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Contralateral hearing loss in children with a unilateral enlarged vestibular aqueduct

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ABSTRACT

Objective: To evaluate the long-term ipsi- and contralateral hearing of patients with a unilateral enlarged vestibular aqueduct (EVA).
Study design: Multicenter retrospective cohort study.
Setting: Three tertiary otology and audiology referral centers.
Patients and diagnostic interventions: A total of 34 children with a unilateral enlarged vestibular aqueduct as identified on CT and/or MR imaging were evaluated with pure tone and speech perception audiometry.
Mean outcome measures: Radiologic measurements of the vestibular aqueduct, ipsi- and contralateral hearing loss, ipsi- and contralateral hearing loss progression over time and DNA test results.
Results: All patients in this cohort with unilateral EVA presented with hearing loss. Hearing loss was progressive in 38% of the ipsilateral ears. In 29% of the children, hearing loss was also found in the contralateral ear without EVA. In 90%, the contralateral hearing was stable, with a mean follow up of 4.2 years. We found a significant correlation between the severity of the hearing loss and the size of the EVA. A genetic diagnosis associated with EVA and/or SNHL was found in only 7%.
Conclusion: About a third of the children with unilateral EVA are at risk of developing hearing loss in the contralateral ear. This indicates that at least in some patients with a unilateral EVA, a bilateral pathogenic process underlies the hearing loss, in contrary to what the imaging results suggest. These findings are important for counseling of EVA patients and their parents and have implications for follow up.

1. Introduction

The prevalence of congenital sensorineural hearing loss (SNHL) in one to two per thousand live births makes this one of the most common congenital disorders [1,2]. A recent study of children referred for sensorineural hearing loss in The Netherlands showed that in 29%, the hearing loss was unilateral [3]. The cause of unilateral hearing loss is frequently a structural abnormality of the labyrinth, as identified by radiology (49%) [3]. In children with unilateral sensorineural or mixed type hearing loss, 9–15% is reported to be caused by an enlarged vestibular aqueduct (EVA) [4–6]. An EVA may be identified as a separate radiologic entity or in association with other inner ear anomalies (incomplete partition type 2, IP-2) [7].

The occurrence and progression of hearing loss in ears affected by EVA is hypothesized to be caused by an increased endolymphatic inner ear fluid pressure or fluctuations in endolymphatic pressure, and results

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in hair cell damage [8]. Although EVA is a congenital disorder, hearing loss may not be present or apparent at birth [9]. When present, hearing loss may be fluctuating, slowly progressive or present with sudden exacerbations. In 12% of EVA patients, there is a clear relation between hearing loss and (minor) head injury, barotrauma or noise trauma [10]. Identification of an EVA as a cause for progressive or fluctuating hearing loss is important for counseling and hearing rehabilitation of these patients. In children with profound (bilateral) hearing loss, cochlear implantation has been proven to be a successful treatment option in children with EVA [11].

Radiology (CT and MR imaging) has become essential in the etiologic analysis of both uni- and (asymmetric) bilateral SNHL because of the high prevalence of causative abnormalities that can be identified. The diagnosis can be made based on visualization of an enlargement of the vestibular aqueduct on CT or enlarged endolymphatic duct and sac on MR imaging. Different methods for measuring the vestibular aqueduct width and different definitions of an enlarged vestibular aqueduct have been described [12,13]. Historically, CT imaging is used to measure the vestibular aqueduct, but MR imaging is more and more used in the etiological diagnosis of SNHL. To date, there is no consensus on the optimal methodology of measuring the VA, nor which definition for EVA best corresponds with the occurrence or severity of hearing loss.

In patients with unilateral EVA, the risk to the affected ear for conductive-, sensorineural- or mixed type hearing loss is well-documented. The development of hearing loss in the contralateral, apparently unaffected ear is somewhat more puzzling. In this study, we focus on the imaging and measurement of the ipsilateral and contralateral VA and correlate this to the observed hearing loss (progression) in both ears.

2. Materials and methods

2.1. Patients

Children diagnosed with unilateral EVA or IP-2 malformation between 2010 and 2019 were selected from the databases of the center of diagnostics of sensorineural hearing loss (CDS) of the VU medical center, the Radboud University Medical Center and the Leiden University Medical Center (LUMC), all tertiary referral centers for the evaluation and management of pediatric hearing loss. The databases consisted of children with uni- or bilateral hearing loss of at least 30 dB, referred for etiological analyses, counseling and rehabilitation. Children included in this study were required to meet the following criteria: adequate otological examination, audiometry, CT of the temporal bone and/or MR imaging of the inner ear. DNA analysis was also evaluated when available.

2.2. Age

The age at detection was defined as the age at which the hearing loss was first diagnosed by the Audiology Center, either by auditory brainstem response (ABR) or pure tone audiometry (PTA).

2.3. Audiometric evaluations

When PTA was performed, an average threshold at 500, 1000, 2000 and 4000 Hz was used for the

Analysis. Children were diagnosed with SNHL if the sensorineural hearing threshold was 30 dB HL or more. Asymmetric bilateral SNHL was defined as one or more frequencies with a greater than 30 dB HL difference, two or more frequencies with a greater than 15 dB difference or three or more frequencies with a greater than 10 dB difference in threshold between the left and right ear. Progression of hearing loss was defined as a decrease in hearing of more than or equal to 30 dB affecting at least three consecutive frequencies [14].

2.4. Evaluation of imaging

Imaging studies consisted of unenhanced temporal bone CT imaging, high resolution T2 weighted MR imaging of the inner ear, or both. Both ears were assessed for EVA. The available imaging was revised in all patients, both of the affected side and the 'normal' contralateral side, using the following criteria: The vestibular aqueduct was defined as enlarged if at least one of two measurements reached the criteria for EVA: 1. Operculum measurement: A line is drawn from the medial border of the operculum perpendicular to the anterolateral wall of the vestibular aqueduct (VA). A VA was defined as EVA if this diameter exceeded 2 mm (Fig. 1A+B). 2. Midpoint measurement: A line is drawn along the operculum, parallel to the posterior fossa dura. Another line is drawn through the center of the EVA along its longitudinal axis. Halfway between the most anterior extension of the EVA and the operculum line is defined as the midpoint of the EVA. The EVA width at the midpoint is measured by drawing a line perpendicular to this longitudinal line at its midpoint, from the medial to the lateral surface of the EVA. A VA was defined as EVA if this diameter exceeded 1.5 mm (Fig. 1C+D). We also performed a third measurement of the VA in the sagittal plane (on CT only) by defining the midpoint of the VA and measuring the diameter at this point of the VA This measurement was not part of the inclusion criteria (Fig. 1E). A VA was defined as EVA if this diameter exceeded 1.5 mm [4]. A VA was defined as 'normal' if the diameter was 1.5 mm or less in the midpoint measurements and 2 mm or less in the operculum measurement. An incomplete partition type 2 (IP-2) was diagnosed if the enlarged vestibular aqueduct was accompanied by two additional components: a cystic cochlear apex with a normal basal turn and a dilated vestibule.

2.5. DNA analysis

Molecular genetic testing, as described previously, was performed and reviewed when available [15].

2.6. Statistical analysis

Statistical analyses were performed using SPSS 22.0. The criterion for statistical significance was set at $p < 0.05$. Descriptive analyses, cross tables and Pearson correlation tests were used to outline results of this study.

This study was approved by the medical ethics review committee of the VU University Medical center Amsterdam (number 2018.402).

3. Results

3.1. Clinical characteristics

A total of 34 children with a unilateral EVA and/or incomplete partition type II were extracted from the databases of the three tertiary referral centers as mentioned above (see Table 1 and Fig. 2). The mean age at diagnosis of the hearing loss ranged from one month to 20 years old (an overall median of 7.2 years). The M/F ratio was 50/50. Thirteen right ears and 21 left ears were affected by EVA (n = 27) or incomplete partition type II (n = 7).

3.2. Hearing loss

The mean age at diagnosis of the hearing loss ranged from one month to 20 years (an overall median of 7.2 years). In 27 of the 34 children, longitudinal measurements of hearing were available. The mean follow-up was 4.2 years (1–11 years).

The mean hearing loss of all 34 children at the ipsilateral side was 60 dB HL (33–120 dB) at the initial measurement. Ipsilateral hearing loss was progressive in 13 children (38%). In this group of patients with progressive hearing loss, the mean hearing loss at the first audiogram

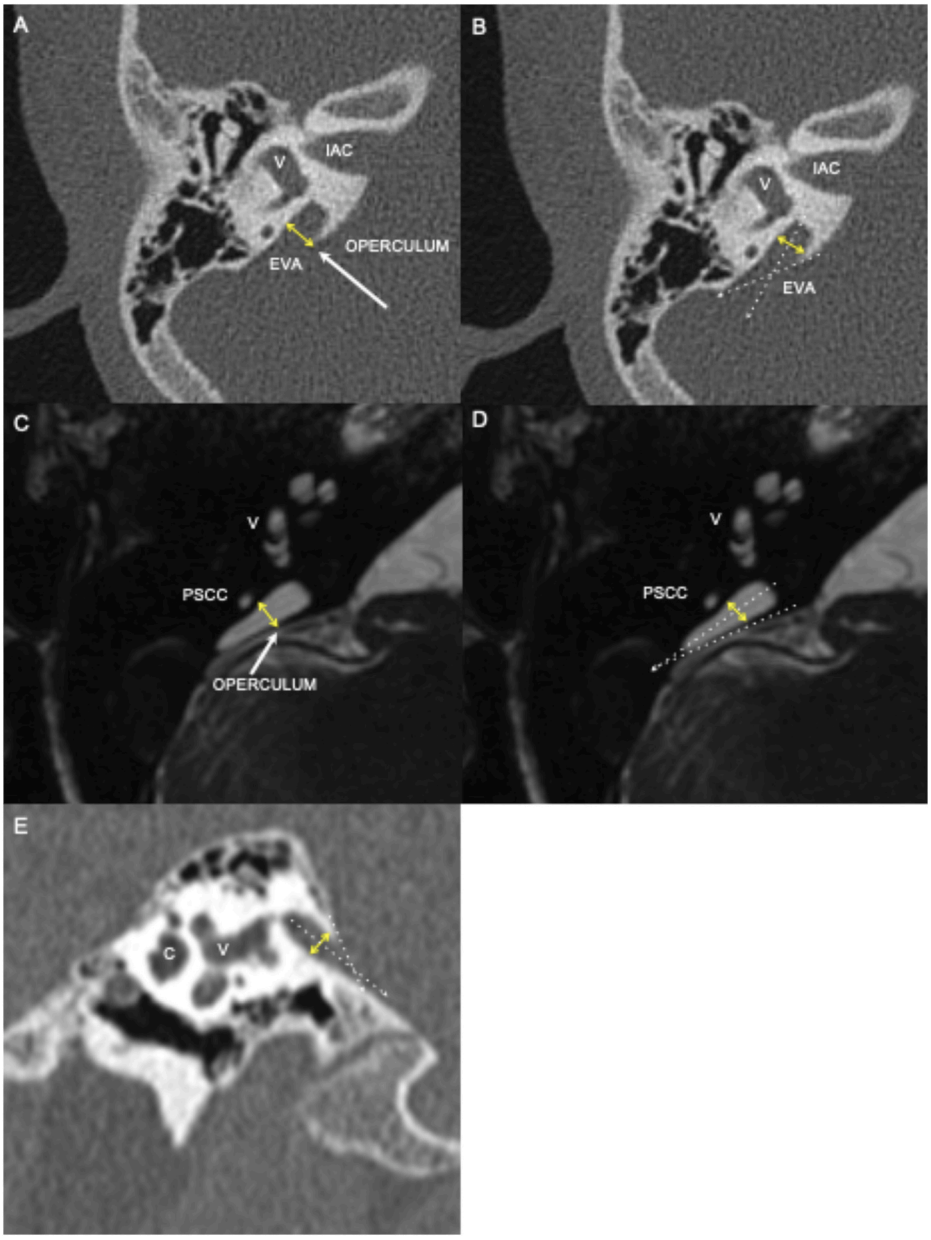

Fig. 1. A, B: axial CT image of the right temporal bone: Operculum measurement is shown by arrow in A, midpoint measurement by arrow in B. **C, D:** axial MR T2 image of the right inner ear revealing an enlarged endolymphatic duct and sac: Operculum measurement is shown by arrow in C; Midpoint measurement s shown by arrow in D. **E** sagittal CT image of the right temporal bone. Midpoint measurement is shown by arrow. C = cochlea, V = vestibulum, IAC = internal auditory canal, EVA = enlarged vestibular aqueduct. PSCC = posterior semicircular canal.

was 39 dB HL (33–87 dB) and 60 dB (47–120 dB) at the last follow up audiogram (equating to a mean hearing loss of 20 dB), with a mean follow-up of 4.8 years. In addition, 2/34 (6%) had fluctuating hearing loss, and hearing loss was already profound at detection in 5/34 (15%) children.

Contralateral hearing loss was found in 10/34 (29%) children. The mean hearing loss of the contralateral ear was 30 dB HL. Audiometric follow-up was available in 6 of these patients, with a mean follow-up of 4.2 years. In all patients with contralateral hearing loss, this hearing loss was already present at presentation. In only one patient, hearing loss was progressive (from 47 to 60 dB between the first and last audiogram, with a follow up of 6 years). When present, the contralateral hearing loss was characterized by a mild sensorineural hearing loss in the lower frequencies in 8/10 children, in one patient the hearing loss was profound on both sides, and one patient suffered from bilateral high frequency hearing loss (Fig. 3). None of the normal hearing contralateral ears developed hearing loss during the follow-up period (mean follow up 4.2 years). Two children with contralateral SNHL were found to have BOR syndrome (see also 'genetics'), no genetic cause was found in 8/10 children with contralateral SNHL. We found no additional predisposing factors for contralateral hearing loss, such as age at diagnosis, morphological characteristics, or severity of hearing loss at the side affected by EVA.

3.3. Imaging

A total of 39 radiological investigations were performed in 34 children (23 CT and 16 MR scans). All patients had a unilateral EVA as diagnosed on imaging using the criteria mentioned above. Twenty-seven children were diagnosed with an isolated EVA and 7 with IP-II. Two of the patients initially diagnosed with unilateral EVA were found to have bilateral abnormalities to the labyrinth, namely an incomplete partition of the cochlea without an EVA (both with only ipsilateral hearing loss). The mean operculum diameter of the VA of the ipsilateral ear was 2.7 mm, the mean midline diameter in this group was 2.6 mm. The mean operculum diameter of the VA of the contralateral ear was 0.6 mm and the mean midline diameter of the non-EVA side was 0.5 mm in this ear (Table 2). In the 10 patients with (asymmetric) bilateral hearing loss, the

Table 1
Demographic and clinical characteristics of the children with a unilateral EVA on CT and/or MR imaging.

Characteristics	N
Number of patients	34
Sex n (M/F)	17
M	17
F	
Age at detection of the hearing loss (mean/range) years	7.2 (0–20)
Hearing loss at detection affected ear (mean/range) dB	60 (33–120)
Follow up time (mean/range) years	4.2 [1–11]
Number of patients with contralateral hearing loss	10
Number of ears with progressive hearing loss	13
Ipsilateral	1
Contralateral	
Imaging studies	39
CT	23
MR	16
DNA test performed	27
Comorbidities	1
Juvenile idiopathic arthritis	1
Minimal facial asymmetry at the side of the hearing loss	1
Branchial arch cleft	
Vestibular symptoms	10
Episodic vertigo	3
Imbalance	3
Developmental delay in motor skills	4

mean operculum diameter of the VA of the contralateral (non-EVA) ear was 0.7 mm, the mean midline diameter in this group was 0.5 mm.

3.4. Imaging vs. hearing loss

We analyzed all ears with hearing loss (both ipsi- and contralateral, n = 44), and found a significant correlation between the severity of the hearing loss at detection and the operculum diameter of the VA (p = 0.05) and between the severity of the hearing loss and the midline diameter of the VA (p = 0.02). When only evaluating the hearing loss of ears affected by EVA, no correlation between severity of hearing loss and operculum or midline diameters was found (p = 0.6 and p = 0.6, respectively). We found no significant correlation between progression of hearing loss and the operculum diameter (p = 0.9) or the midline diameter (p = 0.6). No correlation was found between the diameter of the EVA and the contralateral hearing loss (operculum diameter p = 0.5 and midline diameter p = 0.3).

3.5. Genetics

DNA analysis was performed in 27/34 children, consisting of primarily targeted sequencing of SLC26A4 at first, followed by whole exome sequencing when the initial test was negative. A genetic cause for the hearing loss was found in only three cases. Two patients were diagnosed with branchio-oto-renal (BOR) syndrome. One child was diagnosed with Wolfram syndrome. As of yet, there is no reported relationship between an EVA and the Wolfram syndrome, we therefore assume these to be two unrelated pathologies. All of these patients had bilateral asymmetric hearing loss, with mild SNHL of the lower frequencies at the contralateral ear. In one child who had only ipsilateral hearing loss only, a heterozygous pathogenic variant in *SLC26A4* was found. Single-allele *SLC26A4* mutations have been associated with hearing loss and EVA. In these cases, with apparently heterozygous pathogenic *SLC26A4* alterations, the assumption is that the wild type allele is affected by an as of yet unidentified pathogenic alteration. The spectrum of pathogenic SLC26A4 mutations is still expanding [16].

4. Discussion

In this study we evaluated radiological findings and the presence or development over time of ipsi- and contralateral hearing loss in children with a unilateral EVA. Hearing loss at the side of an EVA is well described and known to be very variable [17]. The hearing loss of the contralateral side is often overlooked in unilateral EVA patients. This study shows that SNHL also occurs in about a third of the patients in the contralateral ear. As bilateral hearing loss has a more pronounced impact on auditive functioning, development of linguistic skills and scholastic performance than unilateral hearing loss, these findings have important implications for counseling, follow-up, and rehabilitation of unilateral EVA patients. While it has been common practice to be less stringent in the follow up of apparently unilaterally affected patients, based on these findings we now advise long term audiological follow up of both ears and feel that adequate counseling of patients and parents should include the risk of bilateral hearing loss, also in unilateral EVA patients.

4.1. Hearing loss

The onset of hearing loss in patients with an EVA may occur at birth until adolescence, with the highest frequency in childhood [18]. In this study, the mean age at detection of the hearing loss was 7.2 years. This is

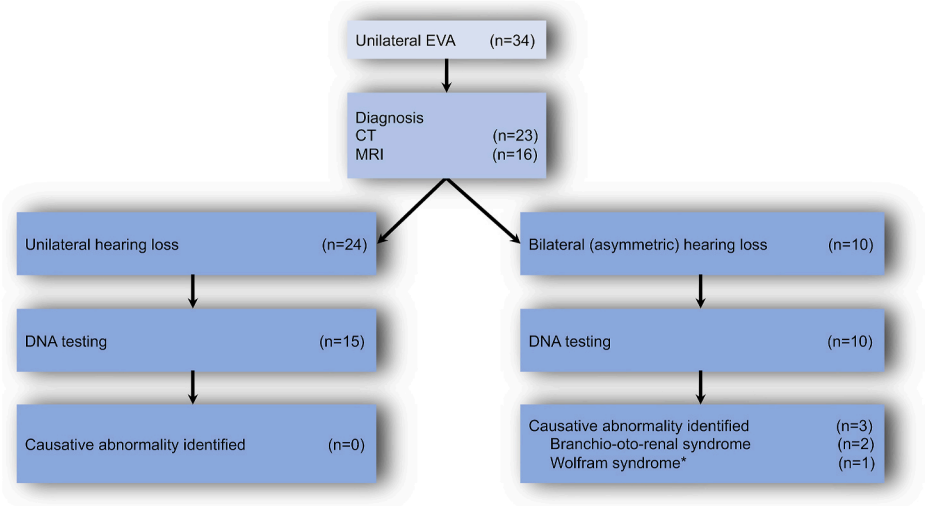

Fig. 2. Overview of the etiological work up.
*One patient was found to have two diagnoses, a unilateral EVA and the Wolfram syndrome. As of yet, there is no known relation between these two diagnoses.

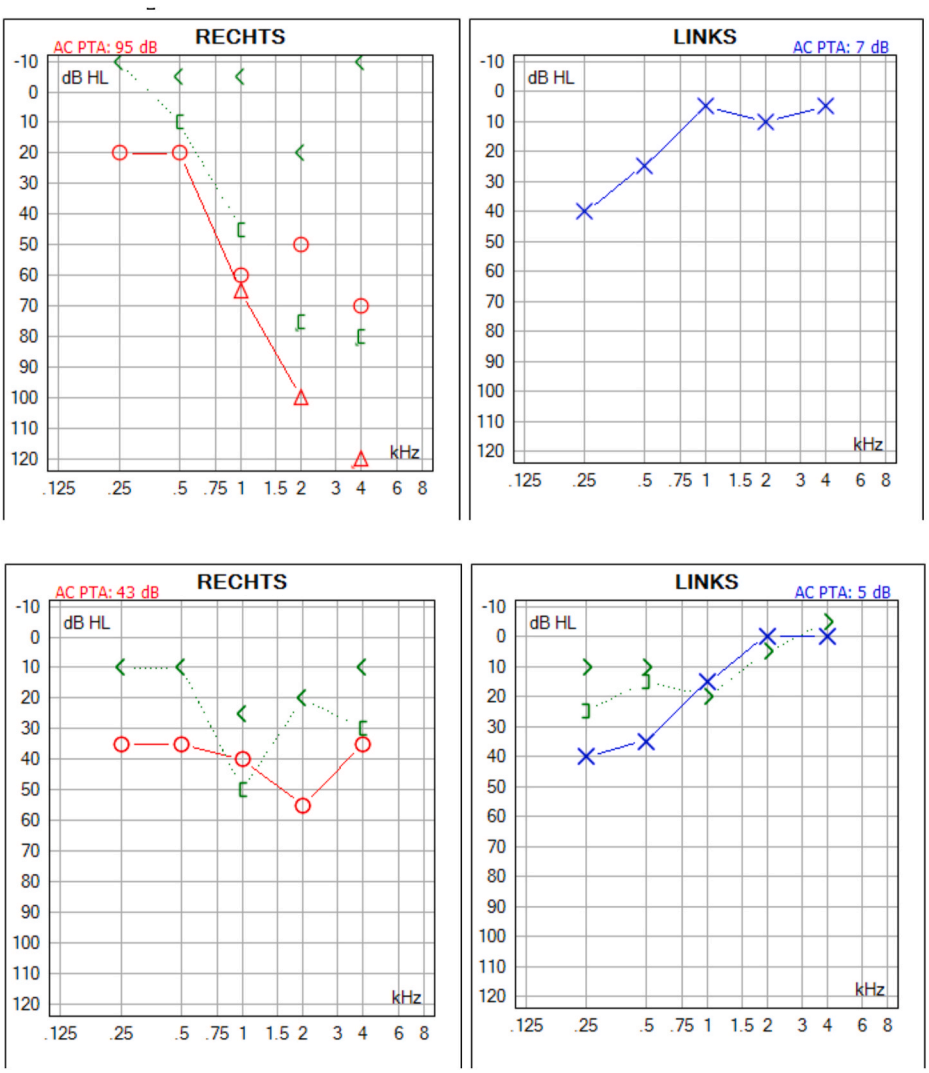

Fig. 3. Two examples of children with a unilateral EVA and bilateral asymmetric hearing loss. A: audiogram of a patient diagnosed with brachio-oto-renal (BOR) syndrome and an EVA at the right side. The ipsilateral hearing loss was progressive; the contralateral hearing loss was present at detection and remained stable. **B** Patient diagnosed with EVA at the right side. The hearing loss remained stable on both ears. DNA testing showed no abnormalities.

Table 2
Hearing loss and mean and range of EVA measurements (mm).

	VA midpoint ipsilateral (mm)	VA midpoint contralateral (mm)	VA operculum ipsilateral (mm)	VA operculum contralateral (mm)	VA sagittal ipsilateral (mm)	VA sagittal contralateral (mm)
EVA patients with normal contralateral hearing (n=24)	2.6 (1.5–3.7)	0.5 (0–1.4)	2.7(1.5–3.6)	0.6 (0–1.8)	2.2 (1.1–2.9)	0.6 (0–1.1)
EVA patients with contralateral hearing loss (n=10)	2.6 (1.7–5.3)	0.5 (0–1.3)	2.7 (1.6–5.3)	0.4 (0–1.4)	2.2 (1.8–3)	0.9 (0–1.5)

Midpoint measurement: A VA was defined as EVA if the diameter exceeded 1.5 mm. Operculum measurement: a VA was defined as EVA if this diameter exceeded 2 mm [4]. VA = vestibular aqueduct. Ipsilateral = side of the enlarged vestibular aqueduct (EVA). Contralateral: side of the normal VA.

somewhat older than the mean age at detection (3.7 years old) of the hearing loss in a large cohort of children with unilateral sensorineural hearing loss (USNHL) evaluated previously [19]. The age difference could be explained by the fact that hearing loss may not be present at birth in EVA patients, as opposed to many other pathologies causative of USNHL.

Hearing loss at the side of the EVA was progressive in 38% of the children. This is in line with previous studies, describing progression of hearing loss in 12–65% of the patients [5,20,21]. Remarkably, we found an incidence of SNHL at the contralateral side in children with a unilateral EVA of 29%. To date, the literature has been sparse regarding the prevalence of contralateral hearing loss in patients was a unilateral EVA. Three studies reported patients with contralateral SNHL, with a prevalence of 5–55%, and a follow-up of 0–3.1 years [20,22,23]. The wide range in the literature may be explained by differences in the study populations, inclusion criteria, imaging modalities and diagnostic criteria. In the current study, the contralateral hearing loss was already present at first detection of the ipsilateral EVA. In children with normal contralateral hearing at first detection, hearing loss did not develop later on, with a relatively long audiological follow up (4.2 years). In most children, the contralateral hearing loss was characterized by a mild sensorineural hearing loss in the lower frequencies. In the majority of

the patients, this hearing loss was stable. In only one child, the contralateral hearing loss was progressive. In addition, children with USNHL that is not associated with EVA can develop contralateral hearing loss as well, for instance SNHL caused by a cCMV infection or children with progressive asymmetric hearing loss caused by temporal bone anomalies. A study focusing on USNHL without EVA found contralateral hearing loss in 11% of the patients. Some of these patients had bilateral temporal bone anomalies other than EVA [24].

4.2. CT and MR imaging

As previous studies have shown, CT and MR imaging are complementary imaging modalities in the diagnosis of hearing loss [25,26]. Generally, CT is considered the better modality for the identification of bony abnormalities, while MR imaging provides superior information about fluid compartments and soft tissue structures such as the intralabyrinthine anatomy, the cochlear nerve and brain. In choosing a radiologic modality, especially in the pediatric population, radiation exposure of CT, logistics, and the need for anesthesia in MR imaging of young children may also play a role [13,19]. In the present retrospective study, the choice for an imaging modality was individualized per patient, based on the type of hearing loss and additional clinical characteristics such as age, neurological signs, developmental impairment, and the clinical setting. An EVA is detectable on both CT and MR imaging. In our study, we found a good correspondence between the CT and MR imaging in the patients in which both modalities have been performed and this is in line with previous literature [13]. Based on our experience, we perform CT as an initial imaging modality in this group of patients. MR imaging is the preferred first modality when cochlear nerve or brain abnormalities are suspected, in case of additional neurological signs or fluctuating hearing loss. There are no standardized diagnostic criteria for EVA, which makes it difficult to compare the measurement outcomes of these two modalities [12,13]. The most commonly used cut-off values for EVA are a VA diameter at the midpoint exceeding 1.5 mm and exceeding 2.0 mm at the operculum on axial images [4]. On CT, a midpoint and an operculum measurement can be performed. When the axial CT images are not conclusive, we find a measurement of the VA in a sagittal reconstruction a good alternative to diagnose EVA. On axial T2 weighted MR, both operculum and midpoint measurements can be performed as well. However, we found the midpoint measurement the most reliable measurement to define an EVA on MR imaging, as the tip of the bony operculum is more difficult to identify. The correct measurement and definition of EVA is particularly relevant in the evaluation of bilateral hearing in unilateral EVA patients. In this study, most contralateral ears were well within the range of normal midpoint and operculum VA diameters. In only one patient had a borderline normal VA, with a midpoint and operculum diameters of 1.4 mm. This patient had normal hearing in this ear.

4.3. Imaging vs. hearing loss

Previous studies do not agree on the relation between hearing loss (severity) and the size of the VA [5,21,27]. In the current cohort, a significant correlation was found between the severity of the hearing loss and the diameter of the VA in ears with hearing loss, in agreement with a previous study by Madden et al. [5]. However, when evaluating ears affected by EVA only, no association between VA diameter and hearing loss severity was found, indicating that the association of hearing loss severity and VA diameter is mainly determined by the presence or absence of an EVA. In other words, on average non-EVA ears with hearing loss have a mild hearing loss, ears affected by EVA have a more severe hearing loss. Two previous studies using the same measurement criteria also did not report a correlation between EVA and hearing loss severity [21,27].

4.4. Genetics

Bilateral EVA is strongly associated with DFNB4/Pendred syndrome but is also regularly reported in patients with other syndromes such as Waardenburg or BOR syndromes [27–31]. Although in patients with a unilateral EVA the relation with a genetic diagnosis is less common, it has also been reported for patients with DFNB4/Pendred, Waardenburg and BOR syndrome [30–33]. In this study, two children with BOR syndrome and one child with Wolfram syndrome had a unilateral EVA and bilateral asymmetric hearing loss. As of yet, no relation between the EVA and Wolfram syndrome has been reported in the literature, and we therefore assume that these are two unrelated identities. The audiological phenotype of these three children was not different from the children with asymmetric bilateral hearing loss without a clear molecular genetic diagnosis.

Currently, the cause for contralateral hearing loss in patients with a unilateral EVA is unclear. It has been suggested that the observation of bilateral hearing loss in subjects with a unilateral EVA is caused by an asymmetric phenotypic expression of a yet unknown disease mechanism [20]. Most likely this is not caused by a monogenetic disorder but a complex disease mechanism, for example a variable expression of key genes in the embryonic development of (both) cochleae.

5. Conclusion

A radiologically ‘normal’ anatomy of the contralateral temporal bone in unilateral EVA patients does not preclude bilateral SNHL. In fact, SNHL at the contralateral side seems to occur rather frequently (in 29%). This information should be shared with the patients and their parents. Regardless of the etiology, bilateral stringent audiological follow-up of unilateral EVA patients is mandatory. As the consequences of bilateral SNHL are more critical than unilateral SNHL, timely intervention and hearing rehabilitation is crucial for the optimal development of hearing, speech, and communication skills.

List.
ABR auditory brainstem response.
EVA enlarged vestibular aqueduct.
IAC internal auditory canal.
SNHL sensorineural hearing loss.
USNHL unilateral sensorineural hearing loss.
IP-II incomplete partition type 2.
PSCC posterior semicircular canal.
PTA pure tone audiometry.
V vestibulum.
VA vestibular aqueduct

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