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Diverse etiologies manifesting auditory neuropathy characteristics from infants with profound hearing loss and clinical implications

Shin Hye Kim [a,b], Hyun Seok Choi [a], Young Eun Han [a], Byung Yoon Choi [a,c,*]

[a] Department of Otorhinolaryngology – Head and Neck Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea
[b] Department of Otorhinolaryngology – Head and Neck Surgery, Korea University Medical Center, Korea University College of Medicine, Seoul, Republic of Korea
[c] Sensory Organ Research Institute, Seoul National University Medical Research Center, Seoul, Republic of Korea

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ABSTRACT

Objective: Auditory neuropathy spectrum disorder (ANSD) is a hearing disorder with impaired signal transmission from the inner ear to the brain. The electrophysiological characteristics of auditory neuropathy (AN characteristics) are marked with presence of otoacoustic emissions (OAE) or cochlear microphonics (CM) in the absence of auditory brainstem response (ABR). This study aimed to review etiologies related to AN characteristics from infants with profound hearing loss (HL), either unilaterally or bilaterally.
Study design: Prospective cohort study for thirty infants with prelingual profound HL.
Methods: ABR, OAE, and/or CM were analyzed to identify electrophysiological characteristics. Temporal bone computed tomography and/or internal acoustic canal magnetic resonance imaging were reviewed to identify anatomical abnormalities. The electrophysiological characteristics and cochlear nerve status were analyzed according to the laterality of deafness (unilateral vs bilateral).
Results: Among the total 41 ears (from 30 infants) with profound HL, 13 ears (7 (36.8%) of 19 ears with unilateral HL and 6 (27.3%) of 22 ears associated with bilateral HL) showed AN characteristics (37.1%), and 21 ears showed cochlear nerve deficiency (CND) (51.2%). AN characteristics was detected about two times more frequently in cases with CND (38.1%) than with anatomically normal cochlear nerve (20.0%), the difference not reaching a statistical significance probably due to a small sample size. Detection of AN characteristics did not differ between unilateral and bilateral profound HL, even though presence of CND was more frequently detected in cases with unilateral profound HL than with bilateral cases. There were at least five types of etiologies related to AN characteristics in 13 ears (from 10 infants) in our series depending on the laterality of deafness and presence of CND.
Conclusions: This study demonstrates that there were diverse etiologies related to AN characteristics from infants with unilateral or bilateral profound HL. Association between CND and AN characteristics is suggestive but not solid at this moment and AN characteristics is not a fully penetrant feature of CND.

1. Introduction

Auditory neuropathy (AN) was first described by Starr et al in 1996 to describe 10 infants with hearing loss (HL) despite having normal cochlear outer hair cells [1]. Since then, numerous infants with absent auditory brainstem response (ABR) but normal cochlear outer hair cell function have been reported [2,3]. AN is defined as a hearing disorder whereby the sound enters the inner ear normally, but signal transmission from the inner ear to the brain is impaired. The electrophysiological characteristics of AN (AN characteristics) are described as having "absent ABR", while having normal otoacoustic emissions (OAE) or cochlear microphonics (CM).

While the preservation of OAE and CM indicates normal function of the outer hair cells, "absent ABR" suggests impaired function of the inner hair cells, the type 1 auditory neurons, or the auditory nerve. Patients with AN may have HL ranging from mild to severe; however, they always have poor speech-perception abilities. This seems to be associated with poor temporal resolution, likely caused by desynchronized neural discharges of the auditory nerve fibers [4]. The term, auditory neuropathy/dyssynchrony, is used based on such postulated hypothesis [5]. Nevertheless, the mechanism of AN has not yet been fully understood; thus, the term, auditory neuropathy spectrum disorder (ANSD), is used frequently [6]. ANSD is associated with impaired signal transmission from the inner ear to the brain, and it may be associated with damages to one or more

* Corresponding author at: Department of Otorhinolaryngology – Head & Neck Surgery, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam 463-707, Republic of Korea. Tel.: +82 31 787 7406; fax: +82 31 787 4057.
E-mail address: choiby@snubh.org (B.Y. Choi).

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of following sites: the inner hair cells, synapse between the inner hair cells and the cochlear nerve, and ascending auditory nerve itself.

Broad and various possible damaged sites suggest that AN characteristics may be manifested by diverse etiologies. Neonatal insults (hyperbilirubinemia and hypoxic damage) [7–9], alterations of certain deafness genes (autosomal recessive *Pejvakin*/DFNB59, *OTOF*/DFNB9, *GJB2*; autosomal dominant *AUNA1* and *PCDH9*; X – linked *AUNX1*; mitochondrial 12SrRNA T1095C and 12SrRNA A1555) [10,11], and even an anatomical defect of the cochlear nerve (small or absent cochlear nerve) [12] can potentially lead to infants exhibiting AN characteristics.

Knowing the correct etiology would significantly help in predicting the prognosis and outcome of hearing rehabilitation. However, it is not always feasible to identify a correct etiology from infants in a clinical setting. Given this, we intended to come up with a marker that can guide us to better determine the underlying etiology of AN characteristics.

2. Materials and methods

We prospectively recruited infants under 24 months of age with documented profound HL – either unilaterally or bilaterally – who were evaluated by both electrophysiological tests and imaging studies at Seoul National University Bundang Hospital, from May 2014 to April 2015 (IRB–B–1007 – 105 – 402). Availability of both ABR and OAE were mandatory for eligibility, and CM were also obtained whenever possible. The results of ABR, OAE, and/or CM were reviewed to identify the electrophysiological characteristics. Infants with syndromes related to HL were excluded. As a result, 30 infants (41 ears) were included.

AN characteristics were defined as having a presence of OAE despite absence of ABR. CM was the determined response to high level (80 and 90 dB normal hearing level [nHL]) click ABR, which was measured separately for condensation and rarefaction single polarity stimuli, and displayed with superimposing averages to identify out-of-phase components [13]. Separate measurements for condensation and rarefaction were always performed even in the absence of recognizable OAE and ABR. If OAE was absent, but CM was shown when measured separately for condensation and rarefaction, we regarded it as AN characteristics (Fig. 1).

Temporal bone computed tomography (TBCT) and internal acoustic canal magnetic resonance image (IAC MRI) were performed and reviewed to identify any potential anatomical abnormalities of the cochlear nerve and the end organ. ANSD was defined when AN characteristics were not associated with any anatomical abnormalities of the cochlear nerve. Accordingly, we divided AN characteristics into two categories: (1) ANSD with anatomically normal cochlear nerve, which indicated a problem with the inner hair cell, synapse dysfunction, or both, and (2) cochlear nerve deficiency (CND). If TBCT shows a narrow or stenotic bony cochlear nerve canal (BCNC), and IAC MRI shows a smaller cochlear nerve in diameter when compared with the adjacent facial nerve, we regarded it the findings of CND. One case without definite AN characteristics (stenotic BCNC and absent cochlear nerve) and another case with AN characteristics (narrow BCNC and small cochlear nerve) were presented as an example for the findings of CND (Fig. 2).

Of the included 30 infants, 20 were boys and 10 were girls, and the average age at the time of the final diagnosis was 9.2 months. Nineteen infants (63%) showed unilateral profound HL, and 58% of them were affected on the left side. Conversely, 11 infants (37%) showed bilateral profound HL. According to the laterality of deafness (unilateral vs bilateral), electrophysiological characteristics and anatomical findings were analyzed. Statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL). Non-continuous variables were compared using the Chi-square test or Fisher's exact test. An association between two variables was estimated by calculating the relative risk and 95% confidence interval; *p*-values of less than 0.05 were considered as significant.

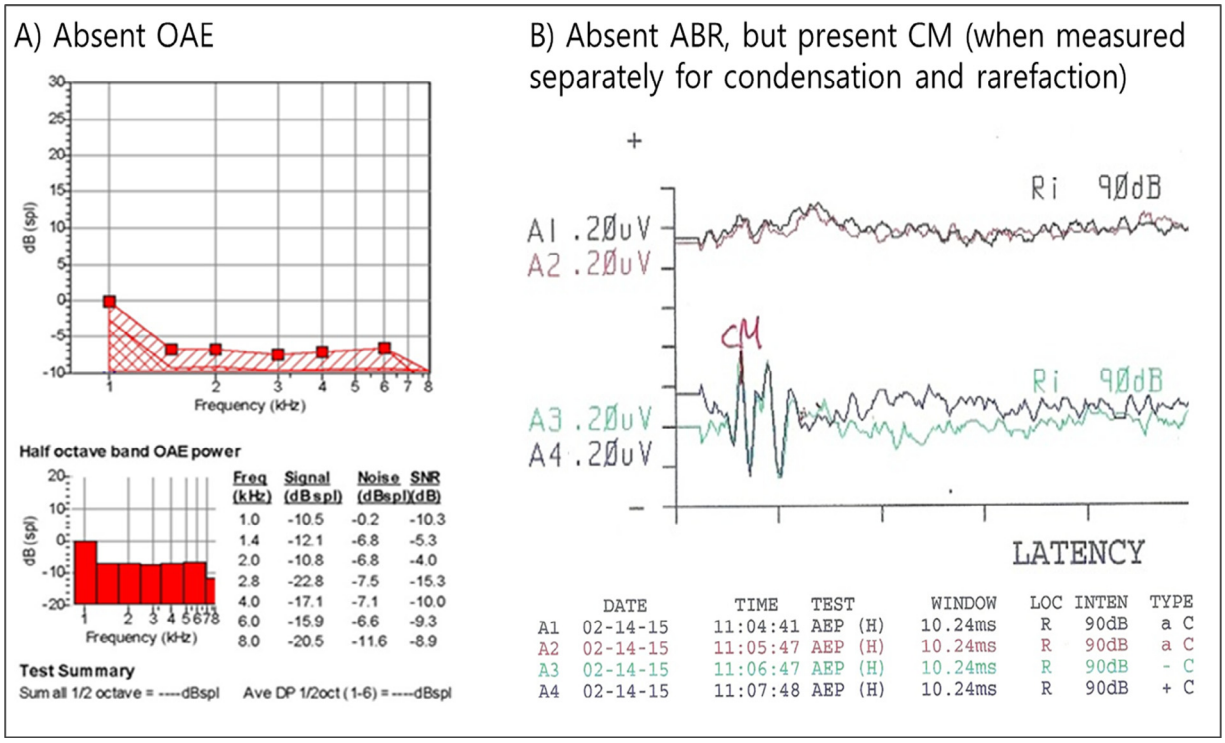

Fig. 1. Definition of AN characteristics: The findings of absent OAE (A), absent ABR, but present CM when measured separately for condensation and rarefaction (B) is regarded as AN characteristics. AN characteristics: electrophysiological characteristics of auditory neuropathy, OAE: otoacoustic emissions, ABR: auditory brainstem response, CM: cochlear microphonics.