Critical Review: Does the evidence support the use of audiological tests to define characteristics specific to EVA?

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This review critically evaluates the existing literature examining two possible characteristics of EVA, an audiometric air-bone gap and a low resonant frequency of the middle ear. Study designs include a cohort study and case-control studies. Overall, the evidence gathered provides consistent support that EVA should be suspected whenever there is a low frequency air-bone gap and low resonant frequency in combination with normal middle ear function. The findings support the inclusion of bone conduction testing, conventional tympanometry, and multi-frequency tympanometry in the assessment of patients with undiagnosed hearing loss.

Introduction

The development of imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) has led to an increasing number of patients diagnosed with an enlarged vestibular aqueduct (EVA). A diagnosis of an EVA is made when the vestibular aqueduct measures greater than 1.5mm in diameter. The vestibular aqueduct is a bony canal that extends from the vestibule to the posterior cranial fossa and contains the endolymphatic duct as it runs to the endolymphatic sac. EVA is reported to be the most common inner ear anomaly in children with permanent hearing loss and is thought to be due to arrested development in embryonic life and/or postnatal development in early childhood (Zhou et al., 2011). EVA is also associated with Pendred syndrome, which is inherited in an autosomal recessive manner as a mutation of the gene *SLC26A4* (Cremers et al, 1998). EVA typically presents with a downward sloping configuration and is bilateral in 81-94% of cases (Emmett, 1985; Jackler & De La Cruz, 1989). Some patients also experience fluctuations of hearing loss and spontaneous vertigo (Bilgen et al., 2009). The prognosis of EVA is variable but is typically progressive in nature. The hallmark of EVA is sudden and severe drops in hearing if the patient experiences a head injury or increases in inner ear pressure. Therefore, an early and accurate diagnosis is of extreme importance and highlights the need to examine the existing research to discern possible characteristics that arouse suspicion of EVA.

The association between a sensorineural hearing loss and EVA has been well established since the first report by Valvassori and Clemis in 1978. However, there is research to suggest that many patients with EVA also have a conductive component, as indicated by an air-bone gap. Although EVA is known to be variable in its presentation, it is possible that many patients with EVA were presumed to have a sensorineural hearing loss because of a lack of proper bone conduction testing. It is also possible that if bone conduction testing is not completed before the hearing loss progresses, the limits of the bone oscillator may prevent the detection of an air-bone gap from being seen. If there is evidence that an air-bone gap is a characteristic of EVA, then bone conduction audiometry could provide valuable information to the clinician in suspecting EVA. Although an air-bone gap in isolation would not be a good predictor of EVA due to its association with middle ear pathology, it is proposed that bone conduction testing in combination with tympanometry and multi-frequency tympanometry may provide enough information for the clinician to suspect that a patient has EVA. Conventional tympanometry is important to rule out middle ear pathology and to prevent unnecessary surgical procedures that may worsen hearing in an attempt to close the air-bone gap. Multi-frequency tympanometry could also prove to be valuable because it can identify a suspected characteristic of EVA; a low resonant frequency. If there is evidence that a low resonant frequency is a characteristic of EVA, then multi-frequency tympanometry could assist in the differential diagnosis. Since the audiologic assessment is often the first step in the clinical evaluation for patients with hearing loss, this review examines the evidence in support of the use of audiological tests to identify characteristics specific to EVA. Specifically, whether air and bone audiometry in combination with multi-frequency tympanometry would provide clinicians with enough information to suspect EVA in patients.

Objectives

The primary objective of this review is to critically evaluate the existing literature examining two possible characteristics of EVA, an air-bone gap and low resonant frequency. The secondary objective is to determine if the results of this review have clinical implications for the assessment of patients with undiagnosed hearing loss.

Methods

Search Strategy

Computerized databases including Pubmed, Scopus and CINAHL were searched using the following search strategy: [(EVA) OR (enlarged vestibular aqueduct) OR (large vestibular aqueduct)] AND [(air bone gap) OR (conductive) OR (bone conduction)] AND [(tympanometry) OR (multi-frequency tympanometry) OR (resonant frequency)]. The search was limited to the English language and humans.

Selection Criteria

Studies included in this review were required to specifically examine both an air-bone gap and the resonant frequency of the middle ear in EVA patients.

Data Collection

Results of this literature search yielded four studies: one cohort study design, and three case-control study designs.

Results

Cohort Study Design:

Bilgen, Kirkim, and Kirazli (2009) used a prospective cohort study design with an evidence level of 2b, to assess the effect of inner ear pressure on the impedance of the middle ear in EVA patients. They recruited eight patients (n=16 ears) who had been diagnosed with EVA by a high resolution CT scan. The patients were matched according to age to one of three normal-hearing control groups. There were 25 subjects in each control group, who were selected according to the age decades of the cases in the study group. Subjects were excluded from the control group if they had any history of physical or laboratory findings of otology disease. Investigations of all subjects included air and bone audiometry to assess the presence of an air-bone gap, and multi-frequency tympanometry to assess the resonant frequency of the middle ear. Conventional tympanometry was also used to determine the status of the middle ear. All of the study patients were deemed to have normal middle ear function, as indicated by normal middle ear pressure in the range of +/- 50mm H_20. In respect to the air-bone gap and resonant frequency, the authors did not apply a statistical analysis to the data due to the small number of cases. Instead the data was compared between the EVA patients and the control groups with regard to the mean values +/- 2 standard deviations (SD) and presented in graph form. Results showed that five EVA subjects had an air bone gap at the lower frequencies. For those remaining, bone conduction could not be completed due to the severity of the loss and the limits of the bone oscillator. The resonant frequency values of six EVA patients were lower than the mean values +/- 2 SD of the control group. Of the remaining two EVA patients, one of them was on the lower limit of +/- 2 SD, however the other one was lower than the mean value +/- 2 SD. Interestingly, the authors noticed that these two patients were the only ones that experienced hearing loss fluctuations at the time of the study. The authors suggested that these patients also had endolymphatic hydrops, which explains some of the vestibular symptoms that EVA patients experience, as well as fluctuations in hearing.

Case-Control Study Design:

Mimura, Sato, Sugiura, et al. (2005) used a prospective case-control study with an evidence level of 2b, to evaluate EVA patients to determine whether the audiometric Bing test is associated with an air bone gap or middle ear dysfunction. They recruited nine patients with EVA (n= 18 ears) and then compared them to a control group of nine patients (n= 18 ears) with sensorineural hearing loss without EVA. A diagnosis of EVA was confirmed by an MRI to determine the volume of the endolympatic sac. Patients were assessed for an air-bone gap using air and bone audiometry, and middle ear resonance using multi-frequency tympanometry. Patients were also tested using the Bing test, based on the principle that an occluded ear canal improves the perception of bone conducted sounds, unless there is a conductive hearing loss. In addition, conventional tympanometry was used as a measure to assess middle ear function; however, it is only assumed that the patients had normal middle ear function as these results were not included. It was reported that an air-bone gap was found in all patients with EVA in at least 250 or 500Hz. This piece of evidence would have been better supported if mean values and standard deviations were reported as well. The resonant frequency in EVA patients (mean = 690.6Hz, n=16 ears) was considered to be lower than that of the control subjects. Performing a statistical analysis between the study and control group for the resonant frequency would have provided better evidence for this claim. In respect to the Bing test, it was found that the bone conduction thresholds improved for all of the control subjects, but thresholds did not change in 17 out of 18 ears with EVA. This also provides evidence that an air-bone gap is present in EVA patients, but also raises the question as to its etiology. The authors suggest that the “third window” theory is a plausible explanation to explain why the EVA patients in their study typically presented with an air-bone gap and a low resonant frequency. This suggestion is reasonable given that the literature also refers to the “third window” theory; however, no explanation was proposed for the results of the Bing test and overall this study is vague in its descriptions and methodology.

Nakashima, Ueda, Furuhashi, et al. (2000) used a retrospective case-control study with an evidence level of 2b, to investigate the cause of the air-bone gap seen in EVA patients and to examine whether the air-bone gap is larger in comparison to those with other types of sensorineural hearing loss. A diagnosis of EVA was confirmed by MRI in the 15 patients (n=28 ears) that were included in the study group. A control group of patients with sudden idiopathic sensorineural hearing loss (n=28 ears) were matched to EVA patients according to similarity in air conduction thresholds. Pure tone air and bone audiometry, as well as multi-frequency tympanometry records were reviewed to examine if there was an air-bone gap and to determine the resonant frequency of the middle ear. Each patient's acoustic reflexes, VEMP and OAE records were also obtained to assess middle and inner ear function. Acoustic reflexes were present in 17 out of 22 ears, suggesting that the majority of EVA patients had normal middle ear function. With respect to the air-bone gap, it was concluded that EVA patients always had a larger air-bone gap in the low frequencies than is seen in those with sudden idiopathic sensorineural hearing loss with the same air conduction thresholds. The comparison was displayed in chart format which clearly indicated a difference; however, including a report of the mean values and standard deviations would have provided the evidence to strengthen this finding. With respect to the resonant frequency of the middle ear, the results of the study group (n=23 ears) were compared to otosclerosis (n=50 ears) and normal hearing (n=35 ears) control groups. The resonant frequency was found to be in contrast to patients with otosclerosis (mean = 1306Hz); and the resonant frequency of EVA patients was considered to be low (mean = 778Hz) in comparison to the normal hearing controls (mean = 946Hz). An appropriate statistical analysis provided evidence that the mean resonant frequency of EVA patients was significantly lower than that in normal hearing control subjects (*t*-test, $p < 0.05$). The authors concluded that a low frequency air-bone gap and low resonant frequency clearly exist in EVA patients, which they suggest does not seem to be the result of stapes restriction. However, the authors do not rule out other middle ear pathology such as ossicular discontinuity.

Sato, Nakashima, Lilly, et al. (2002) used a prospective case-control study design with an evidence level of 2b, to investigate the relationship between the resonant frequency of the middle ear and the volume of the endolymphatic sac. They examined EVA patients that were referred by other physicians to the authors' tertiary care centre. Each of the EVA patients had an MRI to determine the volume of the endolymphatic sac and to confirm diagnosis. Thirteen patients with EVA (n=24 ears) were compared to those with normal hearing (n=29 ears), as well as those with sensorineural hearing loss (SNHL) without EVA (n=21 ears). Control subjects in both groups were matched approximately to the study group according to age. In addition, those in the SNHL group were matched to EVA patients according to their pure tone average. Audiometric information included air and bone audiometry, which was used to assess whether there was an air-bone gap and multi-frequency tympanometry to determine the resonant frequency. Conventional tympanometry was also used to determine if there was normal middle ear function. The authors implemented an appropriate statistical analysis of the data. Using the Fisher's Protected Least Significant Difference test, the researchers found that the mean air bone gap at 250Hz was significantly greater than at higher frequencies ($p <0.1$ at 500Hz and $p< 0.01$ at 1000Hz). Using the Mann-Whitney U test, it was found that the resonant frequency was significantly lower than both control groups ($p= .0064$ normal hearing controls and $p= .0203$ for the SNHL controls). A downward sloping configuration of hearing loss was seen for most EVA patients. All patients with EVA presented with normal middle ear function as indicated by conventional tympanometry. These findings substantiated the authors' claim that EVA should be included in the differential diagnosis for a patient who presents with a moderate to severe mixed hearing loss, a normal tympanogram and a resonant frequency that is abnormally low.

Discussion

All of the reviewed studies involved an evaluation of the audiometric air-bone gap and the resonant frequency of the middle ear in patients with EVA confirmed by either MRI or CT scan, the current standard for establishing this diagnosis. Case-control studies by Mimura, Sato, Sugiura, et al. (2005), Nakashima, Ueda, Furuhashi, et al. (2000) and Sato, Nakashima, Lilly, et al. (2002) provided a high level of evidence that both an air-bone gap and low resonant frequency are characteristics of EVA. The cohort study by Bilgen, Kirkim & Kirazli (2009) provided additional evidence, which is consistent with the previous studies that EVA patients typically present with an air-bone gap and low resonant frequency. For this type of review it is beneficial that the test methods, pure tone audiometry and multi-frequency tympanometry, result in consistent findings across studies. However, all of the findings should be interpreted with caution as there are limitations that are seen in each study.

Sample recruitment was a weakness in Mimura, Sato, Sugiura, et al. (2005) as there were was no explanation as to how the patients were recruited and whether the study used any criteria for inclusion. Similarly, Nakashima, Ueda, Furuhashi, et al. (2000) did not provide an explanation as to how their EVA patients were recruited; however, they did provide an explanation for their control group. By excluding these details, it limits the extent to which their findings can be generalized to other populations of EVA patients. The results of this review are limited to the adult population, as children were not exclusively included in these studies. The size of the sample was also a concern in all of the studies. A small sample size limits the extent to which the studies can be generalized to a wider population of EVA patients. In addition, Bilgen Kirkim & Kirazli (2009) reported that the small sample size prevented a statistical analysis of the resonant frequency values that were obtained in their study. A statistical analysis of the air-bone gap was not completed in any of the studies except for a statistical analysis of frequency by Sato, Nakashima, Lilly, et al. (2002). Since the clinical criterion of 10 dB is well established in the literature as a significant air-bone gap, this is considered an appropriate substitution for statistical analyzes.

Interestingly, most of the studies proposed an explanation for the air-bone gap and low resonant frequency. The most common conclusion was the theory that in addition to the oval and round windows, there is a “third window”; a term used to describe the vestibular aqueduct as a pressure-release point. The enlargement of the vestibular aqueduct increases the size of this release point, decreasing the mechanical impedance of the inner ear, and thus reducing the resonant frequency (Bilgen et al., 2009). Furthermore, air conducted sounds are shunted away from the cochlea, leading to elevated air conduction pure tone thresholds. The enlargement of the volume of endolymph is also suspected to modify the ossicular-inertial mechanism, cochlear-inertial mechanism and compressional mechanism, which could lead to an improvement in bone conducted hearing resulting in an air-bone gap. Even though this theory is well accepted, more research is needed before any conclusion can be made as to why there is an air-bone gap and low resonant frequency in EVA patients.

There is also a need for further research examining characteristics of EVA in young children as this review cannot be generalized to special populations of EVA patients. In addition, more research should be focused on the clinical use of the resonant frequency of the middle ear. Future studies should build on the research of Bilgen et al., (2009) to examine the resonant frequency of the middle ear in cases of both stable and fluctuating hearing loss.

Research should also focus on examining the sensitivity and specificity of bone conduction testing and multi-frequency tympanometry for EVA. Sato, Nakashima, Lilly, et al. (2002) were the only authors that reported the sensitivity and specificity of the resonant frequency for the diagnosis of EVA. It was found to be 58.3% and 78% respectively. This is a promising finding, and the next step would be to calculate the sensitivity and specificity for the resonant frequency and air-bone gap characteristics combined. In addition, the sensitivity and specificity could be determined for normal tympanometry. This review did not specifically focus on whether normal middle ear function, as determined by tympanometry, was a characteristic of EVA. However, upon further review of the studies, there is suggestive evidence that normal middle ear function is characteristic of patients with EVA. However, this finding may not be characteristic of the pediatric population with EVA.

This review focused on two possible characteristics of EVA that could be identified in the audiology clinic. Vestibular evoked myogenic testing (VEMP) has also been proposed as a test for suspecting EVA. However, this test is not routinely done in audiological assessments, due to equipment availability in most audiology clinics and because the test requires patience and vigilance. Bone conduction audiometry and multi-frequency tympanometry therefore, are proposed to be more appropriate in a typical audiology clinic.

Conclusion

The evidence strongly supports contention that EVA is characterized by a low frequency air-bone gap and a low resonant frequency. Since an air-bone gap is typically associated with middle ear pathology, the combination of these characteristics can be useful in the process of differential diagnosis. Therefore, EVA should be suspected whenever there is a low frequency air-bone gap and low resonant frequency in combination with normal middle ear function. In conclusion, results of this review indicate that bone conduction audiometry and multi-frequency tympanometry provide valuable information and thus should be included in the audiometric assessment of patients with undiagnosed hearing loss.

Clinical Implications

EVA should be suspected when a patient has an air-bone gap in the presence of normal tympanometry and a low resonant frequency. This should also warn clinicians that the air-bone gap is not due to middle ear pathology. The awareness of these clinical features should aid in differentiating EVA from middle ear pathology, thus preventing unnecessary and sometimes devastating middle ear surgery in an attempt to close the air-bone gap. Awareness of the presence of these characteristics will help clinicians make a confident referral for further assessment by an otolaryngologist, who can use this information for a prompt referral for a CT scan or MRI. An early and accurate diagnosis can prevent the progression of hearing loss due to head injury or increases in inner ear pressure through appropriate counseling and precautions. For example, patients with EVA may avoid participating in contact sports and avoid barometric pressure changes such as in scuba diving or flying in an airplane. The conclusion made from this review should provide enough support to implement bone conduction testing, conventional tympanometry and multi-frequency tympanometry in the assessment of patients with undiagnosed hearing loss. When these assessments are made in combination with each other they are more valuable as the entire clinical profile can be evaluated.

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