AUDITORY BRAINSTEM RESPONSES IN ACOUSTIC NEUROMA:

A SYSTEMATIC REVIEW

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This Dissertation is submitted as part

fulfilment for the Degree of Master of Science in Audiology

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September 2021

CERTIFICATE

This is to certify that this dissertation entitled **'Auditory Brainstem Responses in Acoustic Neuroma: A Systematic Review'** is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student Registration Number: 19AUD014. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru

September 2021

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DECLARATION

This is to certify that this dissertation entitled **'Auditory Brainstem Responses in Acoustic Neuroma: A Systematic Review'** is the result of my own study under the guidance of Dr. Ajith Kumar U, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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September 2021

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Chapter 1

INTRODUCTION

Acoustic neuromas (ANs; known vestibular schwanomas) are benign tumours that are slow-growing in nature. Acoustic neuroma has an incidence of 1 per 100,000 persons per year (*The National Institutes of Health (NIH) Consensus Development Program: Acoustic Neuroma, 1991*). These tumors evolve from the Schwann cell sheath, which is either extra-axial or intracranial. About 6 -10% of cranial tumors are acoustic neuromas and tends to occupy the cerebellopontine angle accounting for about 80-90% of cerebellopontine angle tumors (CPA) (Kabashi et al., 2020).

The acoustic neuromas are majorly slow progressive, and unilateral. These tumours usually cause high-frequency retro-cochlear hearing loss due to impaired blood supply to the cochlea or cochlear nerve interruption. Individuals with acoustic neuroma can have tinnitus, poor speech understanding, vertigo, headache, and facial numbness (Kabashi et al., 2020). Study by Foley et al. (2017) reported that in 80% of the individuals, there was unilateral hearing loss and unilateral tinnitus is the second most prevalent presenting symptom in individuals with ANs accounting for 6.3 %. Ataxia, vertigo, and headache accounting for 3.8 %, 3.4 %, and 2% of cases, respectively. As mentioned by Montaguti et al. (2007) hearing impairment is the earliest and most common symptom. Audiological evaluation plays a vital role in identifying acoustic neuromas. Studies done using Auditory brainstem responses have reported detection rates of 93% to 98% (Dornhoffer et al., 1994; Schmidt et al., 2001b; Selters & Brackmann, 1977).

Interaural latency difference (ILD) of V peak, inter-peak latency difference (I-III, III-V and I-V) and waveform morphology (abnormal, normal, or absent) were the factors to be considered for the diagnosis of retrocochlear pathology. Table 1.1 gives criteria considered by different authors for identifying acoustic neuroma,

Table 1.1

Literature review

Author	**Parameter considered**	**Rationale stated**
Zappia et al, 1997	Wave V ILD>0.2 ms Absence of wave V Abnormal morphology	None of the cases showed abnormal I, III and V peak absolute latency and I-III, III-V, I-V inter-peak latency with normal wave V ILD
Selters & Brackmann, 1977	Wave V ILD>0.2 ms	In most cases, a person's latencies in both ears are equal.
Schmidt et al., 2001	Wave V ILD>0.2 ms	To avoid false results and better sensitivity
Kim et al., 2016	(I–III >2.3 ms, III–V>2.1 ms, and I–V>4.4 ms), V ILD >0.4 ms, and wave morphology that is poor or absent	To get better sensitivity
Montaguti et al., 2007	ILD V (0.2-0.3-0.4 ms) is considered as indication of retrocochlear pathology	To avoid false responses and to get better sensitivity

ILDV-Interaural latency difference of peak V.

Keeping contralateral ear as a reference may add a negligible source of error, giving rise to false-negative results of up to 10-15%.

According to a meta-analysis by Koors et al. (2013) on the role of ABR in detecting individuals with retrocochlear pathology, ABR has a sensitivity of 93.4 % in detecting vestibular schwanomas of any size, with a relatively higher sensitivity of 95.6% for larger tumours and a slightly lower sensitivity of 85.8% for smaller tumours. This indicates that ABR can be a powerful diagnostic tool on its own. Patients with Vestibular schwannomas had an ABR abnormality at 89.7%, whereas those without Vestibular schwannomas had an ABR abnormality at 81.8 percent (Kim et al., 2016).

The I-V delay and the interaural wave V delay were found to have high sensitivity in detecting mid- and large-sized acoustic tumours. A study by Eggermont et al. (1980) claimed that tumors lesser than (<1 cm) would often not be detected using the criteria mentioned above. Several research found similar results, concluding that utilising ABRs to detect auditory tumours may not be effective (Don et al., 1997). MRIs are being used to detect tumors because of the failure of standard ABR tests to detect small tumors. Don et al. (1997) mentioned the cost, availability and comfort of MRI testing throughout the world and valued to have ABR test for initial screening for detection of small sized acoustic neuromas.

The inability of standard ABR methods to detect smaller tumours is thought to be related to their reliance on wave V latency changes. Because small tumours do not typically impact these high-frequency fibres sufficiently to cause notable changes in ABR, if these high-frequency fibres are not affected, tumours will be missed (Don et al., 1997). Small tumours that were undetected by standard ABR measures were detected using a new Stacked ABR. Sum of synchronous neural activity was considered and measured in Stacked ABR using high pass pink noise for masking (Don et al., 1997, 2005).

In a comparative study between stacked ABR and standard ABR in 54 small tumor cases, as many previous investigations have revealed, the standard ABR tests have a low sensitivity. In comparison to 78 non-tumor normal-hearing participants, the Stacked ABR has a sensitivity of 95 % and a specificity of 88 % (Don et al., 2005)Because each study used various criteria for deciding abnormal ABR, the sensitivity of test is varied and it is difficult to select the criteria to say ABR is abnormal in cases with acoustic neuroma. In this review we will try to define a definite criterion to say ABR is abnormal.

1.1 Need for the Study

From the brief literature discussed above it is clear that audiological evaluation is critical in the identification and diagnosis of the acoustic neuromas. ABRs are shown to be one of the important test in the diagnostic test battery. However, studies regarding the sensitivity and the specificity of ABR in detecting the acoustic tumour are equivocal. In fact, a meta-analyses carried out by Koors et al. (2013) has indicated that sensitivity and specificity of the ABR in identifying the acoustic tumour depends on size of the tumour. Since 2013, there are no systematic reviews or meta-analyses done on utility of the ABR in the detection of acoustic neuroma. Hence the present systematic review was taken up to document the utility of ABR in detection of acoustic neuroma.

1.2 Research Questions

- To identify the sensitivity of different parameters in auditory brainstem responses for diagnosing acoustic neuroma.
- To provide comprehensive evidence with help of recently published articles in diagnosing acoustic neuroma with ABR findings.
- To identify screening and diagnostic criteria for acoustic neuroma using ABR.

Chapter 2

METHODS

A systematic search was conducted using these electronic databases: J-gate, Cochrane library, Com-DisDome, LLBA (Linguistic and Language Behavior Abstract), Global Index Medicus and PubMed for English language articles published in peer-reviewed journals between 01/01/2005 to 31/12/2020. Screening of the articles in the above-mentioned databases was done till February 2021.

2.1 Key words used with appropriate Boolean operators

Acoustic neuroma, vestibular schwanomas (VS), acoustic schwanomas, vestibular neurilonomas, acoustic neurinomas, neurinoma of acoustic nerve, neurofibroma of acoustic nerve, neurofibromatosis type (2), NF2, Acoustic tumour, retrocochlear pathology, BAER- brainstem auditory evoked response, ABR, BERA, Stacked ABR, Speech ABR and stacked ABR.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) guidelines was used to report set of articles considered in the systematic review. Title and abstract screening were conducted to identify the research studies for full-text review, as per the below-mentioned criteria.

2.2 Inclusion Criteria

Studies were included for full-text review if

- they were written in English, published in peer-reviewed journals between 01/01/2005 to 31/12/2020.
- they used auditory brainstem responses as a tool to evaluate acoustic neuroma.

- they considered human subject (irrespective of age and gender).
- they have used a gold standard technique such as MRI or surgery to confirm the presence of tumor.
- the sensitivity of auditory brainstem responses in detecting acoustic neuroma is mentioned or can be calculated by the available data.

2.3 Exclusion Criteria

Studies were excluded if they met the following criteria

- Animal-based studies
- Studies with low methodological quality
- Published in other languages except English
- Single subject-based studies, case reports, review articles

To analyse studies for methodological quality, an eight-item critical evaluation checklist was used to review papers that met the inclusion criteria (see Table 2.1). To figure out probable bias or methodological characteristics that could bring bias into the results, the Critical Appraisal of Diagnostic Evidence (C. Dollaghan, 2007) was utilised to establish essential components of the diagnostic accuracy checklist.

Table 2.1

Quality indicators

Indicator	Quality marker
Study rationale	Was there an adequate and plausible rationale for the study?
Measure and procedure description	Were measures and procedures described clearly?
Independent measure administration	Were the index measure and the reference standard administered independently?
Blinding	Were assessors blinded when interpreting results of the index measure and reference?
Participant selection	Were participants identified through a one-gate procedure[a] in which the participant's diagnosis was unknown at the time of the administration of the index test and the reference test was used to confirm a diagnosis? One-gate designs help minimize spectrum bias and increase the likelihood that the study participants will represent the full range of attributes likely to be encountered in clinical settings
Adequate participant representation	Were participants recognizable and representative of the diagnostic task?
Avoidance of verification bias	Were the index measure and reference standard administered to all participants?
Likelihood ratios and confidence intervals	Were likelihood ratios and confidence intervals reported or calculable

[a]Tacconelli, 2010, (C. A. Dollaghan & Horner, 2011)

Chapter 3

RESULTS

The results of the systematic search, which yielded 706 unique and potentially relevant references, are shown in Figure 3.1. Two reviewers independently did the title and abstract screening and excluded 654 irrelevant studies. Fifty-two publications were considered for full-text screening. Of them, 13 were selected for the systematic review, and 39 articles were excluded as they didn't meet one or more of the criteria for inclusion. The first author checked the list of citations for completeness before final study inclusion. Any differences were resolved through discussion and agreement.

Tables 3.3 and 3.4 display the sensitivity and specificity of the studies with respect to the criterion considered. Quality analysis was done for the selected 13 studies, table 3.5 shows the information on the same. In all 13 articles, adequate study rationale and Adequate description of measures and procedure was mentioned. Reference standard and index measure was administered in all the studies but not independently. Most of the studies were retrospective, and blinding was not observed in any of the studies.

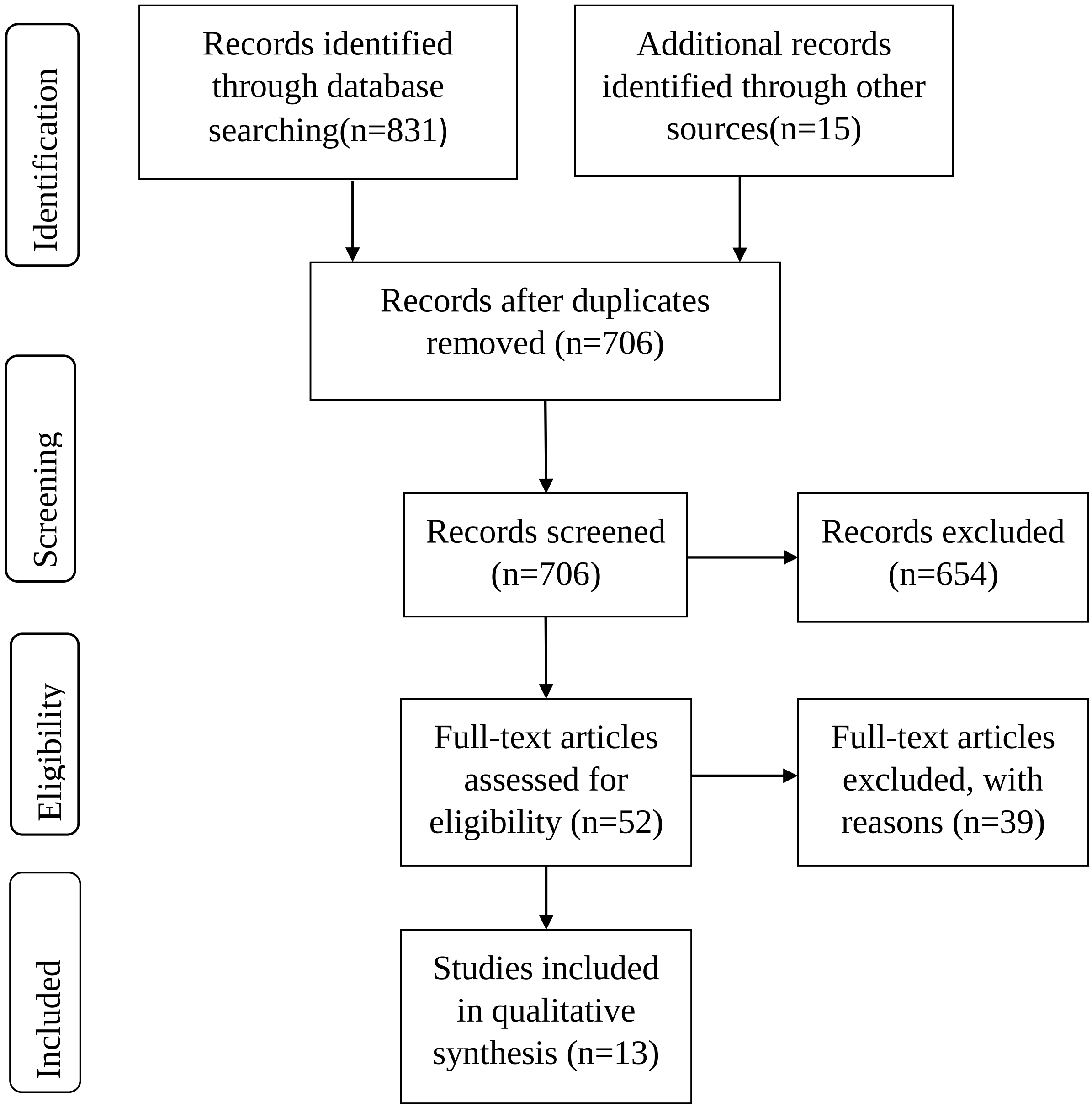

Figure 3.1 PRISMA flowchart for selection of studies

3.1 Participants

A total of 3167 ears were studied in the 13 trials (see table 3.1 for participant variables). The individuals were between the ages of 13 and 87, and they all had acoustic neuroma. Six studies reported participants gender out of which 54% were female, and 46% were male.

Table 3.1

Participants variable

S.No.	Citation	Ears	Age range in years (mean age)	Gender
1	Califano et al., 2017	16	57.73 ± 12.85	NR
2	Salem et al., 2019	133	NR	NR
3	Don et al., 2011	17	M:38–66 (50.8), F:36-62(48.9)	M:9 F:8
4	Bento et al., 2012	381	NR	NR
5	Shih et al., 2009	30	50 ±14 (18-72) M: (56.7) F: (43.3)	M: 17 F: 13
6	Rafique et al., 2016	1447	NR	NR
7	Bush et al., 2008	7	49 - 70 (59)	NR
8	Kim et al., 2016	116	53.9 ± 14.4	M:46 F:70
9	Don et al., 2005	54	M: 28–64 (49) F: 25–66 (50)	M:29 F:25
10	Montaguti et al., 2007	180	NR	NR
11	Bielinska et al., 2016	252	NR	M:115 F:137
12	Kochanek et al., 2015	29	22 - 66 (44)	M:14 F:15
13	Grayeli et al., 2008	508	13-87 (51)	NR

NR- Not reported or not calculated

Table 3.2 ***Study characteristics of the selected articles***

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
1	Sensitivity and specificity of vestibular bed-side examination in detecting VIII cranial nerve schwannoma with sensorineural sudden unilateral hearing loss as presenting symptom Califano et al., 2017	to find out vestibular signs through a bedside vestibular examination protocol for sudden sensorineural unilateral hearing loss individuals.	Retrospective study **Reference standard:** Gadolinium-enhanced MRI centred on internal auditory canals.	**Subjec**t - Cases with apparently idiopathic SSUHL (52 males, 44 women, mean age 57.73 12.85 years). 22 had at least one vestibular symptom 16 /22 ABR were found. **Parameters analysed** Criteria: if waves are absent in relation to pure tone audiometry data, I-III and I-V inter-peaks are lengthening or increase in wave V absolute latency	**Absolute latency-** In 3 cases lengthening of wave V (all 3 found to be having VS in MRI) **Inter-peak latency-** In 5 cases lengthening of I-III and I-V inter- peak latencies (only 2 subjects found to be having VS in MRI) **Interaural latency-** 11 found to have lengthening of wave V with normal I-III and I-V inter peak latencies. (11 subjects had no indication of VS in MRI)	Ruling out VS in sudden unilateral sensorineural hearing loss (SSUHL)is mandatory. Sensitivity and specificity of ABR can be improved if vestibular bedside examination is considered in idiopathic SSUHL. Following the above criteria offers considerable economic savings. MRI should be done to diagnose VS

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
2	Audiological Evaluation of Vestibular Schwannoma Patients with Normal Hearing Salem et al.,2019	To assess the audiological characteristics of patients with vestibular schwannoma (VS) who have normal hearing.	Retrospective study **Reference standard:** MRI evaluation	**Subjec**t - 133 of 162 Kanzaki et al., 2003(classification was used to grade tumors) **ABR parameters** **Stimulus-**click **Intensity**- 80dB **RR**-21.1 **Presentation**- Ipsilateral **Parameters analysed** Distorted/absent waves (no delay) Increased I–III interval > 2.5 ms, III–V interval >2.1 ms, or I–V interval of > 4.4 ms	The ABR becomes abnormal as the tumour grade rises. Sensitivity was 64.5 % (62/96 patients) for small tumours (grades 0 and 1), and 97.2 % (36/37 patients) for tumours of medium to large size (grades 2–5). Using a cut-off of 0.2 ms for ILDs, overall ABR sensitivity was 73.6 percent (98/133 cases), with a false negative rate of 26.3 percent (35/133 instances). There was no correlation between patient age and ABR data.	When it comes to diagnosing VS in NH patients, a low ILD of 0.2 ms is preferred. Smaller tumours may be missed by ABR testing if it is low and the ABR is normal.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
3	Interaural Stacked Auditory Brainstem Response Measures for Detecting Small Unilateral Acoustic Tumors Don et al., 2011	To see how sensitive and specific the Stacked Auditory Brainstem Response (SABR) is in detecting small acoustic tumours	Experimental study **Reference standard:** MRI evaluation	**Subjec**t - Non-tumor normal hearing (NTNH) -39, Small acoustic tumor (SAT) - 17 **Stacked ABR** - **Stimulus**-Click **Intensity**-60dBnHL **Presentation**-Ipsi pink noise **Click alone +** click with high pass filtered noise (8, 4, 2, 1, and 0.5 kHz noise with 96dB/octave slope) **Parameters analysed** Interaural wave V latency and SABR amplitude	**Results - ABR** With 12 cases identified, this measure missed 5 of the 17 tumour cases with IT5 value within normal limits (0.2 ms). **SABR-** In tumour ear's SABR amplitude was always smaller than the non-tumor ear's. As a result, a small tumour reduces the SABR amplitude by 43% when compared to the non-tumor side. **Amplitude:** Interaural stacked ABR (ISABR) In the NTNH group, The percent ISABR amplitude difference should be close to zero, and the left and right ear SABR amplitudes should be equal.	ISABR amplitude difference improves sensitivity and specificity of the SABR in detecting small unilateral acoustic tumors.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
4	Vestibular schwannoma: 825 cases from a 25-year experience Bento et al., 2012	To evaluate Signs, symptoms, and components of clinical diagnosis, such as the results of audiological and imaging examinations, surgical procedures and consequences,	Retrospective study **Reference standard:** Temporal bone Computed tomography (CT) or Magnetic resonance imaging (MRI) of the head.	**Subjec**t – 381 subjects ABR data was available Tumour size on MRI was Grade I in 189 cases (22.9%), Grade II in 401 (48.6%), Grade III in 188 (22.8%), and Grade IV in 47 (5.7%) **ABR parameters-** No information **Parameters analysed** Inter-peak latency Interaural latency	**Results:** ABR showed retrocochlear dysfunction in 352 (42.7%) and was within normal limits in 29 (3.5%).	The first sign of vestibular schwanomas is asymmetric sensorineural hearing loss, and the tumour growth is not proportionate to the level of hearing threshold and speech recognition.

S. No.	Title (Author, year)	**Research question**	**Study design**	**Method**	**Findings of the study**	**Conclusion**
5	Ipsilateral and contralateral acoustic brainstem response abnormalities in patients with vestibular schwannoma Shih et al., 2009	The goal of this study was to look at data from individuals with vestibular schwanomas (VS) to see if there were any associations between abnormal ABR parameters and tumour size.	Retrospective cross sectional study **Reference standard:** MRI evaluation	**Subjec**t - 30 **ABR parameters** **Stimulus-** click **Intensity**-85dBnHL **RR**- 11.1 **Sweeps**-2000 **Parameters analysed** Inter-peak latency- I-V (ILD-I-V) Interaural latency- (ILD) of wave V (ILD-V) absolute latencies of waves I, III, and V; the inter-peak latencies of waves I-III, I-V, and III-V	**Absolute latency**- abnormality of wave I was found in 66.7, III was 76.7, wave V was 96.7 percentage of identification/prevalence **Inter-peak latency-** I-III 56.7 percent, III-V latency was 63.3 I-V latency was 90 percent, ILD-V was 93.3 percent, and that of ILD-I-V was 100 percent. **Contralateral latency-** (76.7%) had an abnormal contralateral ABR Tumor size and ABR abnormality detected in percentage: <1cm- 28.6% 2cm-50% >2cm- 94.4%	Prolonged ipsilateral inter-peak III-V latency, as well as contralateral wave V latency and inter-peak III-V latency, were linked to a tumour size of potentially more than 2 cm in ABR.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
6	Auditory brainstem response – a valid and cost-effective screening tool for vestibular schwannoma? Rafique et al., 2016	To determine the sensitivity, specificity, and positive predictive value of ABR and Also to find out what is the cost-effectiveness of ABR in VS screening as compared to MRI?	Retrospective study **Reference standard:** MRI evaluation	**Subjec**t - 1447 patients **ABR parameters** **Stimulus-** click **Intensity**- 80-110 peSPL **RR**-11/sec **Presentation**-monaural **Parameters analyzed** Inter-peak latency interaural I-V >0.3ms Interaural latency->0.3ms	**Results** sensitivity was calculated to 80.0%(12/12+ 3), specificity 76.5% (1095/1095+337), and positive predictive value 3.4% (12/12+337)	Because of ABRs limited sensitivity, specificity, and positive predictive value, ABR is ineffective as a screening tool. However, with refinement or advancement in technology (new stimuli), the value of ABR may be raised.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
7	Auditory brainstem response threshold differences in patients with vestibular schwannoma: A new diagnostic index Bush et al., 2016	To identify ABR threshold differences in patients with small to medium-sized vestibular schwannomas	prospective pilot study **Reference standard:** Gadolinium-enhanced MRI	**Subjec**t - 7 with unilateral VN 49 to 70years (mean: 59) **ABR parameters** **Stimulus-** click **Intensity**-90 dBnHL- decrease by 10dB increase by 5dB **Presentation**- monaural **Parameters analysed** Inter-peak Latency-I-V- > 4.4ms Interaural latency- >0.4ms Absolute latency –V >6.2ms at 90dBnHL	**Results** **Absolute latency-** 3/7 V latency >6.2ms **Inter-peak latency-** 3/7 > 0.4 ms **Interaural latency-** 2/7> 4.4 ms **Threshold-** 30-dB threshold difference as indicative of retrocochlear pathology. It was found that all 7 patients had an abnormal threshold difference, indicating that retrocochlear pathology can be detected with 100% sensitivity.	ABR threshold can augment sensitivity and improve value of ABR test screening without adding time and cost.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
8	Audiologic evaluation of vestibular schwannoma and other cerebellopontine angle (CPA)tumors Kim et al., 2016	To identify clinical differences between types of CPA tumors- non vestibular schwanomas and vestibular schwanomas	Retrospective study **Reference standard:** Gadolinium-enhanced MRI	**Subjec**t - Two groups: those with VS (n 116) non-VS types of CPA tumor (n 55) **ABR parameters** **Stimulus-** click **RR**- 20/sec **Sweeps**- 2048 **Parameters analysed** Inter-peak latency: (I–III <2.3 ms, III–V<2.1 ms, and I–V<4.4 ms) I nter- aural difference in I–V inter-peak latency (ID I–V) ≥0..4 ms, Absolute delay of wave V> 6 ms or an inter-aural latency difference of wave V (ILD V) of 0.4 ms	**Results** According to tumour size, pure tone thresholds were higher in the VS group than in the non-VS group. ABR was positive in 92 of the 116 individuals in the VS group, absent in 24, and abnormal in 104. (89.7 %). ABR was positive in 45 of 55 non-VS patients, absent in 10, and abnormal in 45. (81.8 %) The two groups had similar audiologic test findings and hearing levels depending on the tumour site.	The most common symptom combination in patients with VS was hearing loss with tinnitus, whereas hearing loss with dizziness was more common in patients with other types of CPA tumours.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
9	The Stacked ABR: A Sensitive and Specific Screening Tool for Detecting Small Acoustic Tumors Don et al., 2005	To identify sensitivity and specificity of the stacked ABR and compare them to the standard ABR measures	Experimental design **Reference standard:** MRI evaluation	**Subjec**t - 78 NTNH with negative MRI, normal PTA 54 SAT Positive MRI **ABR parameters** **Stimulus-** click **Intensity**- 93dBPeSPL (ipsilateral noise high-pass filtered at 8, 4, 2, 1, and 0.5 kHz) **Presentation**- monaural **Parameters analyzed** Inter-peak latency Interaural latency Stacked ABR amplitude	**Results:** **Inter-peak latency-** I-V delay in only 31 of the 54 tumor patients **Interaural latency**- >0.2ms in 20 out of 45 (SAT) small acoustic tumor with 45%sensitivity 18/38 with 60dBnHL 47% sensitivity **Stacked ABR :**95% of the small tumor cases had normalized stacked ABR values of ≤ 0.74.	The IT5 measure's results may be affected by the click level. Stacked ABR has a sensitivity of 95 % and a specificity of roughly 88%. Additionally, with Stacked ABR, 100% of the small tumours were detected with 50% specificity.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
10	Comparative evaluation of ABR abnormalities in patients with and without neurinoma of viii cranial nerve Montaguti et al., 2007	To analyze and compare the electrophysiological alterations observed in patients without an organic retrocochlear disorder with individuals having acoustic neuroma	Retrospective study **Reference standard:** MRI evaluation	**Subjec**t –False Positive(FP) group 130 patients with no tumour and having 2 kHz &4 kHz 34 dB hl (SD = ± 23) and 47 dB hl (SD = ± 24) threshold Tumor (T) Group50 2 &4 kHz -44 dB hl (SD = ± 23) and 52 dB hl (SD = ± 12). **ABR parameters** **Stimulus-**click **Intensity**-120dBPeSPL **RR**-20 /sec **Sweeps**- 2048 **Parameters analyzed** Inter-peak latency Interaural latency	**Results** Wave V was seen in 127 cases (97%) in the FP group and 34 cases in the T group, while the I-V pattern was seen in 90 cases (69%) in the False positive group and 24 cases (48%) in the T group (68%). **In the tumor group:** 50 cases Type of ABR abnormality Complete absence of response: 9 (18%) Presence of wave I only :7 (14%) Increase in V with normal I-V 1 (2%) Increase in wave V- 10 (20%) Increase in wave V and I-V**:** 23 (46%)	The study of brainstem evoked hearing potentials in otoneurological diagnosis is impeded by a high rate of false positives, which appears to be unavoidable based on existing knowledge.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
11	Acoustic neuroma as first sign of inner ear functional disorders Bielinska et al., 2016	To demonstrate neuromas of the vestibulocochlear nerve as the first symptom of inner ear dysfunction in patients.	Retrospective study **Reference standard:** Gadolinium-enhanced MRI	**Subjec**t - 13 (5.16%)/ 3456 diagnosed with vestibulo- cochlear neuromas(VN) (9 W– 3.57%, aged 67-31 years, mean age 48.5 years; 4 M – 1.59%, aged 60-24, mean age 43.5 years). **ABR parameters** **Stimulus-** click **Intensity**- 70/80dBbHL **RR**-11/37 per sec **Parameters analyzed:** Prolongation of inter-peak and interaural latencies than the below-mentioned criteria was sent for MRI I-III > 2.55 ms, III-V > 2.35 ms, I-V > 4.6 ms	**Inter-peak latency**- ABR findings were obtained in all patients (prolongation: I-III >2.55 ms, III-V >2.35 ms, I-V > 4.6 ms) **Interaural latency-** An abnormal ABR test result was found in 252 (7.29%) of the patients, in which 137 (54.337%) were women and 115 (45.63%) men. VN was discovered in 13 patients (5.16 %) based on gadolinium-enhanced MRI scans, with 9 (3.57 %) women and 4 (1.59 %) men.	An abnormal result of ABR, such as prolongation of the V wave, I-III, and I-V, increases the necessity to use contrast-enhanced MRI, which is the gold standard for diagnosing vestibulocochlear neuroma.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
12	Comparison of 3 ABR Methods for Diagnosis of Retrocochlear Hearing Impairment Authors' Kochanek et al., 2016	To compare the sensitivity and specificity of three ABR-based methods for early detection of retrocochlear impairments	Case-control design **Reference standard:** Gadolinium-enhanced MRI	**Subjec**t – NR- 123 persons (246 ears) without retrocochlear impairments Group R: 29 patients with retrocochlear hearing loss **ABR parameters** **1:** ABR standard STD use of click stimuli; **2:** stacked ABR, the method, on derived-band responses **3**: ABR TP- tone pips **Stimulus-** click stimulus was 512 and 1024 **Intensity**-90dBnHL **RR**-31/sec **Presentation**-monaural **Sweeps**-720 2runs	Sensitivity: Stacked ABR -96.6% ABR STD – 44.8% ABR TP -89.7% Specificity: Stacked ABR -25.7% ABR STD – 98.1% ABR TP -89.4% In all cases of tumors, irrespective of their size, the ABR TP test results were positive. Stacked ABR procedure requires more time than ABR TP followed by standard ABR.	ABR STD- gives relatively high positive predictive value (PPV) In its present version, the stacked ABR method is not yet an optimal clinical tool for screening for retrocochlear pathologies.

S. No.	Title (Author, year)	Research question	Study design	Method	Findings of the study	Conclusion
13	Diagnostic value of auditory brainstem responses in cerebellopontine angle tumours Grayeli et al., 2008	To assess the value of ABR in association with other investigation methods to diagnose VS and other CPA tumours	Retrospective study **Reference standard:** MRI evaluation	**Subjec**t – 676 patients 372 -F,304 -M. (13to 87 yrs age range mean age 51) **ABR parameters** **Stimulus-** click **Intensity**-10 to 100 dB **RR**- 20/sec **Presentation**- Monaural **Sweeps-** 1024 **Contra ear** – masking at 30dB **Parameters analyzed –** considered abnormal if there is no reproducible wave with an enhanced I-III interval of >2.5 ms or I-V interval of >4.4 ms, or an interaural difference in V wave delay or I>V interval of >0.2 ms.	**Results** 444 (64.2%) of cases showed no response in ABR, a delayed response in 32 (31%), and a normal response in 32 cases (4.8 %). The majority of individuals with normal ABR had minor lesions: Stage 1 has a 48 % success rate, stage 2 has a 40% success rate, stage 3 has a 4% success rate, and stage 4 has an 8% success rate.	The combination of ABR and a thorough neuro-otological evaluation allowed abnormalities to be identified in most CPA tumours. Apart from VS cases, false-negative ABRs involved small lesions, mostly in elderly patients.

Table 3.3

Results of studies that considered standard clicks as a stimulus

Citation	Reference standard	Stimuli	Criteria considered	Sensitivity	Specificity
Califano et al., 2017	Gadolinium-enhanced MRI	Standard click	Wave V delay, lengthening of I-III and I-V inter-peak latencies	31.25	NR
Salem et al.,2019	MRI	Standard click	ILD >2ms ILD>4 ms	73.6 61.6	26.3 38.3
Bento et al., 2012	CT scan / MRI	Standard click	Signs of retrocochlear dysfunction	92.38	NR
Shih et al., 2009	MRI	Standard click	Abnormality in wave I III V I-III III-V I-V ILD-V ILD-I-V Contralateral latency-abnormal contralateral ABR	66.7 76.7 96.7 56.7 63.3 90 93.3 100 76.7	NR
Rafique et al., 2016	MRI	Standard click	Inter-peak latency interaural I-V >0.3ms Interaural latency->0.3ms	80	76.5

Bush et al., 2016	Gadolinium-enhanced MRI	Standard click	30dB threshold difference in U/L VN	100	NR
Kim et al., 2016	Gadolinium-enhanced MRI	Standard click	I–III> 2.3 ms, III–V>2.1 ms, and I–V>4.4 ms), and inter-aural difference in I–V inter-peak latency (ID I–V) >0.4 ms, an absolute delay of wave V>6 ms or an inter-aural latency difference of wave V (ILD V) of 0.4 ms	89.7	81.8
Grayeli et al., 2008	MRI	Standard click	ABR detected no response and delayed response	93.7 Miss rate 4.8%	NR
Bielinska et al., 2016	Gadolinium-enhanced MRI	Standard click	Abnormal ABR	NR	NR

Table 3.4

Results of studies that considered stimulus other than standard clicks.

Citation	Reference standard	Stimuli	Criteria considered	Sensitivity	Specificity
Don et al., 2005	MRI	Stacked ABR	IT5>0.2 ms at 80dBnHL IT5>0.2 ms at 60dBnHL I-V delay Normalizes stacked ABR amplitude of 0.74 in (F) Normalizes stacked ABR amplitude of 0.74 in (M) Normalizes stacked ABR amplitude of 1	45 47 38 95 88 100	96 - 96 88 88 50
Don et al., 2011	MRI	Stacked ABR	ISABR ILD >2 ms(ITV)	95 78	83 97-98
Montaguti et al., 2007	MRI	Standard click Stacked ABR ABR TP	Complete absence of response Presence of wave I only Increase in V with normal Increase in wave V Increase in wave V and I-V	18 14 2 20 46	NR
Kochanek et al., 2016	Gadolinium-enhanced MRI	Stacked ABR ABR TP Standard click	Interaural latency difference>0,4 ms Interaural latency difference>0,4 ms	96.6 44.4 89.7	25.7 98.1 89.4
TP- tone pips, F-female, M-male, IT5-interaural v peak difference NR-not reported					

Table 3.5

Quality Analysis of selected studies

Quality analysis								
Citation	**Adequate study rationale**[a]	**Adequate description of measures and procedures**[b]	**Independent measure administration**[c]	**Blinding**[d]	**1-gate procedure**[e]	**Adequate participant representation**[f]	**Reference and index standard**[g]	**LR / CI calculable**[h]
Califano et al., 2017	Yes	yes	No	No	Yes	+/-	Yes	No
Salem et al.,2019	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Don et al., 2011	Yes	Yes	No	No	No	+/-	Yes	Yes
Bento et al., 2012	Yes	Yes	No	No	Yes	Yes	Yes	No
Shih et al., 2009	Yes	Yes	No	No	Yes	Yes	Yes	No
Rafique et al., 2016	Yes	Yes	No	No	Yes	yes	Yes	Yes
Bush et al., 2016	Yes	Yes	No	No	Yes	+/-	Yes	No
Kim et al., 2016	Yes	Yes	No	No	Yes	Yes	Yes	Yes

Don et al., 2005	Yes	yes	No	No	No	Yes	Yes	Yes
Montaguti et al., 2007	Yes	Yes	No	No	Yes	Yes	Yes	No
Bielinska et al., 2016	Yes	Yes	No	No	Yes	Yes	Yes	No
Kochanek et al., 2016	Yes	Yes	No	No	Yes	+/-	Yes	Yes
Grayeli et al., 2008	Yes	Yes	No	No	Yes	Yes	Yes	No

+/- Partial representation

a- Was there an adequate and plausible rationale for the study?

b-Were measures and procedures described clearly?

c-Were the index measure and the reference standard administered independently?

d-Were assessors blinded when interpreting results of the index measure and reference?

e-Were participants identified through a one-gate procedure in which the participant's diagnosis was unknown at the time of the administration of the index test and the reference test was used to confirm a diagnosis?

f-Were participants recognizable and representative of the diagnostic task?

g-Were the index measure and reference standard administered to all participants?

h-Were likelihood ratios and confidence intervals reported or calculable

Chapter 4

DISCUSSION

As early as from 1977Auditory brainstem response (ABR) is used to detect acoustic neuroma. The performance of ABR as a detection tool is highly dependent on the protocol and the interpretation criteria. In the present study, out of 13 articles, 12 have used latency change as one of the measures, and only one study by Bush et al. (2016) has taken threshold difference as a criterion. This review showed that the sensitivity of ABR ranges between 31.25 -100% in identifying acoustic neuromas (Bush et al., 2008; Califano et al., 2017; Shih et al., 2009). Interaural latency difference was one of the standard measures considered in the studies. Keeping a strict criterion of >0.2ms yielded better sensitivity in all the studies reviewed. The interaural V peak latency difference, including inter-peak latency difference I-III, III-V, and I-V, gave a better sensitivity (Shih et al., 2009).

Along with latency measures, Bush et al. (2016) showed a 30dB threshold difference in unilateral vestibular schwanomas and normal ears. This finding may not be accurate in all cases with vestibular schwanomas because 70% of acoustic neuromas are non-growing. Up to 15% of patients with acoustic neuroma have normal hearing (Stangerup & Caye-Thomasen, 2012). Grayeli et al. (2008) study showed that associating ABR with the clinical and other routine audio-vestibular examinations, false-negative results can be reduced from 4.8 to 0.7% for VS and from 10 to 0% for other CPA tumours.

In a recent meta-analysis, the pooled sensitivity of the ABR was calculated to be 93%, and the specificity 82% (Koors et al., 2013). The sensitivity of ABR in detecting tumors varies with the size of the acoustic tumor. By retrospective observations, the diagnostic sensitivity of ABR for small lesions (e.g., <1 cm) is low, ranging from 58 to 82% (Godey et al., 1998; Ruckenstein et al., 1996; Schmidt et al., 2001). The sensitivity of ABR is close to 100% in lesions measuring > 1.5 cm (Robinette et al., 2000; Rupa et al., 2003). In the present review, stacked ABR showed better sensitivity in detecting acoustic neuromas of <1cm. Don et al. (2005) showed that for tumours less than 1 cm, the sensitivity of conventional ABR ranged between 45-47%, whereas sensitivity increased to 88-95% with stacked ABR amplitude of 0.74, and it reached 100% when normalized stacked ABR amplitude is kept as 1. A study by Kochanek et al. (2016) also reported a higher sensitivity of stacked ABR in detecting small acoustic tumours. The stacked ABR method provides the highest sensitivity; this sensitivity is obtained at the expense of specificity, which is extremely low because of significant variability of stacked ABR amplitudes leading to many false positives. Lesser testing time with good sensitivity and low cost gives more excellent clinical utility. Standard click and tone pips methods take a shorter time for examination in auditory brainstem responses, whereas the stacked ABR method takes more time, approximately 40 to 50 minutes, for each individual (Kochanek et al., 2016).

When cerebellopontine angle tumour is suspected, MRI is undoubtedly the imaging modality of choice. The reliability of gadolinium contrast-enhanced MRI is approximately 100 %. (Bento et al., 2012). The high costs of MRI is a major limiting factor in screening protocol (Robinette et al., 2000). On the other hand, ABR testing is less expensive, takes less time, and is more accessible. Patients who cannot have an MRI because of ferromagnetic implants, obesity, or claustrophobia can have an ABR instead. (Cheng & Wareing, 2012). ABR testing also aids in deciding on approaches to hearing preservation during surgery of vestibular schwanomas (Stucken et al., 2012). The ABR can be used as a first screening test for VS because of these considerations.

Chapter 5

SUMMARY AND CONCLUSION

The present systematic review was taken up to document the utility of ABR in the detection of acoustic neuroma as there are no systematic reviews or meta-analyses done on the same since 2013. The main aim of this review is to provide the sensitivity of different parameters in auditory brainstem responses for identifying acoustic neuroma. A systematic search generated 706 unique and potentially relevant references. Two reviewers independently did the title and abstract screening and excluded 654 irrelevant studies. Fifty-two publications were considered for full-text screening. Of them, 13 were selected for the systematic review, and 39 articles were excluded as they did not meet one or more of the inclusion criteria. Out of 13 studies, sensitivity was reported or calculable from 12 articles, and it ranged from 31.35%-100%. Considering interaural peak latency difference along with inter-peak latency difference I-III, III-V, and I-V, gave a better sensitivity.

In unilateral tumour cases considering criteria of >0.4 ms, interaural latency difference in standard click ABR gives 60%-80% sensitivity. ABR elicited using tone pips/bursts has sensitivity up to 44% and 98% specificity. However, further research using tone pip/bursts stimuli is required to get a standardized protocol and criteria for better sensitivity. For tumours less than 1 cm, stacked ABR was found to be more sensitive than the conventional ABR recordings. Even though stacked ABR method provides the highest sensitivity in detecting small acoustic tumours, considering the false positive rate and testing time stacked ABR should be judiciously used. Using ABR testing for screening acoustic tumours is less expensive, less time-consuming, and more accessible.

REFERENCES

Bento, R. F., Pinna, M. H., & De Brito Neto, R. V. (2012). Vestibular schwannoma: 825 cases from a 25-year experience. *International Archives of Otorhinolaryngology*, *16*(4), 466–475. https://doi.org/10.7162/S1809-97772012000400007

Bielinska, M., Owczarek, K., Nowosielska-Grygiel, J., Olszewski, J., & Pietkiewicz, P. (2016). Acoustic neuroma as first sign of inner ear functional disorders. *Otolaryngologia Polska*, *70*(5), 19–24. https://doi.org/10.5604/00306657.1202784

Bush, M. L., Jones, R. O., & Shinn, J. B. (2008). Auditory brainstem response threshold differences in patients with vestibular schwannoma: A new diagnostic index. *Ear, Nose and Throat Journal*, *87*(8), 458–462. https://doi.org/10.1177/014556130808700811

Califano, L., Salafia, F., Melillo, M. G., & Mazzone, S. (2017). Sensibilità e specificità della vestibular bed-side examination nell’individuare lo schwannoma dell’VIII nervo cranico con ipoacusia improvvisa come sintomo di esordio. *Acta Otorhinolaryngologica Italica*, *37*(4), 336–340. https://doi.org/10.14639/0392-100X-1284

Cheng, T. C., & Wareing, M. J. (2012). Three-year ear, nose, and throat cross-sectional analysis of audiometric protocols for magnetic resonance imaging screening of acoustic tumors. *Otolaryngology - Head and Neck Surgery*, *146*(3), 438–447. https://doi.org/10.1177/0194599811427384

Dollaghan, C. (2007). *The handbook for evidence-based practice in communication disorders*. Paul H. Brookes Pub.,.

Dollaghan, C. A., & Horner, E. A. (2011). Bilingual language assessment: A meta-analysis of diagnostic accuracy. *Journal of Speech, Language, and Hearing Research*, *54*(4), 1077–1088. https://doi.org/10.1044/1092-4388(2010/10-0093)

Don, M., Kwong, B., & Tanaka, C. (2011). Interaural stacked auditory brainstem response measures for detecting small unilateral acoustic tumors. *Audiology and Neurotology*, *17*(1), 54–68. https://doi.org/10.1159/000329364

Don, M., Kwong, B., Tanaka, C., Brackmann, D., & Nelson, R. (2005). The Stacked ABR: A Sensitive and Specific Screening Tool for Detecting Small Acoustic Tumors. *Audiology and Neurotology*, *10*(5), 274–290. https://doi.org/10.1159/000086001

Don, M., Masuda, A., Nelson, R., & Brackmann, D. (1997). Successful detection of small acoustic tumors using the stacked derived-band auditory brain stem response amplitude. *American Journal of Otology*, *18*(5), 608–621.

Dornhoffer, J. L., Helms, J., & Hoehmann, D. H. (1994). Presentation and Diagnosis of Small Acoustic Tumors. *Otolaryngology–Head and Neck Surgery*, *111*(3P1), 232–235. https://doi.org/10.1177/01945998941113p111

Eggermont, J. J., Don, M., & Brackmann, D. E. (1980). Electrocochleography and auditory brainstem electric responses in patients with pontine angle tumors. *Annals of Otology, Rhinology and Laryngology*, *89*(Suppl. 75). https://doi.org/10.1177/00034894800890s601

Foley, R. W., Shirazi, S., Maweni, R. M., Walsh, K., McConn Walsh, R., Javadpour, M., & Rawluk, D. (2017). Signs and Symptoms of Acoustic Neuroma at Initial Presentation: An Exploratory Analysis. *Cureus*, *9*(11). https://doi.org/10.7759/cureus.1846

Godey, B., Morandi, X., Beust, L., Brassier, G., & Bourdinière, J. (1998). Sensitivity of auditory brainstem response in acoustic neuroma screening. *Acta Oto-Laryngologica*, *118*(4), 501–504. https://doi.org/10.1080/00016489850154621

Grayeli, A. B., Refass, A., Smail, M., Elgarem, H., Kalamarides, M., Bouccara, D., & Sterkers, O. (2008). *Diagnostic value of auditory brainstem responses in cerebellopontine angle tumours*. *November 2007*, 1096–1101. https://doi.org/10.1080/00016480701881803

Kabashi, S., Ugurel, M. S., Dedushi, K., & Mucaj, S. (2020). The role of magnetic resonance imaging (MRI) in diagnostics of acoustic schwannoma. *Acta Informatica Medica*, *28*(4), 287–291. https://doi.org/10.5455/AIM.2020.28.287-291

Kim, S. H., Lee, S. H., Choi, S. K., Lim, Y. J., Na, S. Y., & Yeo, S. G. (2016). Audiologic evaluation of vestibular schwannoma and other cerebellopontine angle tumors. *Acta Oto-Laryngologica*, *136*(2), 149–153. https://doi.org/10.3109/00016489.2015.1100326

Kochanek, K. M., Śliwa, L., Gołębiowski, M., Piłka, A., & Skarżyński, H. (2015). Comparison of 3 ABR methods for diagnosis of retrocochlear hearing impairment. *Medical Science Monitor*, *21*, 3814–3824. https://doi.org/10.12659/MSM.895291

Koors, P. D., Thacker, L. R., & Coelho, D. H. (2013). ABR in the diagnosis of vestibular schwannomas: A meta-analysis. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, *34*(3), 195–204. https://doi.org/10.1016/j.amjoto.2012.11.011

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*, *339*(7716), 332–336. https://doi.org/10.1136/BMJ.B2535

Montaguti, M., Bergonzoni, C., Zanetti, M. A., & Rinaldi Ceroni, A. (2007). Comparative evaluation of ABR abnormalities in patients with and without neurinoma of VIII cranial nerve. *Acta Otorhinolaryngologica Italica : Organo Ufficiale Della Società Italiana Di Otorinolaringologia e Chirurgia Cervico-Facciale*, *27*(2), 68–72.

Rafique, I., Wennervaldt, K., Melchiors, J., & Caye-Thomasen, P. (2016). Auditory brainstem response – a valid and cost-effective screening tool for vestibular schwannoma? *Acta Oto-Laryngologica*, *136*(7), 660–662. https://doi.org/10.3109/00016489.2016.1157726

Robinette, M. S., Bauch, C. D., Olsen, W. O., & Cevette, M. J. (2000). Auditory brainstem response and magnetic resonance imaging for acoustic neuromas: Costs by prevalence. *Archives of Otolaryngology - Head and Neck Surgery*, *126*(8), 963–966. https://doi.org/10.1001/archotol.126.8.963

Ruckenstein, M. J., Cueva, R. A., Morrison, D. H., & Press, G. (1996). A prospective study of ABR and MRI in the screening for vestibular schwannomas. *American Journal of Otology*, *17*(2), 317–320. https://pubmed.ncbi.nlm.nih.gov/8723969/

Rupa, V., Job, A., George, M., & Rajshekhar, V. (2003). Cost-effective initial screening for vestibular schwannoma: Auditory brainstem response or magnetic resonance imaging? *Otolaryngology - Head and Neck Surgery*, *128*(6), 823–828. https://doi.org/10.1016/S0194-5998(03)00358-9

Salem, N., Galal, A., Mastronardi, V., Talaat, M., Sobhy, O., & Sanna, M. (2019). Audiological Evaluation of Vestibular Schwannoma Patients with Normal

Hearing. *Audiology and Neurotology*, *24*(3), 117–126. https://doi.org/10.1159/000500660

Schmidt, R. J., Sataloff, R. T., Newman, J., Spiegel, J. R., & Myers, D. L. (2001). The sensitivity of auditory brainstem response testing for the diagnosis of acoustic neuromas. *Archives of Otolaryngology - Head and Neck Surgery*, *127*(1), 19–22. https://doi.org/10.1001/archotol.127.1.19

Selters, W. A., & Brackmann, D. E. (1977). Acoustic Tumor Detection With Brain Stem Electric Response Audiometry. *Archives of Otolaryngology*, *103*(4), 181–187. https://doi.org/10.1001/archotol.1977.00780210037001

Shih, C., Tseng, F. Y., Yeh, T. H., Hsu, C. J., & Chen, Y. S. (2009). Ipsilateral and contralateral acoustic brainstem response abnormalities in patients with vestibular schwannoma. *Otolaryngology - Head and Neck Surgery*, *141*(6), 695–700. https://doi.org/10.1016/j.otohns.2009.09.015

Stangerup, S. E., & Caye-Thomasen, P. (2012). Epidemiology and Natural History of Vestibular Schwannomas. In *Otolaryngologic Clinics of North America* (Vol. 45, Issue 2, pp. 257–268). Elsevier. https://doi.org/10.1016/j.otc.2011.12.008

Stucken, E. Z., Brown, K., & Selesnick, S. H. (2012). Clinical and Diagnostic Evaluation of Acoustic Neuromas. In *Otolaryngologic Clinics of North America* (Vol. 45, Issue 2, pp. 269–284). Elsevier. https://doi.org/10.1016/j.otc.2011.12.001

Tacconelli, E. (2010). Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases*, *10*(4), 226. https://doi.org/10.1016/s1473-3099(10)70065-7

The National Institutes of Health (NIH) Consensus Development Program: Acoustic

Neuroma. (n.d.). Retrieved November 2, 2020, from https://consensus.nih.gov/1991/1991AcousticNeuroma087html.htm

Zappia, J. J., O'Connor, C. A., Wiet, R. J., & Dinces, E. A. (1997). Rethinking the use of auditory brainstem response in acoustic neuroma screening. *Laryngoscope*, *107*(10), 1388–1392. https://doi.org/10.1097/00005537-199710000-00018