (Miami, Fla) and Amplaid MK 15 (Amplifon; Milan, Italy) evoked systems with electroencephalographic electrodes placed on the vertex (Cz), ground (Fpz), and each earlobe (A1 and A2). Click stimuli of 100 ms' duration, intensity of 90 dB nHL, and repetition rate of 11/s were used in ABR recordings. A band pass filter from 100 to 2500/3000 Hz was applied, and 1024 sweeps were averaged and analyzed using a 10-ms time window. Alternating polarity was used in the first ABR recordings. Later recordings were obtained with condensation and rarefaction polarities and were compared to observe cochlear microphonics.

In MLR recordings, click stimuli of 100 ms' duration, intensity of 90 dB nHL, and repetition rate of 4/s were used. A band pass filter from 5 to 1500 Hz was applied, and 500 sweeps were averaged and analyzed using a 100-ms time window.

OAE: An Otodynamics ILO-92 (Otodynamics Ltd, Hatfield, Herts, England) was used for transient evoked otoacoustic emission (TEOAE). Nonlinear click levels

were 80 dBpSPL (±3 dB). OAE was accepted as present if overall response amplitude was at least 3 dB and waveform reproducibility in at least 3 octave bands was >75 %.

Magnetic resonance imaging (MRI): Cranial MRI was performed on all patients.

Study group: Five patients, aged 4 to 52 years, participated in this study. They were close relatives.

The demographic information of all patients are listed below. Age at first referral to the clinic is indicated.

Case 1: ŞK

ŞK was a 29-year-old woman who complained of hearing loss and poor speech discrimination. She reported occasional tinnitus like a breathing sound bilaterally. She had difficulty distinguishing words when on the phone. She emphasized that the severity of these symptoms fluctuated. She had a history of high fever throughout her childhood, but no history of systemic illness.

Case 2: HE

HE, 52 years old, complained of an inability to discriminate speech during activities of daily life. She sometimes had high-pitched tinnitus and had had episodes of childhood deafness of 2 or 3 days' duration that carried over to adulthood. She had been treated medically for hypertension for 5 years. Additional medical history was unremarkable.

Case 3: HY

HY, now 9 years old, was premature at birth. As an infant, she had had 2 febrile episodes, one requiring hospitalization. Speech was delayed. Although she was adept at lipreading, her chief complaint was her inability to communicate with friends. She reported that her hearing became poorer "sometimes." There was no history of systemic illness.

Case 4: ÖY

ÖY was a 42-year-old man. He complained of hearing loss when he had influenza. There was no history of systemic illness.

Case 5: RY

RY was 4 years old. His family complained that he didn't respond to them from time to time. He was born at 39 weeks' gestation. There was no illness in his anamnesis.

A common characteristic of all 5 patients was the deterioration in hearing when they had influenza. After the first evaluation, control programs were arranged. Further, they were asked to come for retesting when they had episodes of diminished hearing.

The tests were repeated in 6-month intervals over 5 years. Apart from the scheduled audiologic evaluations, the number of retests performed when they felt their hearing became poorer varied for each patient, ranging from 2 to 6. In all poor-hearing episodes, we determined that they had high fever (37.5˚C-39˚C). The pure-tone thresholds were averaged separately for febrile and afebrile periods.

RESULTS

MRI and neurologic examination of all patients were normal. Results from audiometry battery follow.

Afebrile evaluations:

• Pure-tone thresholds showed differences from normal to moderate sensorineural hearing loss (Figure 1a). Speech recognition thresholds were consistent with the pure-tone tests. Speech discrimination scores varied from 64% to 96% in quiet and from 24% to 4% in the presence of noise (Table).

Table 1. Average speech discrimination scores for each patient's right ear in febrile and afebrile evaluations.

Patients	Afebrile Speech Discrimination (%)	Febrile Speech Discrimination (%)
1 (ŞK)	80	0
2 (HE)	96	28
3 (HY)	96	20
4 (ÖY)	76	24
5 (RY)	64	0

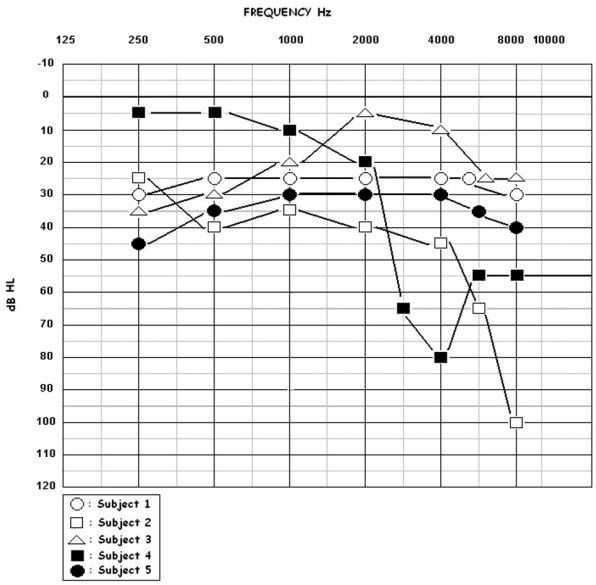


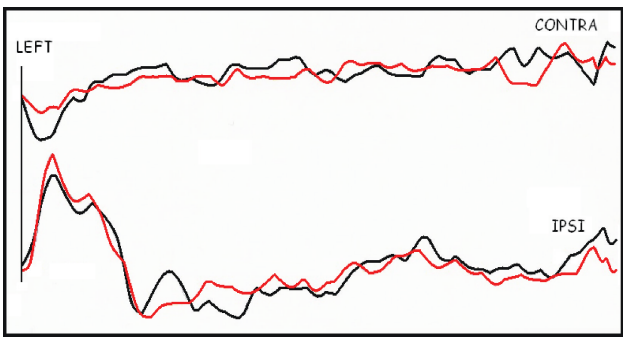
Figure-1a: Average pure-tone thresholds for each patient's right ear in afebrile evaluations.

• Tympanograms were normal bilaterally. Acoustic reflexes were absent for both ears from 500 to 4000 Hz, but contralateral reflex was present with right ear stimulation at 1000 Hz only in 1 patient.

• TEOAEs were present with the amplitudes of 3 dB or more in all frequency bands bilaterally.

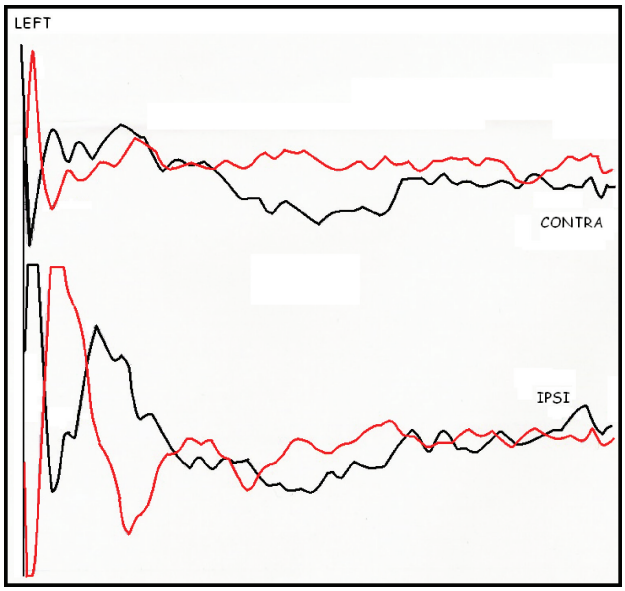
• The ABR results showed no repeatable response at 90 dB nHL bilaterally (Figure 2). Cochlear microphonics were observed when condensation and rarefaction polarities were used (Figure 3).

• The MLRs were present.



Contra = contralateral; ipsi = ipsilateral.

Figure-2: Auditory brainstem response recordings were obtained with alternative polarity.



Contra = contralateral; ipsi = ipsilateral.

Figure-3: Auditory brainstem response recordings were obtained with condensation and rarefaction polarities.

Febrile evaluations:

• Pure-tone thresholds indicated mild to profound sensorineural hearing loss (Figure 1b). Speech discrimination scores varied from 28% to no response in quiet. We added noise only for the patients in whom we obtained a speech recognition score in quiet.

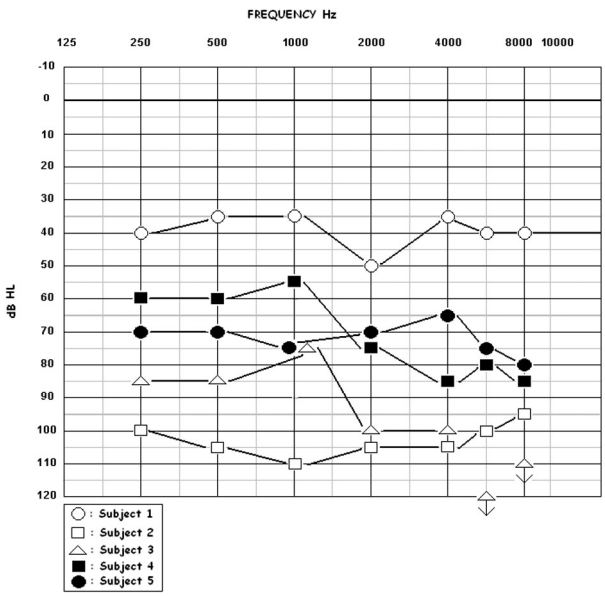


Figure-1b: Average pure-tone thresholds for each patient's right ear in febrile evaluations.

• Tympanometry results did not change in any session. Ipsilateral and contralateral acoustic reflexes were absent for both ears from 500 to 4000 Hz.

• OAEs were normal; the amplitudes were more than 3 dB in all frequency bands bilaterally.

• There were no repeatable responses at 90 dB nHL bilaterally in ABR audiometry. Cochlear microphonics were observed.

• The MLRs were present.

DISCUSSION

AN/AD are disorders of stimulus-timing-related neural synchrony in auditory perception where synchrony is important for understanding speech in the presence of noise.[8]

In identifying AN/AD, psychophysical tests and auditory-evoked potentials should be applied. Patients with AN/AD should have absent or abnormal ABRs, absent middle ear reflexes, normal OAEs, and cochlear microphonic responses that invert with stimulus polarity. Unfortunately, OAE sometimes disappears during the patient's life span.

According to Kim and colleagues, evaluation of outer hair cell function by OAE or cochlear microphonics will clarify diagnosis of AN/AD in families with nonsyndromic deafness.[9] In this study, no evidence of cranial or peripheral neuropathies was seen, and intrafamilial variability was quite common.[9]

In our study, 5 members of the same family were referred to our clinic complaining of difficulty in understanding. After applying the listed test batteries, we diagnosed AN/AD. Our patients' elevated hearing thresholds and degraded speech discrimination scores due to influenza resembled that of patients in a study by Starr and colleagues.[7] Our patients and those in the Starr study had fluctuating hearing so they all learned lipreading at a young age. They had normal articulation and intelligible speech. None of them had used hearing aids.

Starr and colleagues reported on 3 children with transient deafness due to temperature-sensitive auditory neuropathy.[7] Under febrile condition, hearing thresholds were elevated and speech understanding worsened. When these children were tested in the afebrile condition, their hearing sensitivity promptly returned, and their speech scores ameliorated as had happened in our 5 patients. Our patients, however, had dissimilar audiograms and were dissimilar to Starr's patients in ABR results. During the afebrile term, we could not obtain ABR components in any patients. We could only detect summation potentials and cochlear microphonics by inverting the polarity.

Auditory neuropathy comprises a spectrum of problems that affect the auditory pathway from the inner hair cell, such as loss or malfunction of the inner hair cells or a disruption of the driving force for the inner hair cell known as the endocochlear potential. Hearing deficit can also be the result of abnormal transmission of neural signals through the auditory pathway or disordered processing of these signals in the auditory brainstem.[3,10] In contrast, preserved OAEs and cochlear microphonics reflect the integrity of function of outer hair cells in the cochlea.

According to studies by Starr and colleagues in 1991 and Rasminsky and Sears in 1972, maintenance of nerve transmission in the paranodal region of demyelinated axons is temperature dependent and even a slight elevation of temperature can rapidly inactivate the voltage-dependent Na+ channels and cause failure of impulse generation.[3,11,12] Discontinuity of "saltatory conduction" affects temporal information contained in auditory signals. High body temperature is consistent with demyelinating neuropathy of the auditory nerve.

Test results that are markedly abnormal and do not change due to body temperature include brainstem reflex to acoustic stimulation involving middle ear muscles and olivocochlear projections.

The 5 patients reported in this paper are quite similar to the patients reported by Starr and colleagues.[7] Their hearing thresholds and speech test scores were aggravated in the febrile condition; they resolved in the afebrile condition. All 5 had absent middle ear muscle reflexes in the presence of normal tympanograms showing the auditory nerve pathology. The OAEs were obtained in both conditions indicating that the peripheral

auditory system was not affected. Starr suggested a genetic link as the cause of the temperature-sensitive deafness characteristic of AN/AD in his 3 patients.[7]

In separate studies, Butinar and Kalaydjieva and their colleagues studied Romani families and have identified hereditary auditory-vestibular and sensory neuropathies.[13,14] Leonardis and colleagues studied another Romani group and mapped the locus of the gene located on the long arm of chromosome 8 (8q 24).[15]

The complexity of AN/AD suggests that there is no single etiology responsible for its development. In previous reports, a number of etiologies and pathophysiologies were described for AN/AD.[5,16] These includes partial generalized metabolic or toxic neuropathy, genetic or hereditary factors, immune or inflammatory disorders, and infectious processes.

Blood analyses performed on these patients may explain the genetics of this disorder. As the number of AN/AD patients grows and further study on its etiology and pathophysiology is carried out, the exact gene locus and underlying causes will become more clear.

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