



A case of auditory neuropathy revealed by OTOF gene mutation analysis in a junior high school girl

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Abstract

Objective: Congenital auditory neuropathy (AN) affects hearing and speech development. The degree of hearing difficulty in congenital AN varies as a function of pathology at the inner ear hair cell (IHC) synapses or the auditory nerve. We report a case of a Chinese girl with AN revealed by OTOF (otoferrin) gene mutation analysis who had only a mild hearing loss.

Patient: A 13-year-old Chinese girl was diagnosed as having congenital AN on the basis of OTOF gene mutation analysis. She manifest a mild sensorineural hearing loss with 50% maximum monosyllable speech discrimination rate, normal DPOAEs (distortion product otoacoustic emissions) beyond ambient noise levels, only SPs (summing potentials) evoked during ECoG (electrocochleography) and absent ABRs (auditory evoked brainstem responses) bilaterally to clicks presented at 100 dBnHL. She was able to effectively communicate with others by speech reading owing to her mild hearing loss. Moreover, bilateral hearing aids helped her to communicate.

Conclusions: Our patient was demonstrated to have a mutation on the OTOF gene. Nevertheless, she was able to communicate using auditory visual speech reading in spite of a mild auditory threshold elevation probably due to partial pathology at the IHC synapses or in the auditory nerve.

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Keywords: Auditory neuropathy; Auditory nerve disease; Auditory neuropathy spectrum disorders; OTOF; Speech discrimination

1. Introduction

Auditory neuropathy is a type of hearing disorder that is diagnosed on the basis of the absence of auditory brainstem responses (ABRs) but with normal otoacoustic emissions (OAEs). In 1996, Kaga et al. discerned and reported a new type of hearing loss called “auditory nerve disease” (AND) (Kaga et al. 1996). In that same year, Starr et al. also published an article describing a new disease which they termed “auditory neuropathy” (AN) (Starr et al., 1996). AND and AN are now considered to be the same entity pathophysiologically and

are collectively termed auditory neuropathy spectrum disorder (ANSND). Hearing levels in patients with ANSD can range from normal hearing to profound hearing loss. Only a few elements of the ECoG may be evoked. DPOAEs are found to be normal at levels above ambient noise levels. ABRs may be evoked but they are usually abnormal as manifest by prolonged wave latencies and poor wave morphologies.

Various etiologies underlying AN have been suggested in the literature. When AN is syndromic it can be caused by hyperbilirubinemia, anoxia, viral infection, high fever, or immunological disorders (Starr et al., 2000). When AN is non-syndromic, hereditary factors have been reported as a cause. OTOF gene mutations were found to be autosomal recessive in non-syndromic AN (Varga et al., 2003; Matsunaga et al., 2012) and they have been considered to underlie the

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pathogenesis of AN. However, the degree of hearing difficulty of AN patients varies. Most patients with OTOF gene mutations suffer profound hearing loss (Rodríguez-Ballesteros et al., 2003; Kaga, 2016; Rance and Starr, 2015). However, in this study we focus on a girl with OTOF gene mutations with only a mild hearing loss.

2. Case report

A 13-year-old Chinese girl was referred from China to the Tokyo Medical Center in Japan for investigation of the cause of her binaural hearing loss and no history of a balance disorder. She was born full-term with no complications in 2002. She walked independently at 14 months of age. Her language development was noted to be delayed at age 4. Her parents ultimately brought her to Dalian Children's Hospital in China and she was subsequently found to have a profound hearing loss bilaterally.

3. Audiological tests in China

Her parents then took her to Peking Tongren Hospital to undergo objective audiological tests in 2006 at age 4. The ABR and acoustic reflex threshold (ART) test results showed no response to stimuli for either test. She was advised to wear hearing aids and she began to wear them bilaterally. Two years later (2008), at age 6, she enrolled in a regular elementary school program.

In 2009, at age 7, she was reexamined at the Peking Tongren Hospital. Pure tone audiometry revealed a moderate hearing loss in the low-frequencies (75 dBnHL @ 250 Hz) with a rising slope pattern (45 dBnHL @ 8 kHz) (Fig. 1). ART, ABR, and tympanometry test results showed no improvement. DPOAEs were normal except at 4 kHz in the left ear and 2 kHz in the right ear. She continued to wear her binaural

hearing aids on a daily basis. Currently, at age 13, she is a first-year student in a regular junior high school. The audiological test results taken in China are summarized in Table 1.

She was very intelligent and she had good grades in school (she ranked 11th among 40 students in her class). She wrote a novel on her I-phone. She was able to communicate by speech reading and with the use of her hearing aids and she understood her mother's speech better than her father's. In noisy situations or when the weather changed from sunny to rain or when her body temperature increased, she felt that her hearing difficulty worsened. She complained of her poor speech discrimination on the telephone or when listening to TV or to radio broadcasts. She had neither particular contributing medical history nor familial hearing disorders and her pedigree did not show a consanguineous marriage. In 2015, at age 13, her parents took her to the Tokyo Medical Center for further evaluation of her auditory problems.

4. Audiological tests in Tokyo medical center of Japan

Bilateral pure tone audiometry at the Tokyo Medical Center in 2015 revealed a mild hearing loss in the low-frequencies (40 dBnHL @ 250 Hz) and a rising slope pattern (to 20 dBnHL @ 8 kHz) (Fig. 2). Speech audiometry for Japanese monosyllables showed a maximum discrimination rate of 50% in the right ear and 55% in the left ear (Chinese is her native language). However, a numeral hearing test for auditory perception resulted in a score of 100% bilaterally. On an environmental sound test for auditory perception without words, she scored 88% correct with picture matching and 42% correct without picture matching. The Token test of auditory comprehension (a test of receptive aphasia) (De Renzi and Vignolo, 1962) gave a score of 98% correct, $98 \pm 3\%$ being normal. This implicates that her auditory comprehension ability is completely normal. Again, DPOAEs were normal (Fig. 3). Click evoked ABRs at 100 dBnHL could not be evoked from either ear (Fig. 4a) (Table 2). The evoked ECoGs showed only the SPs (summating potentials) and no compound APs (action potentials) from the right ear and no responses from the left ear (Fig. 4b). It was not possible to evaluate the cochlear microphonics (CM) because of electrical artefacts generated by the headphones. Vestibular system evaluations (caloric testing with ice water irrigations and damped rotation chair testing) were normal. The finger-nose test was normal and postural control evaluation was normal. Genetic analysis revealed that her father and mother were heterozygous for OTOF gene mutations but she was homozygous for the gene.

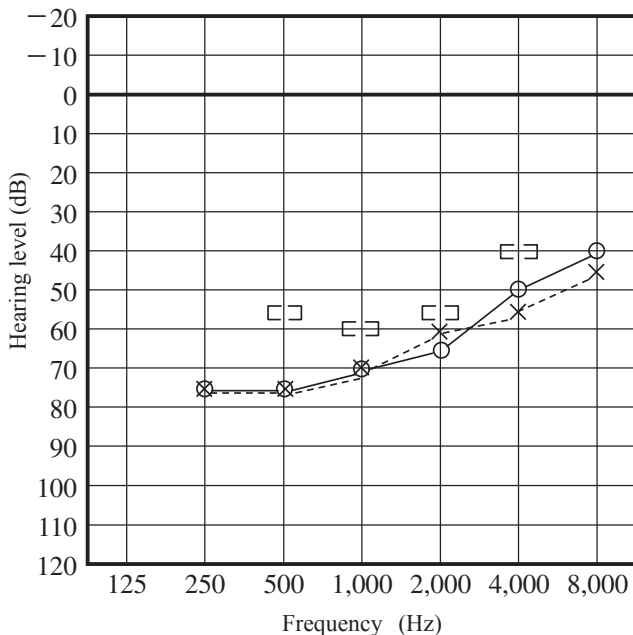


Fig. 1. Pure tone audiogram in China (2009).

Table 1
Audiological tests in China (2009).

	Right ear	Left ear
Pure tone audiometry (PTA)	65 dB	65 dB
Tympanometry	Type A	Type A
DPOAE	Normal beyond noise level	Normal beyond noise level
Click ABR	Absent	Absent

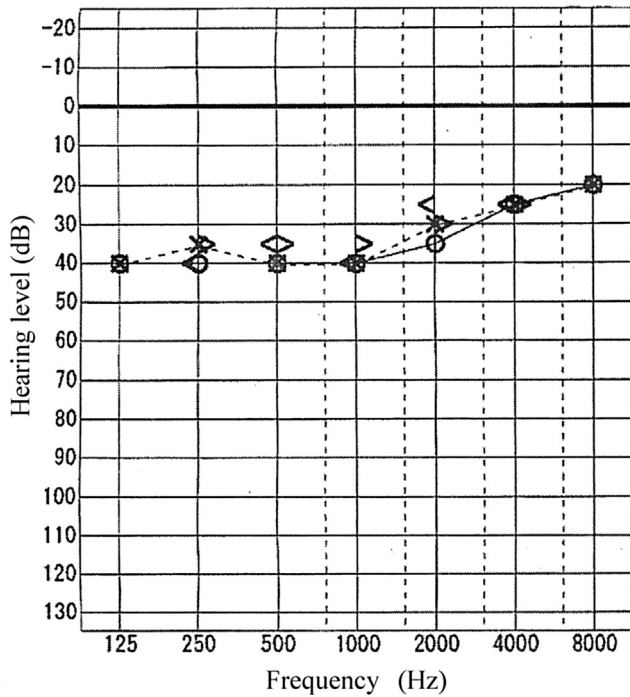


Fig. 2. Pure tone audiogram in Tokyo (2015).

5. Discussion

AN in adult is thought to be an acquired disorder characterized by mild-to-moderate pure tone hearing loss, poor speech discrimination and absence of the ABR, normal DPOAEs and only SPs evoked on ECoG testing (Kaga et al., 1996; Kaga, 2016). After the introduction of newborn hearing screening, the Colorado Children's Hospital group proposed a new term, ANSD (auditory neuropathy spectrum disorder), characterized by normal DPOAEs and absent ABRs in newborns (Northern, 2008).

Kaga (2016) proposed that the classification of ANSD should be parsed into three types.

- Type I – developmental changes which lead to normalization of the ABR and improved hearing levels.
- Type II – developmental changes which lead to profound hearing loss.
- Type III – chronic AN with normal DPOAEs and absent ABRs which do not change over time.

Type III has two subtypes:

Type IIIa, true AN and type IIIb, pseudo AN. Patients with Type IIIa has poor ability to acquire speech and hearing even when aided and good candidates for cochlear implantation. However, patients with pseudo AN have normal speech and normal hearing and do not require hearing aids (Kaga, 2016).

The patient presented in this report has a unique type of congenital AN as revealed by the OTOF gene mutation analysis. She had good auditory comprehension and language development despite having a mild low frequency hearing loss and poor speech discrimination scores.

In Varga et al. (2003), the OTOF gene mutation was the first mutation to be found to underly non-syndromic AN. The OTOF gene was originally found to be a locus that is linked to autosomal recessive, congenital, severe to profound hearing loss. In this report, the genetic analysis of this patient's parents showed that they carried the heterozygous OTOF gene mutation. Therefore, they were acoustically normal but their offspring could carry one of the three genotypes: heterozygote, dominant homozygote or recessive homozygote. Our patient was a recessive homozygote and she had AN. Most patients with OTOF gene abnormalities have profound hearing loss.

Congenital AN children can be trained to hear using hearing aids or they might have a cochlear implant (CI). Some children with AN have demonstrated that their audiometric hearing levels and their ABRs can spontaneously improve to normal levels without amplification and they may even develop normal speech without no intervention (Madden et al., 2002; Attias and Raveh, 2007). These children may have Type I – ANSD as described by Kaga (2016). Spontaneous recovery of hearing has been observed in children under the age

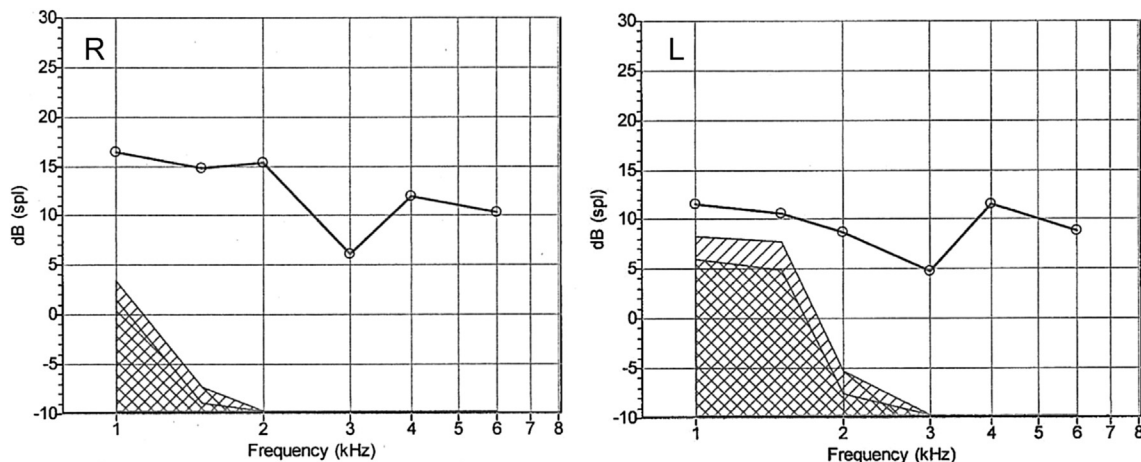


Fig. 3. Distortion product otoacoustic emission (DPOAE) (2015).

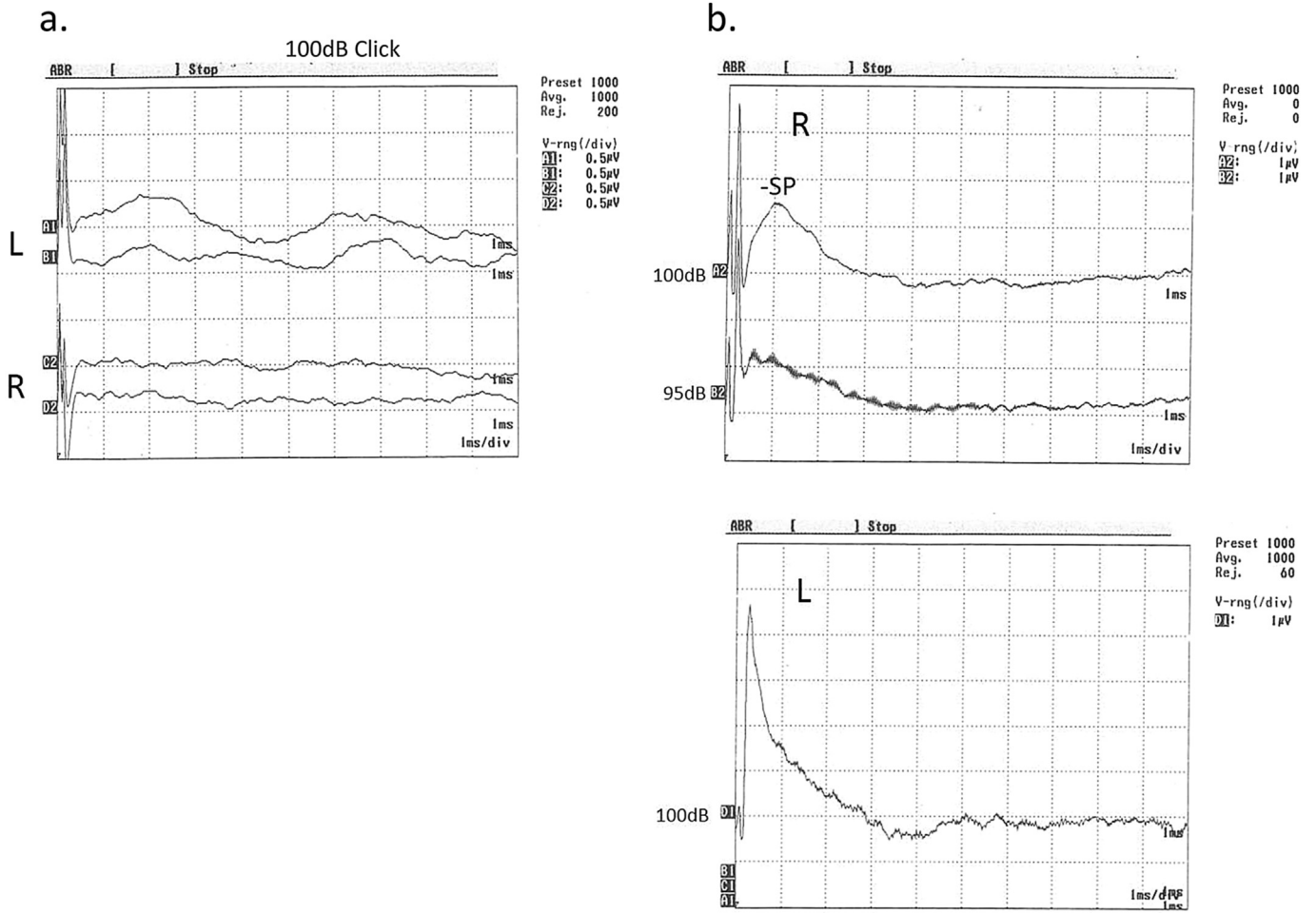


Fig. 4. ABR (a) and ECoG (b) (2015).

of one and half years. Therefore, before performing an invasive intervention in young children, doctors and parents should repeatedly assess the patient's auditory capacity, speech development and ABR and OAE findings to confirm whether AN is persistent or whether the child may spontaneously improve. In approximately 50% of children with AN, just the provision of hearing aid amplification results in significant speech perception improvement (Matsunaga et al., 2012). When hearing aids do not improve communication ability in AN patients, CI (cochlear implants) should be considered. The

use of CIs for AN is controversial and has constraints. Roush et al., reviewed the audiological management of ANSD in children and found fifteen of the 18 studies addressed the use of cochlear implantation and 4 addressed conventional acoustic amplification. All participants demonstrated improved auditory performance; however, all of the 18 studies were considered exploratory and many had methodological limitations (Roush et al., 2011). Several studies have indicated that there is wide variability in outcomes with children with AN who have received CIs (Attias and Raveh, 2007; Rouillon et al., 2006). However, Varga et al. (2003) and Rouillon et al. (2006) have reported the successful use of CIs for AN caused by OTOF gene mutations.

This case report of our patient had Type IIIa non-syndromic AN with no vestibular symptoms. However, a hearing aid was effective in improving her auditory comprehension and normal language development probably due to only partial pathophysiology of her IHC synapses or at the level of the auditory nerve. Therefore, in this case, we have concluded that CI is not indicated. It may be that Type IIIa AN can be subdivided into two subtypes: AN in which hearing aids are effective in improving communication; AN in which hearing aids are ineffective.

Table 2
Audiological tests in Tokyo (2015).

	Right ear	Left ear
Pure tone audiometry (PTA)	38 dBnHL	36 dBnHL
Tympanometry	Normal	Normal
DPOAE	Normal beyond noise level	Normal beyond noise level
Click ABR	Absent	Absent
Numerical perception	100% at 50 dB	100% at 55 dB
Token test	98% correct (Normal average, 96%)	

6. Conclusions

This patient with Type IIIa AN, as determined by audiological studies, was found to have an OTOF gene mutation. Nevertheless, we found it possible to use speech reading with hearing aids to improve this patient's communication, in spite of her mild threshold elevation, and probably because of only partial pathophysiology of her IHC synapses or of the auditory nerve.

Declaration of conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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