Case Report: Temperature-sensitive Recurrent, Reversible Auditory Neuropathy in Two Iranian Siblings

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Citation: Yazdani N, Ahadi M. Temperature-sensitive Recurrent, Reversible Auditory Neuropathy in Two Iranian Siblings. Iranian Rehabilitation Journal. 2021; 19(3):337-342. http://dx.doi.org/10.32598/irj.19.3.1411.1

http://dx.doi.org/10.32598/irj.19.3.1411.1

Article info:
Received: 08 Aug 2021
Accepted: 22 Aug 2021
Available Online: 01 Sep 2021

Keywords:
Auditory neuropathy, Temperature-sensitive, Case reports, Consanguineous marriage

ABSTRACT

Two sibling cases with a temperature-sensitive form of auditory neuropathy from a consanguineous marriage of Iranian descent have been described. They complained about the temporary loss of hearing and compromised speech comprehension after a slight fever or elevating the body temperature by vigorous exercises. A series of tests including brain MRI, pure-tone audiometry, speech audiometry in quiet and noise, tympanometry, reflexometry, TEOAEs, cochlear microphonic, and ABR were performed in a 24-hours interval at both febrile and afebrile states, and results are reported here. This report is the first example of temperature-sensitive auditory neuropathy in this geographical region.

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Highlights

- Auditory neuropathy can be temperature dependent.
- Elevation of body temperature can affect the speech perception ability in patients with auditory neuropathy.
- Temperature-dependent form of auditory neuropathy almost always has a genetic cause.

Plain Language Summary

A rare form of sensory neural hearing loss caused by genetic inheritance is temperature-sensitive auditory neuropathy characterized by poor speech perception ability, especially in noisy environments. Increasing the body temperature after a high fever or physical activities can lead to the poor auditory performance of the patients, and this would be recurrent and reversible. Proper diagnosis of the condition is essential for the intervention and counseling with the families.

1. Introduction

Auditory neuropathy (AN) is a clinical disorder characterized by preserved cochlear outer hair cells function, along with a lesion within the inner hair cells and or auditory nerve [1]. The main diagnostic criteria of AN include the absent or severely abnormal Auditory Brainstem Responses (ABR), in the Presence Of Otoacoustic Emissions (OAE), and or cochlear microphonic (CM) [1, 2]. Other clinical hallmarks of AN encompass a varying degree of sensory neural hearing loss, absent acoustic reflexes, and poor speech perception far more than expected from behavioral audiogram [3].

Temperature-dependent deafness in patients suffering from AN is a rare isolated form of this condition in which hearing thresholds deteriorate with the elevation of the core body temperature. A few case reports exist in the literature that describes this puzzling disorder. Gorga et al. (1995) first reported a 10-year-old girl with several transient episodes of sudden sensorineural hearing loss during her life, usually after a mild illness [4]. No definitive diagnosis had been reached at that time [4]. Three years later, Starr et al. (1998) reported transient deafness due to temperature-sensitive AN in three children (two siblings, ages 3 and 6, and an unrelated child, age 15) when their core body temperature elevated as little as one degree [5].

Authors concluded that those children develop a conduction block of the auditory nerves when their core body temperature rose, most likely, to a demyelinating disorder of the auditory nerve [5]. Cianfrone et al. (2006) also reported a 10-year-old girl who had a temporary bilateral hearing loss, with normal distortion product otoacoustic emissions, and absent ABR when her core body temperature increased by low-grade fever or even exposure to the sun [6]. In the same year, Varga et al. (2006) reported two siblings with temperature-dependent AN, and their genetic analysis suggested that p.I515T mutation of the otoferlin (OTOF) gene is the cause of this condition [7]. Romanos et al. (2009) reported the second case of temperature-sensitive AN associated with mutations in OTOF in a Brazilian girl [8]. They described c.1841G>A and c.3239G>C mutations of the OTOF gene in compound heterozygosis [8]. Marlin et al. (2010) reported three siblings aged 10, 9, and 7 years from a consanguineous family affected by severe or profound hearing impairment when they were febrile [9]. The patients in the non-febrile condition had only a mild degree of hearing impairment. The authors found a novel mutation p.Glu1804del in exon 44 of OTOF. The mutation was found to be homozygous in those patients [9].

Another example of non-syndromic thermal-sensitive AN was also described by Wang et al. (2010) in a 7-year-old Chinese boy, whose phenotype was associated with a compound heterozygous expression of two mutant alleles in the OTOF gene, namely c.2975_2978delAG (p.Q994VfsX6), and c.4819C > T (p.R1607W) [10]. Lastly, Zhang et al. (2016) reported three unrelated Chinese 2- to 6-year-old children suffered from thermal-sensitive AN [11]. Their genetic analysis revealed that those three patients had OTOF homozygous or compound heterozygous mutations with the genotypes c.2975_2978delAG/ c.4819C>T, c.4819C>T/c.4819C>T, or c.2382_2383delC/c.1621G>A, respectively [11].

A review of the literature shows that clinical cases of temperature-sensitive AN remain rare, and their genetic origin is not still fully understood. Here, we report the clinical manifestation of recurrent, and reversible tem-

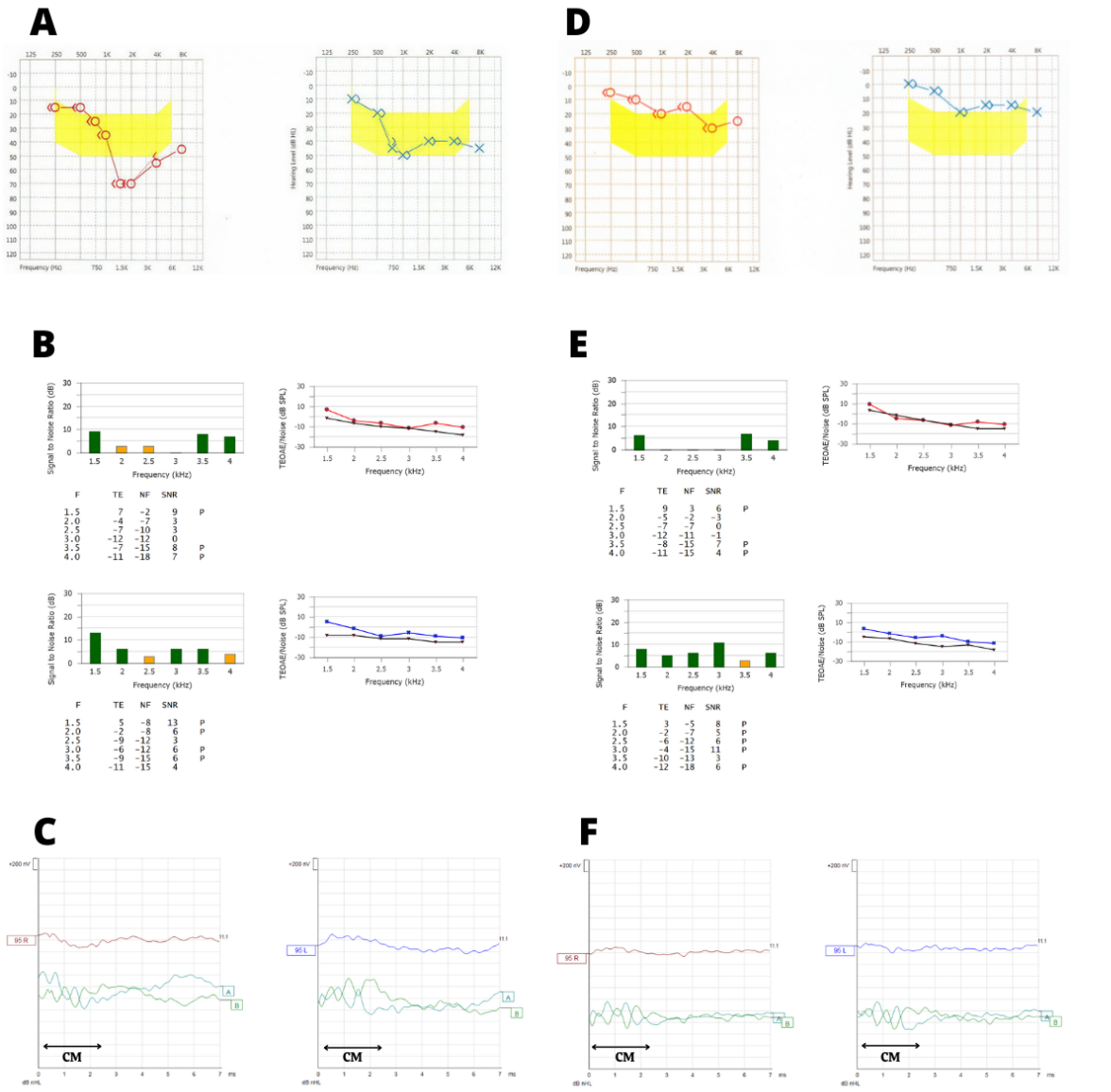

Figure 1. Audiological findings (Audiometry, TEOAE, CM, and ABR) of the Boy subject in febrile (Left Panel A, B, and C) and afebrile state (right panel D, E, and F).

Table 1. Subjects' Speech Recognition Tests (SRT) in quiet and noise, for both febrile and afebrile states

Speech Audiometry	Boy				Girl			
	Febrile		Afebrile		Febrile		Afebrile	
	Right	Left	Right	Left	Right	Left	Right	Left
SRT (dB)	55	55	20	25	30	35	25	25
WRS in Quiet (%)	32	20	92	100	52	40	96	92
WRS in Noise (%)	0	0	80	88	0	0	10	8

WRS: Word Recognition Scores.

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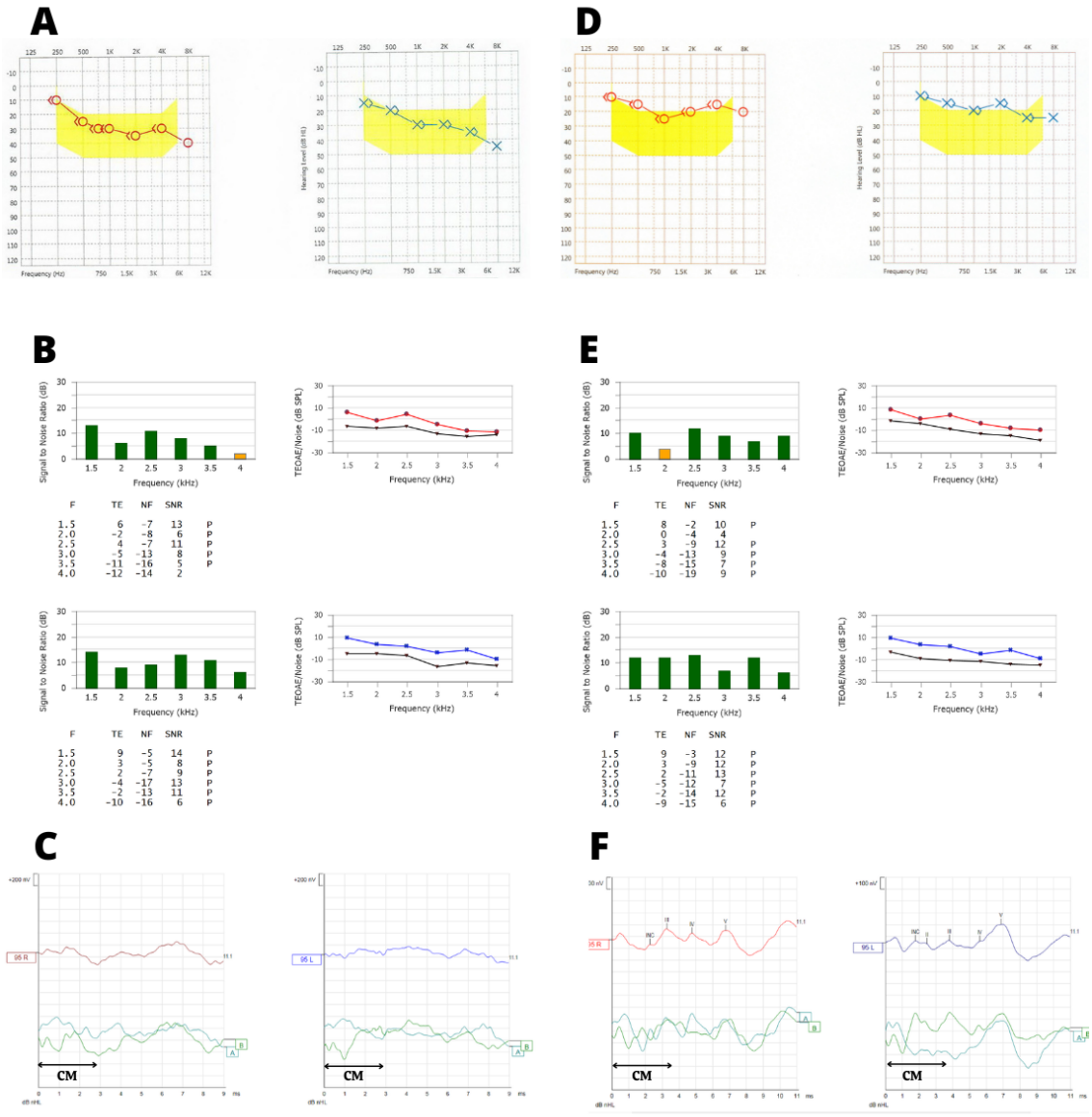

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Figure 2. Audiological Findings (Audiometry, TEOAE, CM, and ABR) of the Girl Subject in the Febrile (Left Panel A, B, and C) and Afebrile State (Right Panel D, E, and F)

perature-sensitive AN in two Iranian siblings from a consanguineous marriage.

2. Case Presentation

Two siblings (a 17-year-old girl and a 15-year-old boy) of Iranian descent from a consanguineous marriage were referred to Tehran Ear Clinic in June 2021 with the chief complaint of recurrent, reversible sudden deafness and communication difficulties after slight fever, or vigorous exercises such as mountain climbing or other sports activities, from early childhood. Episodes usually have lasted for several hours until they became afebrile or their body temperature decreased. Language acquisition was normal without any intervention, and they are doing great at school. However, their social functions are highly affected, and they prefer not to involve in team sports. Medical history was unremarkable, and they normally developed during childhood. No definite diagnosis has been made on previous medical examinations. The parents are first cousins, and the family history of hearing loss among them, grandparents, and extended family were negative. Written informed consent was obtained for participation in this study.

A series of medical examinations and audiological tests were performed over a 24-hour interval in both febrile and afebrile states. Patients came to the clinic with a high fever after a mountain climbing activity. After that, they were referred for brain MRI imaging which yielded essentially normal findings. Puretone audiometry (air and bone) for octave frequencies 250-8000 Hz was performed in a soundproof cabin by using Grason-Stadler (GSI) AudioStar Pro (Minneapolis, US). Speech recognition threshold (SRT) and word recognition scores (WRS) in quiet and ipsilateral noise were obtained using standard Persian open-set phonetically balanced disyllabic and monosyllabic word lists, respectively. Single-frequency tympanometry with a 226-Hz probe tone and acoustic stapedial reflexometry (500-4000 Hz, ipsilateral and contralateral to the stimulated ear) was also performed by using Grason-Stadler (GSI) TympStar Pro (Minneapolis, US). Frequency-specific transient evoked otoacoustic emissions (TEOAEs) were evaluated by MAICO Diagnostics ERO•SCAN (Berlin, Germany). Cochlear microphonic and ABRs were collected by interacoustics eclipse (Middelfart, Denmark) evoked potentials system, using a 2-channel vertical electrode montage. Determination of febrile and afebrile states was made based on core body temperature >38°C [9].

Both patients had several audiograms from the past years, which shows a wide range of hearing fluctuations from normal limits to profound hearing loss. Standard audiometry in our office, in the febrile state for the boy subject, showed normal-sloping-to-moderately severe Sensory Neural Hearing Loss (SNHL) on the right side and normal-sloping-to-moderate SNHL on the left side. However, in the afebrile state, only a slight high-frequency SNHL was observed in the right ear, and essentially normal hearing thresholds were obtained on the left side (Figure 1, A & D). Audiometry in the febrile state for the girl subject showed a mild bilateral SNHL, and hearing thresholds returned to normal limits in the afebrile state on both sides (Figure 2, A & D).

Evaluation of word recognition scores in the febrile state showed very poor performance in the quiet, unrelated to the hearing thresholds, and totally unresponsiveness in the noise for both subjects. However, in the afebrile state, both subject's performance remarkably improved in the quiet. The boy subject's scores in the noise also improved in an afebrile state, but the girl subject's scores remained close to zero. Table 1 summarizes the speech audiometry results for both subjects during febrile and afebrile states.

Tympanometric findings were consistent with normal middle ear function, but no middle ear stapedial reflex (ipsilateral or contralateral to stimulated ear) could be recorded at the maximum output of the instrument for both febrile and afebrile occasions. TEOAEs were bilaterally present at both test intervals, with acceptable signal-to-noise ratios (Figure 1 and 2, B & E). Large amplitude CM was also recognizable at the beginning of the ABRs by superimposing the responses to condensation and rarefaction stimuli at each recording session (Figure 1 and 2, C & F). In the boy subject, ABRs were absent even in the afebrile state, but delayed ABR response with detectable wave V could be recorded in the girl subject in the afebrile condition (Figure 1 and 2, C & F).

3. Discussion

Here, we have reported clinical findings of two Iranian siblings who suffered from recurrent, reversible hearing difficulties when febrile. Based on current diagnostic criteria, we concluded that they have temperature-sensitive auditory neuropathy, which is a rare form of AN. Audiological findings of these cases are following previous reports on temperature-sensitive AN [5, 6, 9-11] and include worsening of hearing thresholds and speech perception abilities with abnormal ABR, and normal outer hair cells function supported by observing CM and OAEs, after slight fever. An unexpected finding was the inconsistent relationship between the presence or absence of ABR with word recognition scores in noise. The boy subject did not show any recordable ABR at both febrile and afebrile states, but his WRS in noise was improved in afebrile condition. However, his sister showed recordable ABR in an afebrile state, but her WRS in noise remained close to zero.

The main causes of temperature-sensitive AN that have been reported in the literature include auditory nerve demyelination, with conduction block of nerve transmission [5], and mutations of the OTOF gene, which encodes otoferlin protein [7-11]. Although current subjects were not genetically analyzed, based on their parent's consanguineous marriage, mutation of the OTOF gene may be the reason for this condition. Otoferlin protein is heat sensitive, and this heat sensitivity is enhanced by specific mutations like Ile515Thr [12]. Further understanding of the site of lesion in this particular form of AN could be accessed by comprehensive genetic testing.

Unfortunately, there is little and unsupported evidence on the effective treatment or management of this type of AN. We advised our cases to use antipyretic agents (acetaminophen) and a medical thermometer to obtain an ac-

curate core body temperature. Initial parent's report after treatment with acetaminophen showed sooner recovery of compromised hearing ability after the elevation of body temperature. In conclusion, it should be emphasized that extensive audiological test battery and genetic tests could help diagnose this condition to improve the effectiveness of early intervention and family counseling.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained for participation in this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Both authors have equally participated in conceptualization, performing and analyzing the tests, writing and preparing the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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