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Letter to the Editor

Enlarged vestibular aqueduct: Audiological and genetical features in children and adolescents

Keywords:
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A B S T R A C T

Background: Enlarged Vestibular Aqueduct (EVA) is one of the most common congenital malformations associated with sensorineural or mixed hearing loss. The association between hearing loss and EVA is described in syndromic (i.e. Pendred Syndrome, BOR, Waardenburg) and non-syndromic disorders, as isolate or familiar mutations of the SLC26A4 gene. The audiological phenotype of the EVA syndrome is heterogeneous, the type and entity of hearing loss may vary and vertigo episodes might also be present.

Objective: The aim of this retrospective study was to describe the clinical and genetic features of a group of adolescent subjects presenting an EVA clinical profile, considering the presence of SLC26A4 gene mutations.

Methods: 14 Caucasian patients were assessed (24 ears in total; 4 patients presented a monolateral EVA), 10 females and 4 males. Their age at the time of diagnosis was between 1 and 6 years (mean age 2.5 years). Subjects were assessed by an ENT microscopy evaluation with a complete audiometric assessment, CT & MRI scans and genetic tests for the evaluation of the pendrin gene mutations (SLC26A4).

Results: Considering the presence of SLC26A4 mutations and thyroid function, we could identify three sub-groups of patients: group 1, non syndromic EVA (ns EVA, no SLC26A4 mutation and no thyroid dysfunction); group 2, EVA with DFNB4 (single SLC26A4 gene mutation and no thyroid dysfunction); group 3, EVA with Pendred Syndrome (two pathological mutation of SLC26A4 and thyromegaly with thyroid dysfunction).

Patients of group 1 (ns-EVA) showed various degrees of hearing loss from mild (55%) to severe-profound (45%). In groups 2 (DFNB4) and 3 (PDS), the degree of hearing loss is severe to profound in 70–75% of the cases; middle and high frequencies are mainly involved.

Conclusions: The phenotypic expressions associated with the EVA clinical profile are heterogeneous. From the available data, it was not possible to identify a representative audiological profile, in any of the three sub-groups. The data suggest that: (i) a later onset of hearing loss is usually related to EVA, in absence of SLC26A4 gene mutations; and (ii) hearing loss is more severe in patients with SLC26A4 gene mutations (groups 2 and 3 of this study).

1. Introduction

Enlarged Vestibular Aqueduct (EVA) is known as the most common form of inner ear abnormality and it may be radiologically diagnosed using temporal bone computed tomography (CT) and Magnetic Resonance Imaging (MRI) [1–3]. The vestibular aqueduct is considered enlarged if its diameter exceeds 1.5 mm, measured in the middle of the aqueduct [1–3]. The location of the measurement (halfway between the orifice at the posterior fossa and the vestibule) is of great importance for the correct diagnosis [3,4]. The CT scan shows the enlargement of the vestibular aqueduct, and T2-weighted MRI provides information of the enlarged endolymphatic duct, within the bony canal and the size of the endolymphatic sac.

The association between hearing loss and EVA has been described in systemic syndromes (i.e. Pendred Syndrome, distal renal tubular acidosis, Waardenburg's syndrome etc) and non-syndromic familial or isolated forms (non-syndromic EVA, ns.EVA). The phenotypic expressions associated with EVA are heterogeneous, the audiological profile can be of a bilateral deafness, progressive sensorineural hearing loss, fluctuating sensorineural hearing loss or sudden sensorineural hearing loss, sometimes subsequent to head trauma. The clinical profile can also include vestibulopathy [5–8].

The association between hearing loss and EVA was first described in a 1978 study by Valvassori and Clemis [1], in which they reported retrospectively findings from 50 patients with EVA profiles and bilateral hearing deficits.

The genesis of EVA is assumed to be the result of an inner ear development blockage approximately in the 7th week of fetal growth. In 40% of the clinical cases EVA represents an isolated inner ear abnormality, while in 60% it can be associated to other inner ear malformations (i.e. enlargement of lateral semicircular canal) [9–11].

Recently, much attention has been given to the hereditary

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nature of this syndrome. It is reported that the gene responsible for sensorineural hearing loss associated with EVA, is located in the chromosome region 7q31, the same region also described as being responsible for Pendred Syndrome [12–14]. Particularly when considering the SLC26A4 gene, a recessive trait that codifies for a membrane transporter able to exchange anions between the cytosol and extracellular fluid, it has been described that its mutation can be responsible of PDS (sensorineural deafness and goiter) and DFNB4, a type of autosomal recessive nonsyndromic deafness in which, by definition, affected persons do not have thyromegaly [15–23].

The objective of the study was to analyze the clinical features of a group of patients with EVA, considering the presence of SLC26A4 gene mutation.

2. Subjects and methods

Between January 2009 and December 2016, 14 Caucasian patients (28 ears, from 10 female and 4 male patients) were assessed retrospectively. The age of diagnosis for hearing loss and EVA varied between 1 and 6 years with a mean diagnosis age of 2.5 years.

The research was conducted in compliance with the Helsinki Declaration (2008). Although informed consent was not required because the study was observational and did not affect patient care in any way, all subjects were informed about the research project during the first visit and gave their consent for their participation.

Each patient underwent a complete ENT and audiological examination, including medical history, oto-microscopic examination, and audiometric tests.

The degree of hearing loss was assessed at the frequencies 0,25–4000 Hz and its definition followed the ASHA recommendation [21,22] as follows: (i) mild hearing loss $\leq$ 45 dB; (ii) moderate loss from 46 to 70 dB; (iii) severe loss from 71 to 90 dB; and (iv) profound hearing loss > 90 dB. Pure tone audiometry and/or Auditory Brainstem Responses (ABRs) were used in the assessment of hearing threshold. Pure tone audiometry was performed within a sound-proof cabin (model E2X2; Mercury, Milan, Italy) using an Amplaid audiometer (Amplaid, Milan, Italy) calibrated to ISO 9001 standards. Click-evoked ABRs were recorded by an EM 12 Mercury apparatus, using a stimulus span of 90–40 dB SPL (and a repetition rate of 10/s) A vestibular assessment (a caloric Fitzgerald-Hallpike test) was performed only in patients with a clinical history of vertigo.

All 14 patients underwent neuro-imaging with temporal bone CT scans; high-resolution cerebral MRI was performed in 8/14 patients. The diameter of the internal auditory canal was measured on axial images of CT and axial images of MRI; According to data in the literature the aqueduct was considered enlarged when its diameter resulted greater than 1.5 mm [1–3]. The simultaneous presence of other inner ear malformations was also assessed.

All patients underwent a thyroid ultrasonography and a thyroid function assessment (TSH, anti-thyroglobulin and anti-peroxidase). The perchlorate test was not performed due to age of the subjects.

Finally, all patients underwent a molecular genetic test for the evaluation of pendrin gene (SLC26A4) mutations.

3. Statistical analysis

Non-parametric tests (Wilcoxon and Mann-Whitney) have been used to evaluate threshold shifts between groups of subjects. Level of significance was considered at $p < 0,05$. The data were analysed using SPSS version 17.

4. Results

From the analysis of the data, considering the presence of SLC26A4 mutations and thyromegaly (see Fig. 1 for details), three sub-groups of patients emerged.

Group 1. Non syndromic EVA (ns-EVA): 12/24 ears (50%), mean age at diagnosis 2.4 years, 6 females and 1 male: hearing loss and enlarged vestibular aqueduct were present, but no pendrin SLC26A4 gene mutations and thyroid dysfunction were observed.
Group 2. EVA with DFNB4 (DFNB4): 10/24 ears (41.6%), mean age at diagnosis 2.2 years, 4 females and 2 males: hearing loss and enlarged vestibular aqueduct were present, as well a single SLC26A4 pathological mutation but no thyroid dysfunction. (DFNB4).
Group 3. EVA in Pendred Syndrome (PDS): 2/24 ears (8.3%), mean age at diagnosis 5 years, 1 male: presence of hearing loss and enlarged vestibular aqueduct with two pathological mutations of the pendrin SLC26A4 gene and thyromegaly with thyroid dysfunction.

4.1. Audiological findings

The audiological profiles of each subgroup are reported in Figs. 2 and 3. Patients of group 1 (ns-EVA) show various degrees of hearing loss from mild (28.5%) to severe-profound (21.4%). In groups 2 (DFNB4) and 3 (PDS), the degree of hearing loss is severe to profound in all cases; middle and high frequencies are mainly involved. Among the onset of hearing loss, patients of group 1 (ns-EVA) have presented hearing loss since childhood in 66.5%, while patients of group 2 (DFNB4) and group 3 (PDS) have presented an early onset. Only few patients of group 1 (22%) and group 2 (33%) reported an history of episodic vertigo.

The threshold level (PTA 0,25–4 kHz) comparison, across

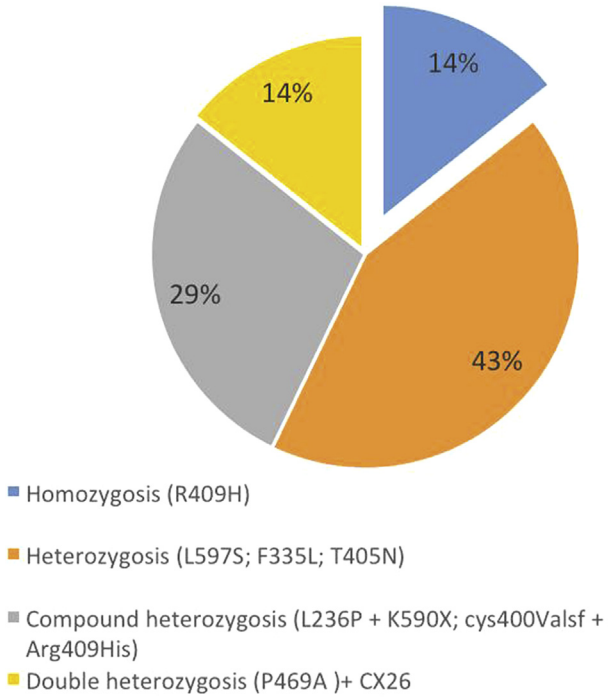

Fig. 1. Type of SLC26A4 mutations detected in the tested patient sample.

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