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A nationwide study on enlargement of the vestibular aqueduct in Japan

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ABSTRACT

Objective: To document the clinical features and associated pure-tone audiometry data in patients with enlargement of the vestibular aqueduct (EVA), and to identify risk factors for fluctuating hearing loss (HL) and vertigo/dizziness in EVA patients.

Methods: In this nationwide survey in Japan, a first survey sheet was mailed to 662 board-certified otolaryngology departments to identify the ones treating EVA patients. A second survey sheet, which contained solicited clinical information and the results of the hearing tests, was mailed to all facilities that reported treating EVA cases. We analyzed clinical information, including age at the time of the most recent evaluation, gender, EVA side, age at onset, initial symptoms, precipitating factors, and etiology from survey responses, and assessed 4-frequency (500, 1000, 2000, and 4000 Hz) pure-tone average (PTA) from accompanying pure-tone audiometry data. A multivariate logistic regression analysis was utilized to identify the possible risk factors for fluctuating HL and vertigo/dizziness.

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Results: In total, 513 hospitals (response rate, 77.5%) responded to the first survey, and 113 reported treating patients with EVA. Seventy-nine out of the 113 hospitals (response rate 69.9%) responded to the second survey, and the data of 380 EVA patients were registered and analyzed. Of the 380 patients, 221 (58.2%) were female, suggesting female preponderance. The patient age ranged from 0 to 73 years (mean, 16.7 years; median, 13 years; interquartile range, 6–24 years). EVA was bilateral in 91.1% of the patients (346/380). The most prevalent initial symptom was HL (341/380), followed by vertigo/dizziness/imbalance (34/380). Sudden HL occurred secondary to head trauma in 5.3% of the patients and upper respiratory infection in 5.0%. Pure-tone audiometry showed profound HL (PTA >91 dB) in 316 (52.0%) of the 608 ears in the 304 patients tested, and asymmetric HL, defined as >10 dB, in 147 (48.4%) of the 304 patients. The mean PTA was 83.7 dB (median, 91.3 dB; interquartile range, 71.3–103.8 dB), and the severity in PTA did not correlate with age. Multivariate logistic regression identified age ≥10 years (compared to age of 0–9 years), bilateral HL (compared to unilateral HL/normal hearing), a history of head trauma, and Pendred syndrome (compared to the other EVA-associated disorders) as significant risk factors for fluctuating HL and/or vertigo/dizziness.

Conclusion: The present nationwide survey of 380 EVA patients provided a more precise description of the clinical features, including risk factors for fluctuating HL and vertigo/dizziness.

1. Introduction

Enlargement of the vestibular aqueduct (EVA) is the most common radiological anomaly of the inner ear [1] and accounts for 13–15% of pediatric sensorineural hearing loss (HL) [2,3]. It accompanies a variety of disorders, including autosomal recessive nonsyndromic hereditary HL (DFNB4) [4], Pendred syndrome [5], branchio-oto-renal/branchio-oto (BOR/BO) syndrome [6,7], distal renal tubular acidosis (dRTA) [8], Waardenburg syndrome [9], and CHARGE syndrome [10]. The most common disorders associated with EVA are DFNB4 and Pendred syndrome, which are caused by mutations in *SLC26A4* that encodes the anion exchanger Solute Carrier Family 26, Member 4, or pendrin [11,12]. A study of North American Caucasian EVA patients reported that 25% had two mutant *SLC26A4* alleles and 25% had one mutant allele [13]. *SLC26A4* mutations may account for an even higher proportion of EVA in Asians, as two mutant alleles were found in 66–88% of EVA patients in South Korea [14] and Japan [15]. Other genes associated with EVA include *EYA1* [16] and *SIX1* [7], the causative genes for BOR/BO syndrome, and *ATP6V1B1* [17] and *ATP6V0A4* [18], the causative genes for dRTA.

While EVA is now widely recognized as a common manifestation of genetic mutations underlying pediatric HL, many controversies remain due to the paucity of large-scale studies. The reported incidence of sudden deterioration of HL in EVA patients precipitated by such events as minor head trauma, barotrauma, and upper respiratory infection widely varies across studies [19]; hence, it is unknown whether these events are major risks. Moreover, it is uncertain whether EVA itself is the sole or predominant cause of HL. For instance, a minority of patients with EVA exhibits normal hearing [20]. Furthermore, fluctuating HL and vertigo/dizziness are characteristic symptoms of EVA [21,22]; however, there is no reliable method to predict progression of symptom severity.

To address these issues, we conducted a nationwide survey in Japan to gather information on a large cohort of EVA patients. Clinical and demographic data were used for constructing a more detailed picture of symptomology and disease progression and identifying risk factors for EVA-associated HL and vestibular dysfunction.

2. Materials and methods

2.1. Patients and data collection

A nationwide survey was performed using two survey sheets: the first was mailed in 2011 to 662 board-certified otolaryngology departments of 108 university hospitals and 554 other hospitals in Japan to identify the ones treating EVA patients. EVA was defined as a vestibular aqueduct or endolymphatic duct diameter of ≥1.5 mm at the midpoint or ≥2 mm at the operculum on temporal bone, as seen on CT scans and/or MRI [3]. A second survey sheet was mailed in 2012 to all facilities that reported treating EVA cases. This sheet solicited clinical information, including EVA side, age and symptoms at onset, the incidence of fluctuating HL and vertigo/dizziness during the entire course, the incidence of head trauma and upper respiratory infection as precipitating factors, the incidence of syndromes (Pendred syndrome, BOR/BO syndrome, dRTA, Waardenburg syndrome, and CHARGE syndrome) and accessory findings (ear pit, auricular anomaly, middle ear anomaly, and inner ear anomaly other than EVA), family history of HL, and the results of hearing tests, from the medical records of eligible patients. The hearing tests included pure-tone audiometry, conditioned orientation response audiometry, auditory brainstem responses, and auditory steady-state responses.

The data were collected and analyzed at the Department of Otolaryngology of Tokyo Medical and Dental University. This study was approved by the Institutional Review Board

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