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Audiological Evaluation of Vestibular Schwannoma Patients with Normal Hearing

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Keywords
Vestibular schwannoma · Auditory brainstem response · Normal hearing

Abstract
Objective: To evaluate the audiological aspects of vestibular schwannoma (VS) patients with normal hearing. ***Study Design:*** Retrospective study. ***Setting:*** Quaternary referral center for skull base pathologies. ***Patients:*** The records on 4,000 patients who had been diagnosed with VS between 1986 and December 2017 were retrospectively reviewed. The patients included in the study were the ones who complied with the strict audiological normality criteria, as follows: a pure tone hearing threshold (at the 6-octave-spaced frequencies from 250 to 8,000 Hz) ≤25 dBHL; a word recognition score >90%; and interaural differences ≤10 dB at each frequency. ***Interventions:*** Auditory brainstem response (ABR) testing and radiological imaging. ***Main Outcome Measures:*** The incidence of normal objective hearing among VS patients, and the diagnostic utility of the ABR and the effect of tumor size and site on the response. ***Results:*** The incidence of normal hearing among VS patients was 4.2%. Tinnitus and vertigo were the most common symptoms across tumor grades; 5.6% of the tumors were large and giant tumors. The ABR yielded a sensitivity of 73.6%, with a false negative rate of 26.3% using a cutoff point of 0.2 ms for interaural latency differences. ***Conclusions:*** The diagnosis of VS should not be based on audiometric thresholds alone. Alarming signs of VS should be clear to the physician in order not to miss or delay the diagnosis of the disease. The ABR is useful in the diagnosis of VS, but normal results do not exclude the occurrence of the disease in patients with normal hearing.

Introduction

Vestibular schwannoma (VS) represents 80% of all cerebellopontine angle masses and 6% of all intracranial tumors [Sanna et al., 2011]. Hearing loss is the index symptom in 95% of patients presenting with VS [Johnson, 1977]. Nevertheless, a subset of VS patients presents

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with normal hearing (NH), and they have previously been assessed in several studies [Johnson, 1977; Beck et al., 1986; Musiek et al., 1986b; Roland et al., 1987; Ogawa et al., 1991; Selesnick and Jackler, 1993; Shaan et al., 1993; Morrison and Sterkers, 1996; Saleh et al., 1996; Kanzaki et al., 1997; Magdziarz et al., 2000; Day et al., 2008; Pinna et al., 2012], with the incidence ranging from 1.5 to 12%. Schuknecht [1964] suggested that up to 75% of auditory nerve fibers can be damaged with a negligible effect on the pure tone average (PTA). On the other hand, some authors stated that functional abnormalities in electrical responses appear before the structural defect appears [Josey et al., 1988]. Hence, in 1977, auditory brainstem response (ABR) testing became a fundamental tool to screen patients for VS [Selters and Brackmann, 1977]. The ABR sensitivity for detecting large tumors is 95.6%, while it is 85.8% for small tumors [Koors et al., 2013]. Since magnetic resonance imaging (MRI) has 100% sensitivity for detecting VS [Vandervelde and Connor, 2009], some authors [Cueva, 2004; Rafique et al., 2016] argue that MRI should supersede the ABR as the initial screening test for VS, but other authors [Grayeli et al., 2009] have disagreed. Hence, the role of the ABR in investigating a potential retrocochlear pathology remains controversial.

The aim of the present work was to study the prevalence of NH among patients with VS and the characteristics of the ABR in such patients. Ours being a quaternary referral center for the treatment of VS, with one of the largest published series in the literature, we attempted to study the diagnostic benefit from further testing by ABR prior to MRI in the presence of any other symptoms of VS, harboring a high index of suspicion for the disease. We also studied the relation between ABR abnormality and the extent of involvement of the 8th nerve or brainstem by the tumor along with the effect of tumor size or site. Saleh et al. [1996] had previously studied NH in VS patients at our center. We have expanded the series, taking into consideration the exponential increase in patients since then, as well as a commentary [Qiu and Morgan, 1997] on that work.

Patients and Methods

The database used belongs to Gruppo Otologico, a quaternary center for the treatment of skull base tumors in Piacenza/Rome, Italy. The records on 4,000 patients who had been diagnosed with VS between 1986 and 2017 were retrospectively reviewed. Patients with neurofibromatosis type 2 and other cerebellopontine angle tumors were not included, as they are different entities [Kanzaki et al., 2003].

On each patient, the following information was gathered: (1) demographic data – sex and age at time of diagnosis; (2) presenting symptoms and associated signs; (3) audiological examination data, which included (a) the pure tone hearing threshold at the 6-octave-spaced frequencies from 250 to 8,000 Hz and (b) the ABR; and (4) details on the available imaging technique (CT or MRI) – the showing side, site, and size of the lesion.

NH was defined as (1) a PTA ≤25 dBHL [WHO, 1991], (2) thresholds at each frequency ≤25 dBHL [WHO, 1991], (3) a word recognition score (WRS) >90%, and (4) interaural differences ≤10 dB at each frequency (on the basis of 5-dB variation in audiometrics and 10-dB test-retest reliability).

Different evoked systems were used during the past 30 years, but with the same parameters for ipsilateral stimuli. The ABR was recorded with a 2-channel system with the standard electrode montage. Clicks were presented at 80 dBnHL via TDH-39 headphones with a rate of 21.1/s, an alternating polarity, 2,000 sweeps, an epoch of 12 ms, a digital high-pass filter at 100 Hz, a low-pass filter at 3 kHz, and a gain of 100K.

The following criteria were defined for a normal ABR at 80 dBnHL: (1) bilateral well-defined waveforms (waves I through V clearly discernible), even if waves IV and V could appear as a single complex; (2) replicated ABR waveforms; (3) assessment of recorded interaural latency differences (ILDs) between waves I, III, and V and intervals I–III, III–V, and I–V; and (4) consideration of any ILD ≤0.2 ms as normal. The contralateral ear was taken as a reference for normative data on which an intrasubject comparison of absolute and interwave latencies was done. Any deviations from the abovementioned normality criteria were considered as abnormal ABRs.

In patients with available MRI data, VS tumor size was measured as the maximum diameter of the extracanalicular portion of the tumor in any one plane on MRI and was assessed by investigators who were blinded to the ABR data. In addition, occupation of the fundus of the internal auditory canal by the tumor was recorded (fundus status). Tumor size was classified according to the Consensus Meeting for Reporting Results in Vestibular Schwannoma held in Tokyo in 2003 [Kanzaki et al., 2003]: grade 0 = intrameatal; grade 1 = small (1–10 mm), extrameatal; grade 2 = medium (11–20 mm); grade 3 = moderately large (21–30 mm); grade 4 = large (31–40 mm); and grade 5 = giant (>40 mm).

Facial nerve damage was documented and recorded according to the House-Brackmann grading [House and Brackmann, 1985].

Statistical Analysis of the Data

Microsoft Office Excel 2007 and was used for data management. The data were entered into the computer and analyzed using the IBM SPSS software package version 20.0.

Results

A total of 4,000 patients with VS were treated at our center; however, records on 232 of them were unavailable. Of the 3,768 remaining patients, 162 had NH (4.2%).

Data on presenting symptoms were available for 136 of the 162 patients (Tables 1, 2). ABR data were available

Table 1. Distribution of the studied cases according to symptoms (n = 136)

Symptoms	Total		Only symptom	
	n	%	*n*	%
Tinnitus	74	54.4	15	11.0
Hearing loss	41	30.1	5	3.6
Sudden hearing loss	18	13.2	7	5.1
Fullness	18	13.2	1	
Vertigo	48	35.3	10	7.3
Instability	31	22.8	6	4.4
Dizziness	6	4.4	0	
Dropping attacks	5	3.7	1	
Facial nerve	4	2.9	1	
Headache	5	3.7	1	
Paresthesia of the face (TN)	10	7.4	2	
Incidental diagnosis	5	3.7	3	
Impaired comprehension	2	1.5	1	

Data on presenting symptoms were available for 136 of the 162 patients. TN, trigeminal neuralgia.

for 133 of the 162 patients (Tables 3, 4; Fig. 1). Data on both symptoms and the ABR together were available for 114 of the 162 patients (Fig. 2).

Table 2 describes the relation between tumor grade and symptoms. The most frequent tumor grade was grade 0 (intrameatal) (in 64/162 patients; 39.5%), followed by grade 1 (in 48/162 patients; 29.6%). Notably, 5.6% of the tumors were large (3.7% [in 6/162 patients] were large [grade 4] and 1.9% [in 3/162 patients] were giant [grade 5] tumors), with the patients presenting with normal objective hearing. Tinnitus and vertigo were the most common symptoms across tumor grades.

Auditory Brainstem Response

ABR sensitivity was 73.6% (98/133 cases), with a false negative rate of 26.3% (35/133 cases) using a cutoff of 0.2 ms for ILDs. The ABRs were categorized from the least to the most distorted, as described in Table 3.

Our findings are as follows:

1. As presented in Figure 1, there was a statistically significant relation ($p < 0.001$) between tumor grade and ABR, i.e., as the tumor grade increased, abnormalities in the ABR increased as well
2. There was no statistically significant relation between internal auditory canal fundus status and ABR results ($p = 0.384$)
3. No relation was observed between patient age and ABR results ($p = 0.696$)
4. No significant association between ABR results and presenting symptoms was noted; however, there was a near-significant incidence of normal ABR in cases presenting with dropping attacks ($^{FE}p = 0.055$) (Fig. 2)
5. No statistically significant difference was found upon comparing the original normative data for ABR indices and the contralateral ear indices ($p = 0.313$) (Table 4)

Cervical vestibular-evoked myogenic potential data were available for 7 patients, but they were not beneficial.

Discussion

In contrast to clinical estimates of VS incidence (0.7–1/100,000/year) [Berrettini et al., 1996], cadaveric studies have suggested a much higher incidence of 2.4% [Lin et al., 2005]. This discrepancy may be related to the two facts that 70% of VSs are nongrowing [Stangerup and Caye-Thomasen, 2012] and that up to 15% of patients with VSs have NH, which makes the diagnosis of VS more arduous. Consequently, asymptomatic or minimally symptomatic patients might be missed.

Incidence

Though Magdziarz et al. [2000] applied strict criteria for audiological normality, the PTA was their main parameter for a normal audiogram, not taking into consideration the remaining frequencies. In addition, they did not exclude patients with poor WRSs alone. Saleh et al. [1996] reported using two different criteria for NH, one including all frequencies ≤25 dB and the other excluding 8,000 kHz, and the incidence of NH among VS patients was 8.6 and 16%, respectively; however, they also included abnormal WRSs. These variable criteria for NH led to a wide range of incidence rates (1.5–12%) [Johnson, 1977; Beck et al., 1986; Musiek et al., 1986b; Roland et al., 1987; Ogawa et al., 1991; Selesnick and Jackler, 1993; Shaan et al., 1993; Morrison and Sterkers, 1996; Saleh et al., 1996; Kanzaki et al., 1997; Magdziarz et al., 2000; Day et al., 2008; Pinna et al., 2012]. A probable explanation is that most patients report no hearing impairment when their PTA levels (used by most authors) are ≤25 dBHL [Beck et al., 1986].

To the best of our knowledge, the present study is the first to use strict audiometric parameters (including ≤25 dBHL in all frequencies) [WHO, 1991; Selesnick and Jackler, 1992] while exclusively examining a large number of VS patients (4,000 patients). The reason we adopted these criteria was that even if a patient is not complain-

Table 2. Relation between tumor size and symptoms (n = 136)

Symptoms	Tumor size												χ^2	^{MC}p
	grade 0 (intrameatal) (n = 55)		grade 1 (small 1–10 mm, extrameatal) (n = 39)		grade 2 (medium 11–20 mm) (n = 25)		grade 3 (moderately large 21–30 mm) (n = 9)		grade 4 (large 31–40 mm) (n = 5)		grade 5 (giant >40 mm) (n = 3)			
	n	%	n	%	n	%	n	%	n	%	n	%		
Tinnitus	26	47.3	24	61.5	14	56.0	6	66.7	2	40.0	2	66.7	3.217	0.692
Hearing loss	18	32.7	11	28.2	8	32.0	1	11.1	2	40.0	1	33.3	2.346	0.837
Sudden hearing loss	7	12.7	7	17.9	4	16.0	0	0.0	0	0.0	0	0.0	2.216	0.802
Fullness	3	5.5	7	17.9	5	20.0	3	33.3	0	0.0	0	0.0	8.391	0.093
Vertigo	19	34.5	15	38.5	8	32.0	3	33.3	3	60.0	0	0.0	2.944	0.738
Instability	14	25.5	8	20.5	3	12.0	3	33.3	2	40.0	1	33.3	4.380	0.478
Dizziness	3	5.5	1	2.6	1	4.0	0	0.0	0	0.0	1	33.3	5.016	0.365
Dropping attacks	4	7.3	0	0.0	1	4.0	0	0.0	0	0.0	0	0.0	4.117	0.497
Facial nerve	0	0.0	2	5.1	2	8.0	0	0.0	0	0.0	0	0.0	5.942	0.279
Headache	1	1.8	0	0.0	3	12.0	0	0.0	0	0.0	1	33.3	10.341*	0.030*
Paresthesia of the face (TN)	2	3.6	1	2.6	2	8.0	2	22.2	2	40.0	1	33.3	13.417*	0.009*
Incidental diagnosis	0	0.0	1	2.6	2	8.0	0	0.0	2	40.0	0	0.0	12.695*	0.009*
Impaired comprehension	1	1.8	0	0.0	0	0.0	1	11.1	0	0.0	0	0.0	6.940	0.268

Data on presenting symptoms were available for 136 of the 162 patients. χ^2, p: χ^2 and p values for χ^2 test. ^{MC}p: Monte Carlo p values for χ^2 test. TN, trigeminal neuralgia. * Statistically significant at $p \leq 0.05$.

Table 3. Distribution of the studied cases according to ABRs (n = 133)

ABRs	n	%
Normal	35	26.3
Abnormal	98	73.6
Distorted/absent waves (no delay)	2	1.5
Delayed ILD	22	16.5
Delayed and distorted waves	26	19.5
Extremely delayed ILD V or ILD I–V ≥1 ms	20	15.0
Absent ABR (maybe wave V)	28	21.0

ABR data were available for 133 of the 162 patients. ABR, auditory brainstem response; ILD, interaural latency difference.

Table 4. Comparison between two methods of ABR assessment (n = 133)

ABRs	Contralateral ear indices		Fixed indices		χ^2	p
	n	%	n	%		
Normal	35	26.3	28	21.1	1.019	0.313
Abnormal	98	73.7	105	78.9		

ABR data were available for 133 of the 162 patients. χ^2, p: χ^2 and p values for χ^2 test. ABR, auditory brainstem response.

ing of hearing loss, the presence of any threshold at any frequency >25 dB or any interaural asymmetry should raise the suspicion of the examiner. In addition, high-frequency thresholds are important clinical indicators that should not be missed, because VS often causes high-frequency sensorineural hearing loss [Selesnick and Jackler, 1992]. Consequently, the PTA should not be the only measure defining NH.

The incidence of NH among our patients with VS was 4.2%. This did not include either cases of abnormal WRS or sudden hearing loss (SHL). We agree with the literature that a high WRS does not exclude VS [Roland et al., 1987; Magdziarz et al., 2000], since 100% of our cases had excellent WRSs >90%. However, a low WRS should raise the suspicion of retrocochlear pathology. Patients with SHL with their hearing completely recovered after treatment were excluded owing to their previous history of hearing loss and to the fact that 10–15% of VSs induce SHL [Pensak et al., 1985; Berg et al., 1986].

Demography

We report a 2.3:1 female-to-male ratio, which is similar to the ratio (3:1) reported in the literature [Swensson et al., 2008; Pinna et al., 2012]. In accordance with the literature, the present study showed a slight preponderance of the left side (51.9%) [Swensson et al., 2008; Pinna et al., 2012].

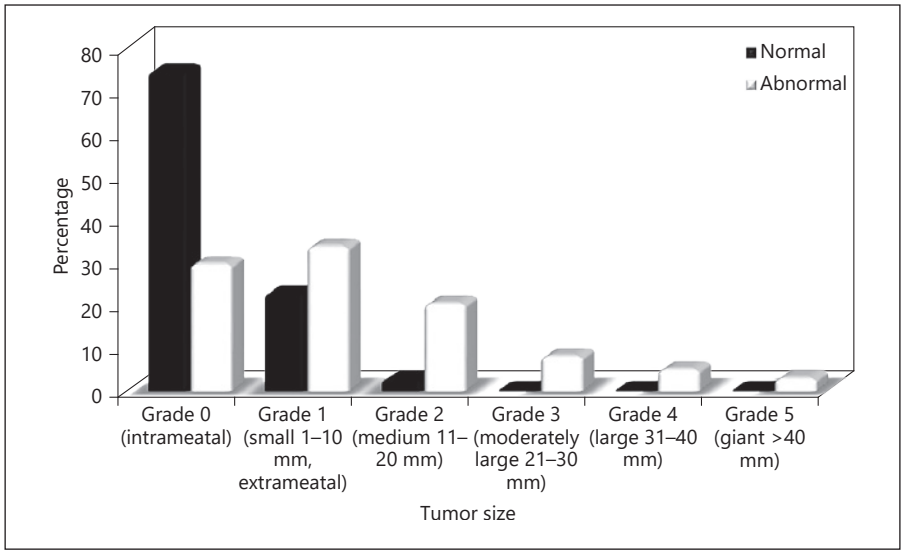

Fig. 1. Relation between auditory brainstem response and tumor size (grade) (n = 133).

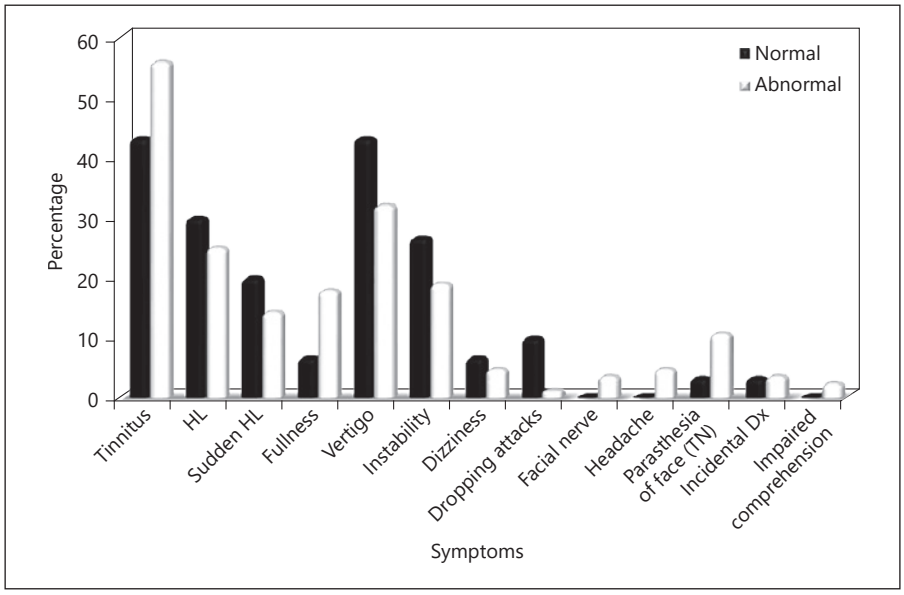

Fig. 2. Relation between auditory brainstem response and symptoms (n = 114). HL, hearing loss; TN, trigeminal neuralgia; Dx, diagnosis.

VS has been diagnosed in patients of all ages, but it is more frequent above the age of 50 years [Swensson et al., 2008]. For the subset of NH patients, the mean age is 10 years lower (40 years) [Ogawa et al., 1991; Morrison and Sterkers, 1996; Magdziarz et al., 2000], which is similar to the 40.27 years in the present study. Most of our patients (64.7%) were aged between 30 and 50 years. The youngest patient in our study was 10 years old, whereas the youngest reported case was a 7-year-old child [Krause and McCabe, 1971]. An explanation for the younger age of those patients could lie in the fact that symptoms such as tinnitus, subjective hearing loss, or vertigo might be more distressing to young patients and that, therefore, they seek medical care earlier. Moreover, neural plasticity is greater in young patients [Ogawa et al., 1991], and their nerves are more tolerant to compression and stretching.

Symptomatology

In our study and others [Roland et al., 1987; Selesnick et al., 1993; Magdziarz et al., 2000], VS patients with NH had high variability in symptoms. VS could easily have been overlooked in these patients if clinicians were unaware of the less common presenting symptoms.

In multiple studies, tinnitus was the most frequent symptom, as in ours (54.4%), presenting alone or with other symptoms [Roland et al., 1987; Ogawa et al., 1991;

Saleh et al., 1996]. Subjective hearing loss was the second most frequent symptom (43.3%), similar to what was reported by Roland et al. [1987] and less than what was reported by Ogawa et al. [1991] (who found an incidence of 70%). Hearing loss presented without any previous or current change in audiometric test measures. Two patients (1.5%) experienced impaired comprehension, which could be related to a subjective sense of hearing loss.

Vertigo was the third most frequent symptom (35.3%). The frequency of vertigo in our study was higher than in the general population of VS patients [Roland and Glasscock, 1991; Swensson et al., 2008], since most of our patients who complained of vertigo had tumors in early stages (grades 0 and 1), when no adequate central compensation [de Vries et al., 1985] has happened yet. One patient had a history of benign paroxysmal positional vertigo. Consequently, if a patient with benign paroxysmal positional vertigo is resistant to repositioning maneuvers, a retrocochlear pathology should be suspected. Five patients suffered from dropping attacks (3.7%), more frequently occurring among patients with grade 0 tumors (4/5 patients).

Generally, a sense of instability and imbalance is secondary to tumor growth and probably a result of cerebellar compression in VS patients [Roland and Glasscock, 1991]. In disagreement with this, but in accordance with the results of Kentala and Pyykkö [2001], we found no association between these symptoms and tumor size. Meanwhile, our results demonstrated a trend relating aural fullness to moderately large tumors of grade 3 ($p = 0.09$). Among our patients, 13.2% complained of aural fullness, while in the study by Roland et al. [1987], it was 25%.

The facial nerve was affected in 4 of our patients (2.9%) of slightly younger age (mean age 30 years). This percentage was lower than in the literature (10–18%) [Edwards and Paterson, 1951; Selesnick et al., 1993; Stucken et al., 2012] because of the smaller tumor size in the subset of patients in this study. Owing to the small number of patients, we did not draw any conclusions regarding a relation between facial nerve affection and tumor size. Facial nerve affection occurred in the form of hemifacial spasm in 1 patient (a 10-year-old child), as well as a grade 2 and grade 3 House-Brackmann classification [House and Brackmann, 1985] in 2 patients; 1 patient had a history of facial paralysis that had recovered 1 year before the diagnosis. Trigeminal nerve affection was observed in 10 patients (7.4%) in the form of trigeminal neuralgia, paresthesia, dysesthesia, or corneal hypoesthesia. Saleh et al. [1996] reported a 25% rate of affection of the 5th cranial nerve among their cases. In agreement with the literature [Selesnick et al., 1993; Stucken et al., 2012], our results show a statistically significant relation between 5th nerve dysfunction and great tumor size, especially of grades 4 and 5 ($p = 0.009$).

Headache has been linked to tumor size in VS patients, since it is considered a symptom of increased intracranial pressure [Selesnick et al., 1993; Stucken et al., 2012], along with optic nerve papilledema, which was seen in 2 of our patients with grade 3 and 4 tumors. In our study, headache was encountered in 5 cases (3.7%) and was statistically significantly associated with grade 5 tumors ($p = 0.03$). The prevalence of incidental diagnoses ranged from 0.02 to 0.2% on brain MRI [Lin et al., 2005; Morris et al., 2009]. In our study, incidental diagnosis occurred in 5 patients (3.7%). The appearance of a specific symptom was not related to patients' age, except for aural fullness, which was more often observed at a mean age of 44 years.

Auditory Brainstem Response

The ABR is a sensitive test for detecting alterations induced by tumors; its sensitivity for any size is 93.4% according to the meta-analysis by Koors et al. [2013]. Pressure of the tumor against the auditory nerve does not cause conduction block but desynchronization of the firings of its fibers [Selters and Brackmann, 1977; Eggermont et al., 1980], which appears as abnormal ABR findings.

An abnormal ABR was identified according to the previously mentioned criteria in the Patients and Methods section. We chose the ear contralateral to the tumor as a reference for normative data for the following reasons: Hall [2015] stated that "ABR latency values for equivalent right- and left-ear stimulation are typically rather symmetrical"; therefore, abnormalities due to hearing loss were not expected to be found in the contralateral ear in NH patients. In addition, using the patient as her or his own control in the analysis of ILDs eliminates the possible influence of certain subject factors such as age, gender, and body temperature [Hall, 2015].

Generally, when the ABR is used for screening, maximum sensitivity (i.e., a low number of false negatives) is essential [Guyot et al., 1992] to decrease the need for MRI. Therefore, we defined the normal limit for interaural ear differences as ≤0.2 ms to obtain the lowest frequency of false-negative results based on the findings of Kanzaki et al. [1991]. Though improving sensitivity comes at the expense of losing some of the specificity (i.e., a high number of false positives) [Guyot et al., 1992], false positives were unlikely to occur among our patients with NH.

In our study, ABR testing yielded a sensitivity of 73.6% (98/133) with a false negative rate of 26.3% (35/133) using a cutoff of >0.2 ms for ILDs. Increasing the cutoff to >0.4 ms, the sensitivity decreased to 61.6% with a false negative rate of 38.3%. Our results agree with other studies in which sensitivity was found to be lower when the interaural difference was >0.4 ms [Wilson et al., 1992; Dornhoffer et al., 1994]. Some studies have reported the ABR to be highly sensitive for screening for VS [Musiek et al., 1986b; Ogawa et al., 1991], whereas others did not [Saleh et al., 1996; Magdziarz et al., 2000]. The drawback of the previous studies is their limited sample size.

In a large prospective study by Cueva [2004] on patients with asymmetric hearing loss, owing to the low sensitivity of the ABR (71%) in his results, the author advised against using the ABR for VS screening and was in favor of using MRI only, but under certain conditions. Though our ABR sensitivity (73.6%) was similar to that found by Cueva [2004], by applying his protocol to our 162 NH patients, neither the ABR nor MRI would have been assessed, and they would have been missed. To our knowledge, the present study was the first to examine a large number of NH patients. We deducted that in NH patients, an abnormal ABR strongly indicates the presence of VS, though having a normal ABR does not exclude VS.

It is worth mentioning that a higher sensitivity was obtained when we evaluated the ipsilateral ABR with different normative data for ABR indices. ABR sensitivity increased to 78.9% (105/133), with a false negative rate of 21.1% (28/133). Evaluating ABR indices against fixed values resulted in diagnosing 7 more patients when compared to using intrasubject comparison; however, the difference between the two methods did not reach statistical significance (Table 4). It is obvious that the occurrence of false negatives is inevitable, but the key is choosing criteria that yield the lowest number of false negatives.

For most authors [Musiek et al., 1986a; Josey et al., 1988; Kanzaki et al., 1991; Dornhoffer et al., 1994; Godey et al., 1998; Schmidt et al., 2001; Shih et al., 2009] and in our study, the most sensitive criteria for identifying VS were ILD V and ILD I–V, since they yielded the lowest false-negative values. However, if they were unobtainable, we relied on other ABR parameters for diagnosis. The fact that wave V was the most persistent wave in our study even in the absence of other waves might be explained by two factors: first, it arises from the inferior colliculus, which is located away from the tumor; second, the remaining undamaged fibers of the cochlear nucleus may be adequately intact to propagate impulses to the brainstem, resulting in a present – but usually delayed – wave V [Musiek et al., 1986a].

Our study is in accordance with studies [Kanzaki et al., 1991; Chandrasekhar et al., 1995; Kanzaki et al., 1997; Magdziarz et al., 2000; Grayeli et al., 2009] that proved affection of ABR sensitivity by tumor size. A statistically significant relation ($p < 0.001$) was detected: as the tumor grade increases, abnormality of the ABR increases. In the literature, a low diagnostic sensitivity (between 58 and 82%) of the ABR for small lesions (e.g., <1 cm) was reported [Godey et al., 1998; Schmidt et al., 2001; Grayeli et al., 2009]. In the present study, the sensitivity for small tumors (grades 0 and 1) was 64.5% (62/96 patients), while for tumors of medium to giant size (grades 2–5), the sensitivity was 97.2% (36/37 patients). Hence, we can relate our relatively low overall ABR sensitivity to the fact that 69.1% of our patients had small tumors (grades 0 and 1).

Since an established relationship was found between tumor size and ipsilateral ABR, the contralateral ABR should be evaluated as well. According to Shih et al. [2009], VS should be suspected when the contralateral wave I or wave V is abnormal, and an abnormal contralateral interpeak III–V latency and wave V suggests that the tumor size may be >2 cm. In agreement with these results, we observed that giant tumors altered the contralateral ABR. All 3 cases with a tumor size of grade 5 in our study had an absent or extremely delayed ipsilateral ABR, while 2 of them had an altered contralateral ABR. Still, this was not the case for tumors of grades 3 and 4, as none of the patients had an abnormal contralateral ABR. We calculated the delay in contralateral ABR using these ABR indices: increased I–III interval >2.5 ms, III–V interval >2.1 ms, or I–V interval of 4.4 ms. One may wonder why we used interaural comparison of latencies using the ABR of the contralateral ear as a reference even though it can be affected by the tumor. Our justification is that among all of our cases, the contralateral ABR was only affected with giant tumors, and only if the ipsilateral ABR was extremely distorted or completely absent; therefore, there was no need to use a reference in these cases.

No significant association between ABR results and symptoms was noted. There was a near-significant incidence of normal ABRs in cases presenting with dropping attacks ($p = 0.05$). Facial nerve and trigeminal nerve affection, headache, and tinnitus were more often observed with abnormal ABRs. In our study, age had no influence on the ABR results, in contrast to the study by Grayeli et al. [2009], where false-negative ABRs occurred in their senior patients. In accordance with other studies [Musiek et al., 1986b; Dornhoffer et al., 1994; Day et al., 2008], we

did not find any significant differences in ABR findings in relation to occupation of the fundus by the tumor (tumor site).

Magnetic Resonance Imaging

In a huge Danish study [Rafique et al., 2016], MRI screening was reported to be more cost-effective than ABR testing. On the other hand, considering the discrepancy between VS incidence rates obtained from cadaveric, clinical, and radiological studies, a very large number of MRI scans performed for diagnosing VS will be expected to be negative. According to a recent estimation, only 1.09–5.23% (specificity) of all MRI scans performed for assessment of asymmetric hearing loss lead to a VS diagnosis [Cheng and Wareing, 2012; Waterval et al., 2018]. Consequently, in the case of NH, the specificity percentage will be much lower. The high costs of MRI – a major limiting factor in any screening protocol, along with its unavailability – are peculiarly relevant in developing countries where health insurance programs and medical resources are restricted. In contrast, ABR testing is less expensive, less time-consuming, and more accessible. The ABR also has a role in patients for whom MRI is contraindicated because of ferromagnetic implants, obesity, or claustrophobia [Cheng and Wareing, 2012]. ABR testing is also important for deciding on approaches to hearing preservation [Stucken et al., 2012]. These factors support the use of the ABR as an initial screening test for VS.

Modified MRI (fast spin-echo MRI) techniques are more cost-effective than ABR testing. However, they are not as widely available and may yield occasional false-negative results according to Daniels et al. [1998].

The latest EAONO statement on VS concluded that the authors did not find any prospective studies on indications for performing MRI in the case of asymmetric hearing loss. Therefore, in the case of NH, ABR testing will definitely be a helpful tool [Waterval et al., 2018].

We advise that ABR testing be included in the routine test battery on the patients' first visit even if the patients have NH, as long as they present with symptoms, since with bilaterally symmetrical NH, it is unlikely that abnormalities in the ABR are produced without the presence of a tumor or a retrocochlear pathology.

We found that ABR results were one of the major reasons for MRI referral. However, in cases of NH and normal ABR findings there still are other reasons for MRI referral, such as neurological complaints (facial palsy and trigeminal neuralgia), which will help reduce the false negative rate. Other patients with vague symptoms (fullness or dizziness) and normal PTA and ABR results should be followed up with PTA and ABR testing. These patients are highly unlikely to have a VS – and, if so, most likely have only a very small one. On the other hand, the rest of the patients (the true-positive 73%) normally would be missed or referred to other departments – for example, patients with bilateral tinnitus. Consequently (considering the incidence of VS), it is expected to be cost-effective to start with ABR testing before making a decision about MRI.

Limitations

As an inherent effect in retrospective analyses, our study is limited by the accuracy and completeness of the medical records of the patients. We could not include prospective control cases saving the cost and the hazard of exposing normal individuals to MRI to confirm the absence of VS. In addition, the records of retrospective control cases were deficient.

Conclusions

Diagnosis of VS might be hindered if the physician considers a normal audiogram as an exclusion criterion for a retrocochlear pathology. A wide range of symptoms including unilateral tinnitus, subjective hearing loss, and others highlighted in this work should warrant further workup, as should any aberration in concomitant test batteries such as the WRS. The diagnosis of a large subset of NH patients may have been missed without the use of ABR testing. A low ILD cutoff of 0.2 ms is preferred when it is the aim to diagnose VS in NH patients. However, the presence of false-negative ABR findings may delay the diagnosis of VS. Therefore, the interpretation of ABRs must be adapted to the index of suspicion: if it is high and the ABR is normal, then the ABR should be considered inconclusive and MRI should be demanded, as ABR testing may miss smaller tumors; if it is low and the ABR is normal, irrespective of the audiogram, the physician should either proceed to MRI or conduct a close follow-up.

Statement of Ethics

This study was undertaken with approval from the Research Ethics Committee of the Faculty of Medicine, Alexandria, Egypt, and the CDC, Piacenza, Italy.

Disclosure Statement

The authors have no conflict of interest to declare.

References

Beck HJ, Beatty CW, Harner SG, Ilstrup DM. Acoustic neuromas with normal pure tone hearing levels. Otolaryngol Head Neck Surg. 1986 Jan;94(1):96–103.

Berg HM, Cohen NL, Hammerschlag PE, Waltzman SB. Acoustic neuroma presenting as sudden hearing loss with recovery. Otolaryngol Head Neck Surg. 1986 Jan;94(1):15–22.

Berrettini S, Ravecca F, Sellari-Franceschini S, Bruschini P, Casani A, Padolecchia R. Acoustic neuroma: correlations between morphology and otoneurological manifestations. J Neurol Sci. 1996 Dec;144(1-2):24–33.

Chandrasekhar SS, Brackmann DE, Devgan KK. Utility of auditory brainstem response audiometry in diagnosis of acoustic neuromas. Am J Otol. 1995 Jan;16(1):63–7.

Cheng TC, Wareing MJ. Three-year ear, nose, and throat cross-sectional analysis of audiometric protocols for magnetic resonance imaging screening of acoustic tumors. Otolaryngol Head Neck Surg. 2012 Mar;146(3):438–47.

Cueva RA. Auditory brainstem response versus magnetic resonance imaging for the evaluation of asymmetric sensorineural hearing loss. Laryngoscope. 2004 Oct;114(10):1686–92.

Daniels RL, Shelton C, Harnsberger HR. Ultra high resolution nonenhanced fast spin echo magnetic resonance imaging: cost-effective screening for acoustic neuroma in patients with sudden sensorineural hearing loss. Otolaryngol Head Neck Surg. 1998 Oct;119(4):364–9.

Day AS, Wang CT, Chen CN, Young YH. Correlating the cochleovestibular deficits with tumor size of acoustic neuroma. Acta Otolaryngol. 2008 Jul;128(7):756–60.

de Vries N, Bles W, Feenstra L. Patients with an acoustic neurinoma examined with a tilting room. Clin Otolaryngol Allied Sci. 1985 Apr;10(2):103–8.

Dornhoffer JL, Helms J, Hoehmann DH. Presentation and diagnosis of small acoustic tumors. Otolaryngol Head Neck Surg. 1994 Sep;111(3 Pt 1):232–5.

Edwards CH, Paterson JH. A review of the symptoms and signs of acoustic neurofibromata. Brain. 1951;74(2):144–90.

Eggermont JJ, Don M, Brackmann DE. Electrocochleography and auditory brainstem electric responses in patients with pontine angle tumors. Ann Otol Rhinol Laryngol Suppl. 1980 Nov-Dec;89(6 Pt 2):1–19.

Godey B, Morandi X, Beust L, Brassier G, Bourdinière J. Sensitivity of auditory brainstem response in acoustic neuroma screening. Acta Otolaryngol. 1998 Jul;118(4):501–4.

Grayeli AB, Sterkers O, Toupet M. Audiovestibular function in patients with otosclerosis and balance disorders. Otol Neurotol. 2009 Dec;30(8):1085–91.

Guyot JP, Häusler R, Reverdin A, Berney J, Montandon PB. Diagnosis of cerebellopontine angle tumors. ORL J Otorhinolaryngol Relat Spec. 1992;54(3):139–43.

Hall JW III. eHandbook of auditory evoked responses: principles, procedures and protocols. London: Pearson Education, Inc.; 2015.

House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg. 1985 Apr;93(2):146–7.

Johnson EW. Auditory test results in 500 cases of acoustic neuroma. Arch Otolaryngol. 1977 Mar;103(3):152–8.

Josey AF, Glasscock ME 3rd, Musiek FE. Correlation of ABR and medical imaging in patients with cerebellopontine angle tumors. Am J Otol. 1988 Dec;9 Suppl:12–6.

Kanzaki J, Ogawa K, Inoue Y, Shiobara R. Hearing preservation surgery in acoustic neuroma patients with normal hearing. Skull Base Surg. 1997;7(3):109–13.

Kanzaki J, Ogawa K, Ogawa S, Yamamoto M, Ikeda S, O-Uchi T. Audiological findings in acoustic neuroma. Acta Otolaryngol Suppl. 1991;487:125–32.

Kanzaki J, Tos M, Sanna M, Moffat DA, Monsell EM, Berliner KI. New and modified reporting systems from the consensus meeting on systems for reporting results in vestibular schwannoma. Otol Neurotol. 2003 Jul;24(4):642–8; discussion 648–9.

Kentala E, Pyykkö I. Clinical picture of vestibular schwannoma. Auris Nasus Larynx. 2001 Jan;28(1):15–22.

Koors PD, Thacker LR, Coelho DH. ABR in the diagnosis of vestibular schwannomas: a meta-analysis. Am J Otolaryngol. 2013 May-Jun;34(3):195–204.

Krause CJ, McCabe BF. Acoustic neuroma in a 7-year-old girl. Report of a case. Arch Otolaryngol. 1971 Oct;94(4):359–63.

Lin D, Hegarty JL, Fischbein NJ, Jackler RK. The prevalence of "incidental" acoustic neuroma. Arch Otolaryngol Head Neck Surg. 2005 Mar;131(3):241–4.

Magdziarz DD, Wiet RJ, Dinces EA, Adamiec LC. Normal audiologic presentations in patients with acoustic neuroma: an evaluation using strict audiologic parameters. Otolaryngol Head Neck Surg. 2000 Feb;122(2):157–62.

Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2009 Aug;339:b3016.

Morrison GA, Sterkers JM. Unusual presentations of acoustic tumours. Clin Otolaryngol Allied Sci. 1996 Feb;21(1):80–3.

Musiek FE, Josey AF, Glasscock ME 3rd. Auditory brain-stem response in patients with acoustic neuromas. Wave presence and absence. Arch Otolaryngol Head Neck Surg. 1986a Feb;112(2):186–9.

Musiek FE, Kibbe-Michal K, Geurkink NA, Josey AF, Glasscock M 3rd. ABR results in patients with posterior fossa tumors and normal pure-tone hearing. Otolaryngol Head Neck Surg. 1986b Jun;94(5):568–73.

Ogawa K, Kanzaki J, Ogawa S, Tsuchihashi N, Yamamoto M. Acoustic neuromas with normal hearing. Acta Otolaryngol Suppl. 1991;487:144–9.

Pensak ML, Glasscock ME 3rd, Josey AF, Jackson CG, Gulya AJ. Sudden hearing loss and cerebellopontine angle tumors. Laryngoscope. 1985 Oct;95(10):1188–93.

Pinna MH, Bento RF, Neto RV. Vestibular schwannoma: 825 cases from a 25-year experience. Int Arch Otorhinolaryngol. 2012 Oct;16(4):466–75.

Qiu WW, Morgan MJ. Normal hearing in acoustic neuroma patients: a critical evaluation. Am J Otol. 1997 Jul;18(4):534–5.

Rafique I, Wennervaldt K, Melchiors J, Caye-Thomasen P. Auditory brainstem response – a valid and cost-effective screening tool for vestibular schwannoma? Acta Otolaryngol. 2016 Jul;136(7):660–2.

Roland PS, Glasscock ME 3rd, Bojrab DI, Josey AF. Normal hearing in patients with acoustic neuroma. South Med J. 1987 Feb;80(2):166–9.

Roland PS. Acoustic neuroma. 3rd ed. Philadelphia: WB Saunders Company; 1991.

Saleh EA, Aristegui M, Naguib MB, Cokesser Y, Landolfi M, Sanna M. Normal hearing in acoustic neuroma patients: a critical evaluation. Am J Otol. 1996 Jan;17(1):127–32.

Sanna M, Mancini F, Russo A, Taibah A, Falcioni M, Di Trapani G. Atlas of acoustic neurinoma microsurgery. 2nd ed. Thieme; 2011.

Schmidt RJ, Sataloff RT, Newman J, Spiegel JR, Myers DL. The sensitivity of auditory brainstem response testing for the diagnosis of acoustic neuromas. Arch Otolaryngol Head Neck Surg. 2001 Jan;127(1):19–22.

Schuknecht HF. The Pathology of Several Disorders of the Inner Ear Which Cause Vertigo. South Med J. 1964 Oct;57(10):1161–7.

Selesnick SH, Jackler RK, Pitts LW. The changing clinical presentation of acoustic tumors in the MRI era. Laryngoscope. 1993 Apr;103(4 Pt 1):431–6.

Selesnick SH, Jackler RK. Atypical hearing loss in acoustic neuroma patients. Laryngoscope. 1993 Apr;103(4 Pt 1):437–41.

Selesnick SH, Jackler RK. Clinical manifestations and audiologic diagnosis of acoustic neuromas. Otolaryngol Clin North Am. 1992 Jun;25(3):521–51.

Selters WA, Brackmann DE. Acoustic tumor detection with brain stem electric response audiometry. Arch Otolaryngol. 1977 Apr;103(4):181–7.

Shaan M, Vassalli L, Landolfi M, Taibah A, Russo A, Sanna M. Atypical presentation of acoustic neuroma. Otolaryngol Head Neck Surg. 1993 Nov;109(5):865–70.

Shih C, Tseng FY, Yeh TH, Hsu CJ, Chen YS. Ipsilateral and contralateral acoustic brainstem response abnormalities in patients with vestibular schwannoma. Otolaryngol Head Neck Surg. 2009 Dec;141(6):695–700.

Stangerup SE, Caye-Thomasen P. Epidemiology and natural history of vestibular schwannomas. Otolaryngol Clin North Am. 2012 Apr; 45(2):257–68, vii.
Stucken EZ, Brown K, Selesnick SH. Clinical and diagnostic evaluation of acoustic neuromas. Otolaryngol Clin North Am. 2012 Apr;45(2): 269–84, vii.
Swensson RC, Swensson RP, Pizzini FE, Boldorini PR, Jorge Júnior JJ. An uncommon presentation of an VIII nerve tumor. Braz J Otorhinolaryngol. 2008 Jul-Aug;74(4):628–31.
Vandervelde C, Connor SE. Diagnostic yield of MRI for audiovestibular dysfunction using contemporary referral criteria: correlation with presenting symptoms and impact on clinical management. Clin Radiol. 2009 Feb; 64(2):156–63.
Waterval J, Kania R, Somers T. EAONO Position Statement on Vestibular Schwannoma: Imaging Assessment. What Are the Indications for Performing a Screening MRI Scan for a Potential Vestibular Schwannoma? J Int Adv Otol. 2018 Apr;14(1):95–9.
WHO. Report of the Informal Working Group on Prevention of Deafness and Hearing Impairment Programme Planning, Geneva, 18-21 June 1991. Geneva: WHO; 1991.
Wilson DF, Hodgson RS, Gustafson MF, Hogue S, Mills L. The sensitivity of auditory brainstem response testing in small acoustic neuromas. Laryngoscope. 1992 Sep;102(9):961–4.