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Sex-specific enlarged vestibular aqueduct morphology and audiometry[☆]

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ABSTRACT

Objective: Enlargement of the vestibular aqueduct (EVA) is one of the most common congenital malformations in pediatric patients presenting with sensorineural or mixed hearing loss. The relationship between vestibular aqueduct (VA) morphology and hearing loss across sex is not well characterized. This study assesses VA morphology and frequency-specific hearing thresholds with sex as the primary predictor of interest.

Materials and methods: A retrospective, longitudinal, and repeated-measures study was used. 47 patients at an academic tertiary care center with hearing loss and a record of CT scan of the internal auditory canal were candidates, and included upon meeting EVA criteria after confirmatory measurements of vestibular aqueduct midpoint and operculum widths. Audiometric measures included pure-tone average and frequency-specific thresholds.

Results: Of the 47 patients (23 female and 24 male), 79 total ears were affected by EVA; the median age at diagnosis was 6.60 years. After comparing morphological measurements between sexes, ears from female patients were observed to have a greater average operculum width (3.25 vs. 2.70 mm for males, p = 0.006) and a greater average VA midpoint width (2.80 vs. 1.90 mm for males, p = 0.004). After adjusting for morphology, male patients' ears had pure-tone average thresholds 17.6 dB greater than female patients' ears (95% CI, 3.8 to 31.3 dB).

Conclusions: Though females seem to have greater enlargement of the vestibular aqueduct, this difference does not extend to hearing loss. Therefore, our results indicate that criteria for EVA diagnoses may benefit from re-evaluation. Further exploration into morphological and audiometric discrepancies across sex may help inform both clinician and patient expectations.

1. Introduction

Enlargement of the vestibular aqueduct (EVA) is the most common radiographic finding associated with hearing loss in the pediatric population, with some studies finding an incidence approaching 15% of all pediatric patients with sensorineural hearing loss (SNHL) [1]. Hearing loss in EVA is most frequently considered SNHL, but can also demonstrate characteristics of conductive or mixed hearing loss on audiometry [2–6]. EVA is an inner ear abnormality that can lead to impairment of both the auditory and vestibular processing systems [7]. Patients typically present with hearing loss from birth or during early childhood [8]. The natural course can be erratic with some never regaining previous hearing acuity, while others may partially recover. Hearing loss can demonstrate progressive, abrupt, or fluctuating patterns [9–11], and previous studies have reported a preponderance of females to males with EVA diagnoses [2,5,9,12,13].

In 1978 Valvassori and Clemis proposed a clinical definition of EVA, which includes an abnormal dilation of the vestibular aqueduct (VA) measured at its midpoint (> 1.5 mm) [15]. This measurement is performed halfway between the orifice of the posterior fossa and the

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vestibule. Since then the clinical definition has changed and EVA is now typically diagnosed by temporal bone imaging (either computerized tomography (CT) or magnetic resonance imaging (MRI)) using the Cincinnati criteria, which defines EVA as ears having a VA midpoint width > 0.9 mm *or* an operculum width > 1.9 mm [4,14,15]. Additionally, a battery of audiological tests are used to evaluate hearing loss among ears with EVA, including audiological measurements such as pure tone audiometry, acoustic immittance, auditory steady-state response, and auditory brainstem response [4].

Testing for EVA is complicated by its heterogeneous manifestations across different populations including ethnicity [16,17] and potentially sex. EVA can be syndromic, associated with genetic conditions like Pendred syndrome, or non-syndromic; it can also be isolated or concurrent with other inner ear malformations such as incomplete partitioning of the interscalar septum between the upper turns of the cochlea, called Incomplete Partition Type II (IP-II) [2,4,18].

Given that several studies find that the majority of patients with EVA are female [2,5,9,12,13], the objective of this study was to examine whether morphological and audiometric profiles vary between males and females with EVA. This knowledge may provide insight into what factors affect disease presentation and progression. By examining hearing loss across sex, clinicians may be able to more precisely tailor their indexes of suspicion to individual patients.

2. Materials and methods

2.1. Study design

This was a retrospective, longitudinal study of EVA patients seen at a tertiary care facility between the years of 2000 and 2016, and was approved by the University Hospitals Institutional Review Board as study number 05-15-29.

2.2. Study population

Study participants were identified by a two-step process. University Hospitals patients from January 2000 to June 2016 who received computed tomography (CT) scans of the internal auditory canal (IAC) and predetermined diagnosis codes were flagged as potential candidates. Presence of EVA was diagnosed by CT scan of the IAC upon meeting Cincinnati criteria (VA midpoint width > 0.9 mm or operculum midpoint width > 1.9 mm). EVA diagnosis was then confirmed by a second measurement of the patient's CT scan, as demonstrated in Fig. 1. Only patients born during or after the year 1990 were included due to implementation of newborn hearing screens at that period of time. (See Table 1.)

Diagnosis codes were chosen as previously described in Ascha et al. and included sensorineural hearing loss (389.1, range: 389.10 to 389.18), unspecified congenital anomaly of ear causing impairment of hearing (744.00), congenital anomaly of inner ear causing impairment of hearing (744.05), and unspecified anomaly of the ear (744.3) [19].

2.3. Statistical methods

Descriptive statistics across clinical and demographic characteristics are presented with corresponding tests of difference, including *t*-tests, Wilcoxon rank-sum, or chi-square tests as appropriate for the skew and type of data.

Pure-tone audiometry data was collected for measurements performed at 250, 500, 1000, 2000, and 4000 Hz. Tests of difference in frequency-specific pure-tone audiometry across sex were also performed. For these tests of difference, the mean of all available measurements was taken to be the frequency-specific pure-tone threshold for each ear.

The average of pure-tone thresholds across frequency was used as the outcome for a mixed-effects model identifying the effect of morphology and sex on hearing loss, affording greater statistical resolution by accounting for the correlation between measurements within each ear. Random effects included intercepts across each ear and random slopes over time, and the assumption of normality of residuals was verified graphically using plots of Pearson residuals over fitted values, and also using normal quantile-quantile plots of those residuals.

All analyses were performed using R version 3.3.3 (R Foundation, 2017) and the lmerTest package was used to fit mixed-effects models. p values < 0.05 were considered statistically significant.

3. Results

Of 3078 patients analyzed for this study who presented with a correct diagnosis code, 506 had a CT procedure performed. From this group, 95 patients' radiological reports made mention of an enlarged vestibular aqueduct. 47 of these patients, 23 females and 24 males, were confirmed to have an ear with EVA on second measurement of the vestibular aqueduct midpoint and operculum widths by Cincinnati criteria. Fig. 2 demonstrates this selection process.

Seventy-nine ears from the 47 patients met Cincinnati criteria for EVA, of which 40 belonged to female patients and 37 belonged to male patients. Within the cohort, there were no statistically significant difference in age at diagnosis ($p = 0.147$) or laterality ($p = 1.000$). The median age at diagnosis was 6.6 years overall, 6.2 years for our female patients and 8.5 years for our male patients. The proportion of ears with IP-II among female patients was greater than for male patients, though this difference was not statistically significant (52.5% and 35.9%, $p = 0.208$).

The median vestibular aqueduct width in our EVA cohort was 2.20 mm, while the median operculum width was 3.00 mm. Ears from female patients had both greater median operculum and VA midpoint widths: ears from female patients had a median VA midpoint width of 2.80 mm compared to those of male ears' at 1.90 mm ($p = 0.004$), and had a median operculum width of 3.25 mm compared to 2.70 mm ($p = 0.006$), respectively. The median VA midpoint width among females was 0.72 mm greater than that of males (95% CI: −1.34, −0.11, $p = 0.0227$), and their operculum width was 0.82 mm greater (95% CI: −1.56, −0.08, $p = 0.0315$) than that of males' (Table 2, Fig. 3a, b).

Although ears from male patients had greater median thresholds for all frequencies than ears from female patients in this population, these differences were not statistically significant (Table 3). However, multivariable models adjusting for IP-II and vestibular aqueduct midpoint width revealed that pure-tone average thresholds among ears from male patients were 17.6 dB (CI: 3.8, 31.3) greater than those of ears from female patients (Table 4).

4. Discussion

Past studies have highlighted that females are more commonly diagnosed with enlargement of the vestibular aqueduct (EVA) than males [2,5,9,12,13]. However, whether sex plays a role in EVA morphology and associated hearing loss is not well explored. This study reports on a cohort of patients with EVA that demonstrate meaningful differences in both morphology and hearing loss across sex.

The females in our cohort presented with vestibular aqueducts that were on average 0.72 mm larger than their male counterparts. Furthermore, males demonstrated higher hearing thresholds for each frequency tested and consequently worse hearing ability than females. Though frequency-specific differences were not statistically significant due to sample size restrictions, a multivariable analysis adjusting for morphology demonstrated clear differences with males reporting a 17.6 dB greater pure tone threshold measurement when compared to females (95% CI: 3.8, 31.3). Moreover, we did not find a relationship between incomplete partition type II status and hearing loss, which supports previous findings [20].

Interestingly, past research exploring the relationship between EVA

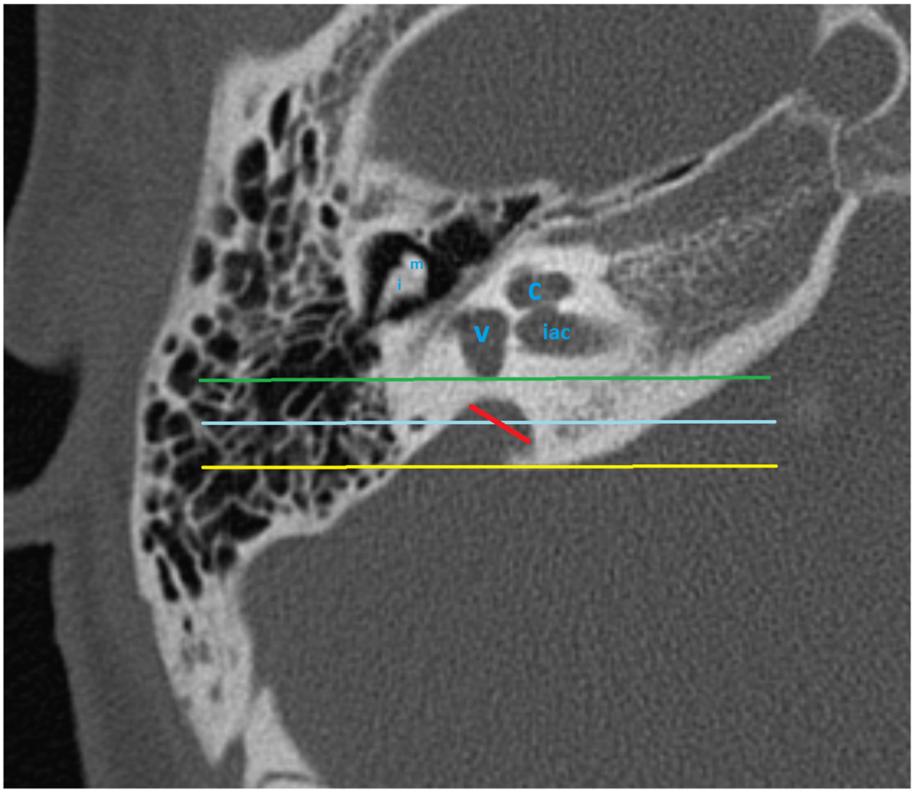

Fig. 1. Axial CT projection of the temporal bone to demonstrate VA sizing method
This axial computed tomographic image of the right temporal bone shows the coronal planes drawn to define the vestibular aqueduct (VA) midpoint plane. The green line represents the vestibular plane, at the level of the posterior wall of the vestibule. The yellow line represents the opercular plane, at the level of the opercular edge. The midpoint plane (light blue line) is equidistant from the vestibular and opercular planes. The actual measurement of the vestibular aqueduct width (short red line) spans the walls of the vestibular aqueduct, and is placed symmetrically above the midpoint plane. The internal auditory canal (iac), cochlea (C), vestibule (V), head of the malleus (m), and long process of the incus (i) are also denoted. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic characteristics (morphology).

n	Overall	Female	Male	p
	79	40	39	
Laterality = right (%)	36 (45.6)	18 (45.0)	18 (46.2)	1.000
IP = positive (%)	35 (44.3)	21 (52.5)	14 (35.9)	0.208
Operculum width (mm)	3.00 [2.15, 4.05]	3.25 [2.65, 4.40]	2.70 [2.00, 3.15]	0.006
Vestibular aqueduct width (mm)	2.20 [1.50, 3.05]	2.80 [1.80, 3.20]	1.90 [1.40, 2.55]	0.004
Age at diagnosis (yrs)	6.60 [5.05, 10.67]	6.18 [4.20, 8.71]	8.50 [5.40, 11.27]	0.147

Table 2
Sex-specific differences in demographic and morphological characteristics.

	Estimate	Confidence interval Range		p value
Age at diagnosis	1.41	−0.8257	3.646	0.2109
VA size difference	−0.72	−1.335	−0.1051	0.02269
Operculum size difference	−0.82	−1.564	−0.07583	0.0315

morphology and hearing loss describe inconsistent findings, with one group of studies reporting a correlation between VA morphology and hearing loss [21,22]. Conversely, a second group of studies report that, after an EVA diagnosis has been established, any increase in VA size does not directly correlate with more severe hearing loss [5,7,14,23]. The results of this study seem to support the latter group's findings, by demonstrating a sex-specific divergence between VA size and hearing loss.

The majority of vestibular aqueduct growth occurs during embryological development, but is fixed at its adult size by 3 years of age [24]. Hence, despite difficulties imaging physical structures in utero, sex-specific morphological differences would ideally be examined at the prenatal level. Interestingly, the McFadden group has previously found that otoacoustic emissions, sounds produced in the inner ear in response to acoustic stimuli, are weaker in males than in females, leading them to the conclusion that the auditory system is sexually dimorphic in infancy [25,26]. They hypothesized that greater prenatal exposure to androgens leads to a weakening of cochlear amplifiers and a small loss

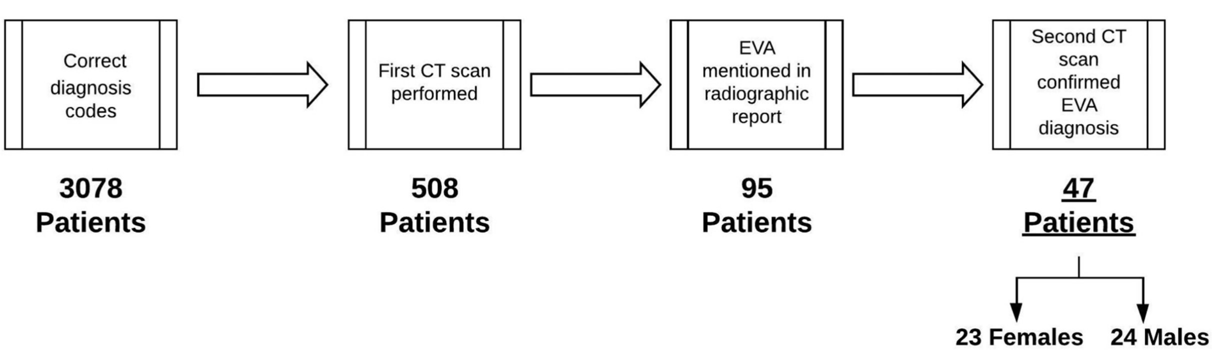

Fig. 2. Study participant inclusion process.

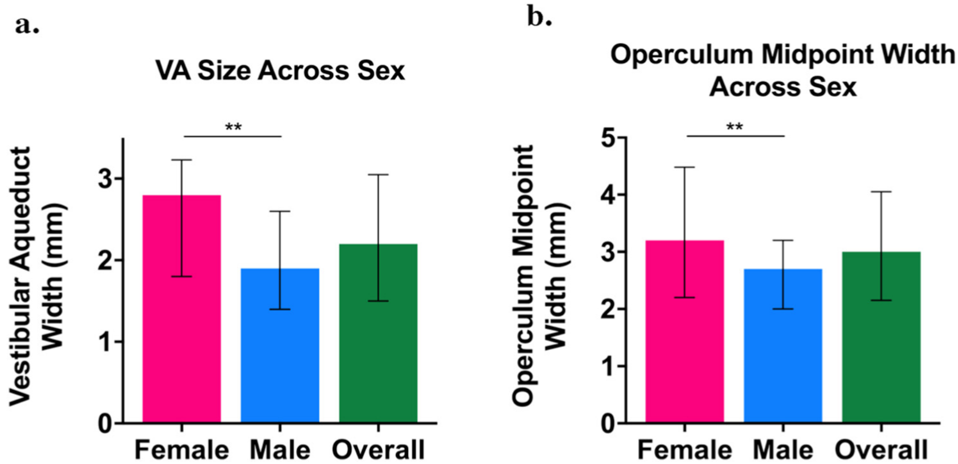

Fig. 3. Morphological differences across sex.
The bars in panels A and B represent mean vestibular aqueduct midpoint width and mean operculum midpoint width respectively; error bars represent 95% confidence intervals. ** indicates $p < 0.01$ by an unpaired two-tailed *t*-test.

of hearing sensitivity. The timing of these prenatal events and the physiological development of the vestibular aqueduct coincide and consequently, this theory may shed light on why females, despite having larger vestibular aqueducts, tended to have better hearing outcomes.

Pathophysiological explanations for EVA and associated hearing loss have not been fully substantiated, but various theories have been proposed, exploring the role of genetics, cochlear dysplasia, elevated pressure waves that damage hair cells [27], reflux of hyperosmolar fluids [11] and electrolyte imbalance [2]. Alternatively, some have argued that a third-window lesion, an abnormal opening in the middle ear, similar in mechanism to semicircular canal dehiscence, facilitates the shunting of sound waves and subsequent hearing loss [23]. How discrepancies of EVA morphology and hearing loss are related to sex is unclear, but weakened cochlear amplifiers and reduced hearing sensitivity in males may predispose them to higher risks of hearing loss due to damaging hyperosmolar fluid reflux or shunting of sound-waves from a third-window lesion.

Since Valvassori and Clemis first defined EVA [15], the clinical criteria of EVA has changed a number of times [4], in part due to morphological heterogeneity. Jackler, Arcand and Levenson all defined EVA as a vestibular aqueduct midpoint measurement > 2 mm [2,11,28]. Alternatively, Okumura proposed that positive EVA diagnoses could either include a vestibular aqueduct midpoint width > 4 mm or a distance between the vestibule and traceable component of the VA < 1 mm [12]. Wilson considered EVA as a vestibular aqueduct midpoint width measuring twice the diameter of the posterior semicircular canal [29].

More recently, Dewan et al. identified that a significant proportion of hearing loss patients did not have EVA by the Valvassori criterion, but who nevertheless had abnormally large vestibular aqueducts, prompting newer definitions of EVA, leading to the now widely-used Cincinnati criteria [14]. Vijayaserkaran et al. found that 95% of pediatric patients without SNHL presented with vestibular aqueducts midpoint widths < 0.9 mm and operculum midpoint widths < 1.9 mm, lending support to this set of criteria [30].

Table 4
Multivariable and univariable analysis of differences in pure-tone average thresholds in males versus females.

Predictor	Multivariable	Univariable
Positive IP status	11.7 (CI: −1.5, 24.9)	5.4 (CI: −8.2, 19.1)
Male sex	17.6 (CI: 3.8, 31.3)	2.9 (CI: −10.7, 16.5)
VA size	14.3 (CI: 8.2, 20.4)	11.0 (CI: 5.1, 16.9)

Despite continuous development of the clinical definition of EVA, one that incorporates sex-specific differences has not yet been explored. However, given the results of the present study, sex-specific discrepancies in morphology and hearing loss in patients with EVA merit further research.

While a clinical definition for EVA that incorporates any sex-specific differences has not yet been explored, given the results of the present study, further examination in sex-specific discrepancies in morphology and hearing loss in patients with EVA should be examined.

5. Conclusion

Further exploration of how demographic factors affect EVA morphology and corresponding hearing outcomes may change the way EVA is approached, potentially leading to an alteration of the current EVA diagnosis criteria. A more comprehensive definition of EVA may help guide clinical management of patients with EVA, hopefully alleviating some of the uncertainty that accompanies a diagnosis of EVA.

Table 3
Frequency specific measure of per-ear median audiometric thresholds.

n	Overall	Female	Male	p
	47	23	24	
250 Hz	43.58 [30.00, 55.79]	33.81 [28.54, 52.68]	50.00 [32.29, 57.82]	0.305
500 Hz	42.50 [30.09, 57.58]	36.49 [30.61, 50.08]	48.25 [29.36, 59.15]	0.401
1000 Hz	48.85 [28.44, 60.24]	42.50 [27.25, 55.07]	52.71 [31.03, 61.57]	0.278
2000 Hz	51.91 [32.07, 63.99]	44.62 [32.07, 61.14]	57.67 [33.72, 63.71]	0.407
4000 Hz	52.69 [37.50, 74.24]	49.09 [41.25, 71.28]	60.40 [34.26, 74.43]	0.725

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