

The Role of Vestibular Evoked Myogenic Potentials in Multiple Sclerosis: A Systematic Review

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Abstract

Background: A chronic autoimmune condition that affects the central nervous system is called multiple sclerosis (MS). The immune system starts a protective attack against its own tissues (the myelin sheath). MS may affect peripheral vestibular apparatus of the ear, or central vestibular pathways, or both. **Aim:** The aim of the study is to summarize the evidence on the role of vestibular evoked Myogenic potential (VEMP) as a tool to detect lesions in the vestibular pathways in the patients of MS. **Methods:** During the development of this meta-analysis, we adhered to the PRISMA statement's principles and followed the Cochrane handbook of systematic reviews of interventions for each step. We searched PubMed, Google Scholar, and Egyptian Knowledge Bank (Scopus) till February 2022 with relevant keywords. **Results:** Final qualitative synthesis contained 24 studies in all, and 1257 patients were involved in the quantitative analysis (352 Male, 655 Female). A statistically difference in the latency of P13 in cVEMP, N1 in oVEMP, P1 in oVEMP between MS patients and controls with a P value < 0.0001. The latency of N23 in cVEMP has no significant difference between multiple sclerosis patients and healthy controls. MS patients with normal VEMP response have significantly lower vestibular symptoms than those with abnormal VEMP results. **Conclusion:** VEMPs can be used as an adjuvant tool in assessment of MS patients as it can detect lesions in the vestibular system, but it cannot determine the exact location of the lesion.

Keywords: VEMPs, MS, Vestibular Evoked Potentials, Multiple Sclerosis

Introduction

A chronic disorder of central nervous system (CNS), multiple sclerosis (MS) can have mild to severe effects on a person's quality of life. Multiple sclerosis has been hypothesized by many researchers to be an autoimmune disease, in which the immune system unintentionally attacks its tissues (nerve-insulating myelin sheath). Possible environmental causes for these kinds of attacks include viruses ⁽¹⁾.

About 2 million people throughout the world live with multiple sclerosis. It affects people of many cultures and ethnicities, but its prevalence varies widely ⁽²⁾. Most people are diagnosed with multiple sclerosis at the age of 20 to 40 years ⁽³⁾.

Since CNS regulates all bodily functions, symptoms of MS can manifest anywhere on the body. Weakness in muscles, numbness and tingling, exhaustion, dizziness and vertigo,

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problems with eyesight and gait and mobility, mood swings and depression, pain, difficulty learning and remembering, and bladder issues are the most often reported symptoms of multiple sclerosis ⁽⁴⁾.

A distinguishing feature of the pathogenesis of multiple sclerosis is multifocal demyelinating lesions of the white matter. Magnetic resonance imaging (MRI) is the gold standard imaging method for locating the lesions used to support a clinical diagnosis of MS. Additionally, MS can be discovered in some individuals after a clinically isolated episode ⁽⁵⁾.

The VEMP is a short-latency response brought on by pulses of air-conducted sounds, bone-conducted vibrations, or electrical stimulation, using surface electrodes applied to muscles ⁽⁶⁾. The utricle and saccule of the inner ear are tested using this neurophysiological method to ascertain their level of functionality⁽⁷⁾.

Testing for VEMP can be either cervical (cVEMP) or ocular (oVEMP). Surface electrodes can capture the averaged response of the ipsilateral sternocleidomastoid (SCM) muscles to a sound stimulus applied to the affected ear (cVEMP). The strongest response to a sound stimulus is likewise recorded from the contralateral inferior oblique muscle using a surface electrode and then averaged (oVEMP) ⁽⁸⁾.

Cervical (cVEMP) is used for assessment of saccular or inferior vestibular nerve function. It is a test of the vestibule-colic reflex. Ocular (oVEMP) is used for assessment of utricular or superior vestibular nerve

function. It is a test of the vestibulo-ocular reflex ⁽⁹⁾.

The aim of this study is to summarize the evidence on the role of VEMPs as a tool to detect lesions in the vestibular pathways in the patients of MS.

Methods

We followed PRISMA statement guidelines⁽¹⁰⁾ and we followed the Cochrane Handbook for Systematic Reviews of Interventions throughout the entire process of preparing this systematic review and meta-analysis⁽¹¹⁾

Search strategy and study selection

We searched PubMed, Google Scholar, Egyptian Knowledge Bank (Scopus) till February 2022 with relevant keywords. The following search strategy used in this study for searching different databases: ("Disseminated Sclerosis" OR MS OR "Multiple Sclerosis") AND ("Vestibular Evoked Myogenic Potential" OR "Ocular Vestibular Evoked Myogenic Potential" OR "Cervical Vestibular Evoked Myogenic Potential" OR "Evoked Neurogenic Vestibular Potential" OR "Vestibular Evoked Neurogenic Potential" OR VEMPs OR "oVEMP" OR "cVEMP"). Relevant studies were identified by searching the references of all included research.

Studies comparing diagnosis accuracy in patients with MRI-confirmed multiple sclerosis; clinical studies describing diagnostic results and follow-up assessment of MS patients; patient ages 15-60; studies must be written in English; studies must involve humans; were included. Clinical comparative studies may be prospective or retrospective; double-arm designs are acceptable; publication

dates may range from 2000 through September 2021; study designs may include randomized controlled trials.

We did not include studies that had fewer than five instances, those that had patients with vertigo owing to conditions other than MS, those conducted on animals, those not published in English, and those with a single treatment arm.

There were no limits placed on the type of published papers that were screened. We first screened the titles and abstracts, and then the whole texts. To ensure that no potentially relevant papers were missed during the process, the reference lists of the included research were thoroughly checked.

Assessment of quality

Studies were evaluated for quality and potential for bias using criteria developed by the Agency for Healthcare Research and Quality (AHRQ) ⁽¹²⁾. Source, inclusion/exclusion criteria, duration, consecutive patients, quality assurance, masking, explanation of exclusions, data withdrawal, confounder control, completeness of data, and follow-up are just a few of the 11 evaluation criteria included here. If something is mentioned in the article, it receives a 1; if it isn't, it receives a 0. Quality of the study is assessed as follows: Good quality: 8-11 score, moderate quality: 6-7 score, poor quality: lower than 6.

Extraction of Data

The following information was collected from the articles: year of publication, total number of patients, gender, mean age, presence of vertigo only if linkable to MS (we included the articles where authors excluded other

causes of vertigo rather than MS), presence and location [brain or internal auditory canal (IAC)] of White Matter Hyperintensities (WMHs) in T2-MRI sequences, and VEMPs (latency, amplitude and presence or absence of response).

We focused on these results:

We measured the N1 (ms) and P1 (ms) latencies, the N1-P1 interpeak latencies, the N1-P1 difference in latencies between ears, the P1 difference in latencies between ears, and the amplitude asymmetry ratio in oVEMP. We measured the P13 (ms) and N23 (ms) latencies, as well as the interpeak P13-N23 latencies, the P13-N23 interaural latencies, the N23-P13 interaural latencies, and the amplitude asymmetry ratio, in cVEMP.

Using the aforementioned inclusion and exclusion criteria, two writers (Ibrahim I.H& Ashry Y.M) assessed the research for potential inclusion without taking the findings into account. Disagreements were hashed out in roundtable discussions until everyone agreed. If needed, a third author was consulted.

Statistical Analysis

We presented the results of our review in a narrative way. Using figures and tables, the results of each study was provided for outcomes. Specifically, we included the characteristics of the included studies.

We conducted this meta-analysis by using Review Manager Software 5.4(Computer program), Version 5.4, the Cochrane Collaboration, 2020. We also used Open Meta-analyst software in the analysis outcomes. Regarding the study outcomes, mean difference (MD)

and 95% confidence interval (CI) was used for continuous variables. Heterogeneity among the studies was analyzed using Cochrane's P values and I². Both clinical and methodological variables likely contributed to a high degree of variability.

Results

1. Literature search results

An initial search of Google Scholar, PubMed, and the Egyptian Knowledge

Bank (Scopus database) yielded a total of 608 studies. The manual search yields 21 studies from other databases. There are a total of 629 entries before duplicates are removed. We eliminated 52 entries from the original set of 629 because they were duplicates. After reviewing the titles and abstracts of 577 papers, 544 were deemed ineligible for inclusion (**Figure 1**).

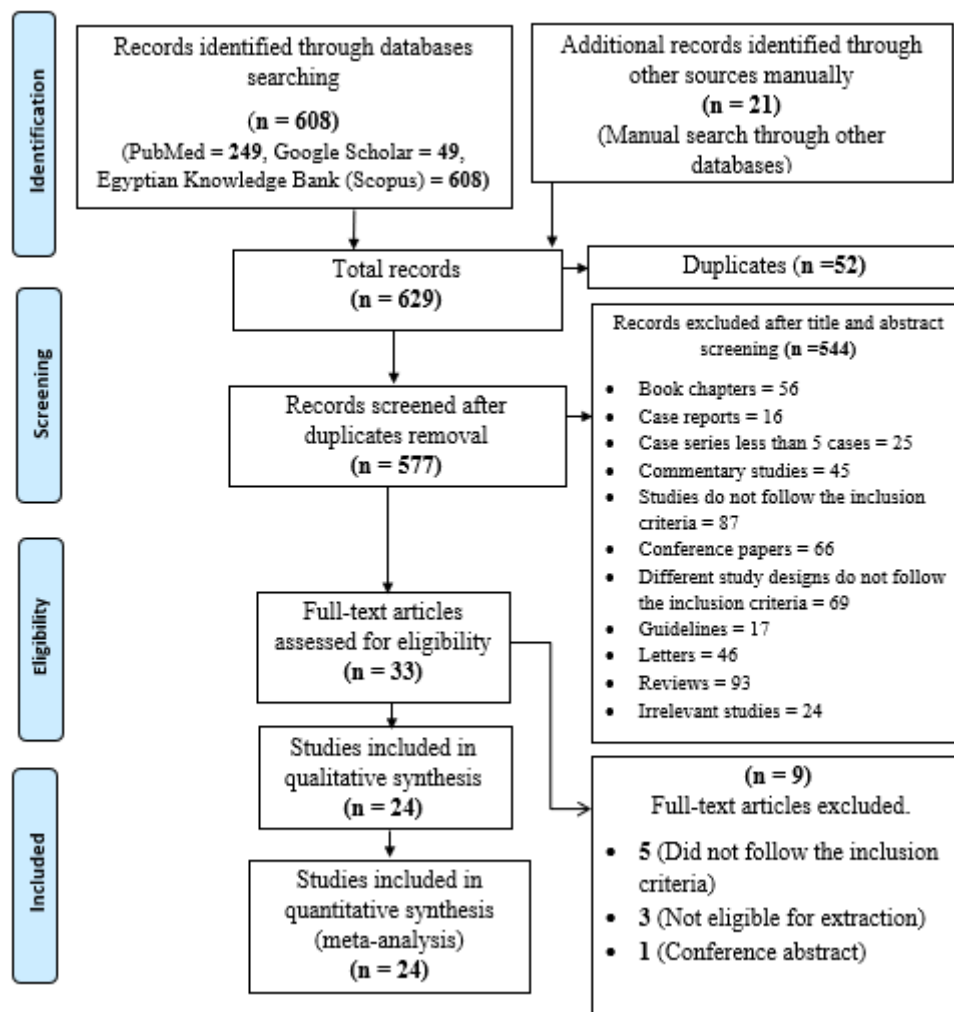


Figure (1): Flow chart of the study.

Full-text analysis was performed on the remaining 33 articles. The final qualitative synthesis and quantitative analysis used data from 24 research.

Five papers did not meet our inclusion criteria, three papers were not eligible for extraction, and one paper was a conference abstract, therefore they

were all left out of the full-text screening.

2. Characteristics of the included studies

In the current study, the data of 1257 patients (352 Male, 655 Female) were revised. The included studies focused on validity of using VEMP either oVEMP or cVEMP for diagnosis in patients suffering from MS. The outcome that was the main focus of a large number of the included studies included Vertigo and white matter hyperintensities (WMHs) and the correlation between VEMPs results and MRI findings in MS patients.

3. Risk of bias assessment

The overall quality of the included studies was moderate to good quality

which enables us to generate a higher quality of evidence from the included studies. There were 19 studies have good quality; 5 studies have moderate quality.

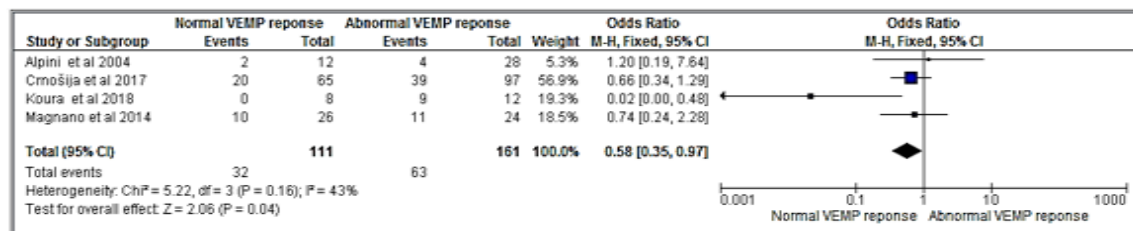
4. Outcomes

I.VEMPs and MRI findings in MS patients (Figure 2).

Figure (A) showed that MS patients with normal VEMP response have significantly lower brain stem lesions than those with abnormal VEMP results (OR: 0.58; CI 95% [0.35, 0.97]; $P = 0.16$).

Figure (B) showed that MS patients with normal VEMP response have statistically significant lower vestibular symptoms than those with abnormal VEMP results.

(A) Forest plot of relation between brain stem lesion on VEMP response.



(B) Forest plot of relation between vestibular symptoms on VEMP response.

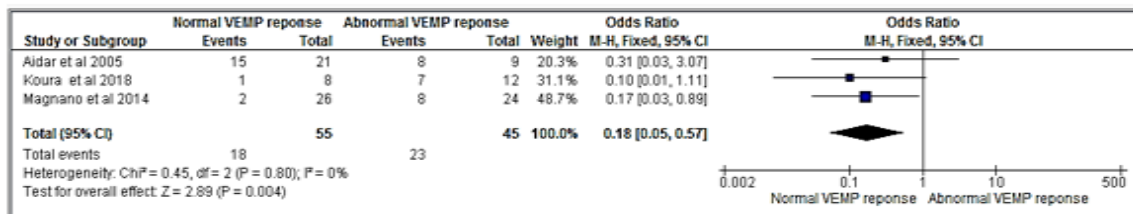


Figure (2): VEMPs and MRI findings in MS patients.

II.Latency P13 (ms) in cVEMP and N1 (ms) in oVEMP (Figure 3)

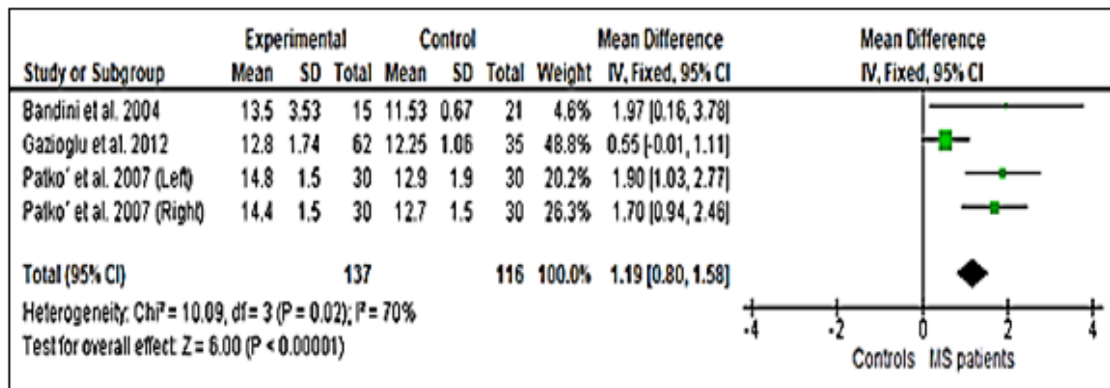
Figure (A) showed that there was a statistically significant difference in the latency of P13 in cVEMP between MS patients and healthy controls with a P value < 0.0001 indicating that VEMP can be reliable for assessment of function

of the vestibular system in MS patients. The pooled studies were heterogenous ($I^2 = 70\%$, $P = 0.02$).

Figure (B) showed that there was a statistically significant difference in the latency of N1 in oVEMP between MS patients and healthy controls with a P

value < 0.0001 indicating that VEMP can be useful in diagnosis of MS.

(A) Forest plot of mean difference (MD) in latency P13 (ms) in cVEMP



(B) Forest plot of mean difference (MD) in latency N1 (ms) in oVEMP

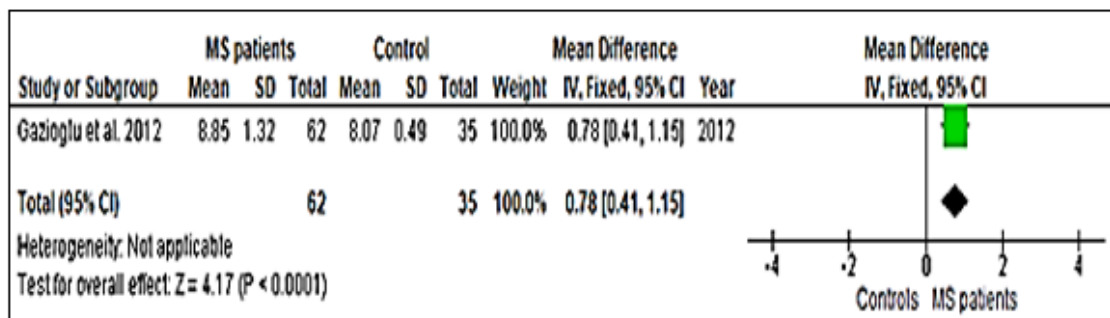


Figure (3): Latency P13 (ms) in cVEMP and N1 (ms) in oVEMP

III. Latency N23 (ms) in cVEMP and P1 (ms) in oVEMP (Figure 4)

Figure (A) showed that the latency of N23 in cVEMP has no significant difference between MS patients and healthy controls with a P value $= 0.31$ indicating that latency of N23 in cVEMP cannot be reliable for detecting lesions in the vestibular pathway. The pooled included studies were homogenous ($I^2 = 0\%$, $P = 0.31$).

Figure (B) showed that there was a statistically significant difference in the latency of P1 in oVEMP between MS patients and healthy controls with a P value $= 0.0001$ indicating VEMP can be useful in diagnosis of MS. The pooled heterogeneity of the included studies

could not be assessed due to limited number of the included studies.

IV. Interaural latency diff N23 in cVEMP and Interaural latency diff. P1 in oVEMP (Figure 5).

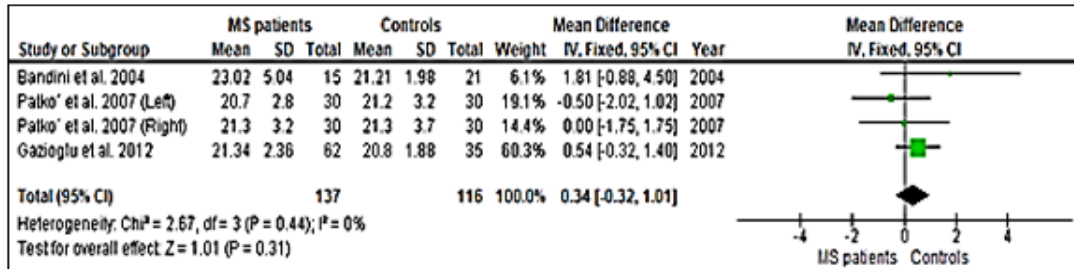
Figure (A) showed that the interaural latency difference N23 in cVEMP has no positive significant results in MS patients with a P value $= 0.18$ indicating that the interaural latency difference N23 in cVEMP cannot be reliable for MS diagnosis. The pooled heterogeneity of the included studies could not be assessed due to the limited number of the included studies.

Figure (B) showed that there was a significant interaural latency difference of P1 in oVEMP between MS patients

and healthy with a P value < 0.0001 indicating that VEMP can be reliable for detecting lesions in the vestibular pathway. The pooled heterogeneity of

the included studies could not be assessed due to limited number of the included studies.

(A) Forest plot of mean difference (MD) in latency N23 (ms) in cVEMP



(B) Forest plot of mean difference (MD) in latency P1 (ms) in oVEMP

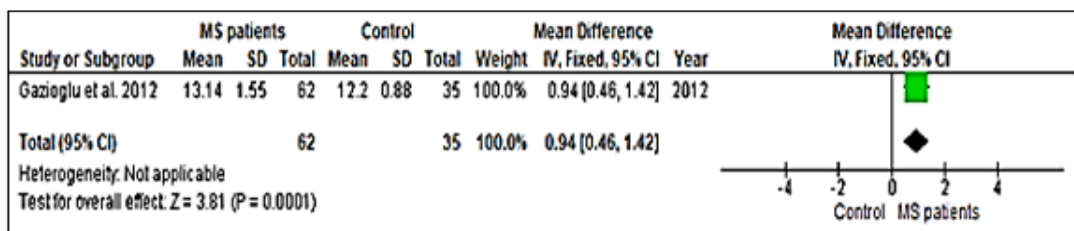
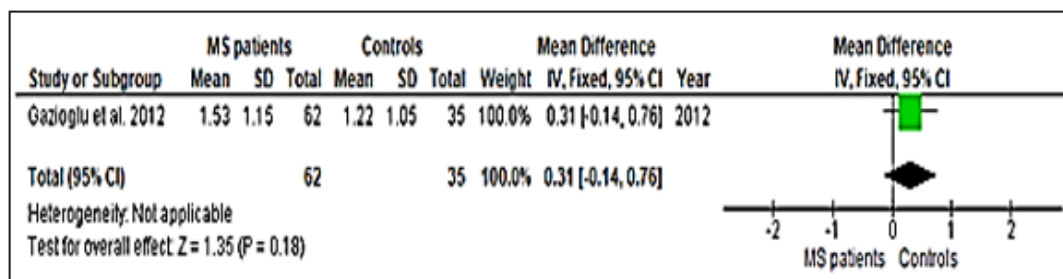


Figure (4): Latency N23 (ms) in cVEMP and P1 (ms) in oVEMP

(A) Forest plot of mean difference (MD) in interaural latency diff. N23 in cVEMP



(B) Forest plot of mean difference (MD) in interaural latency diff. P1 in oVEMP

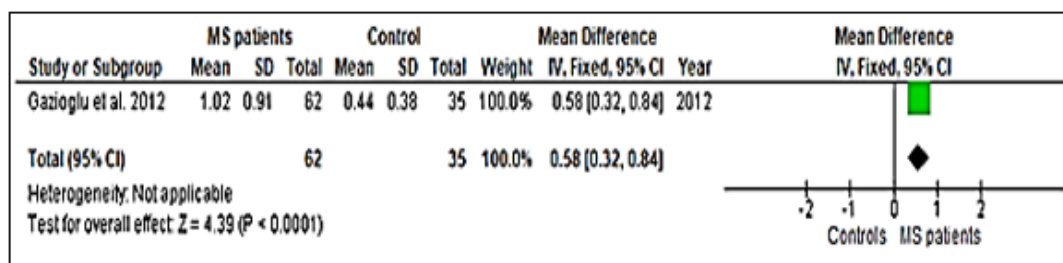


Figure (5): Interaural latency diff N23 in cVEMP and Interaural latency diff. P1 in oVEMP.

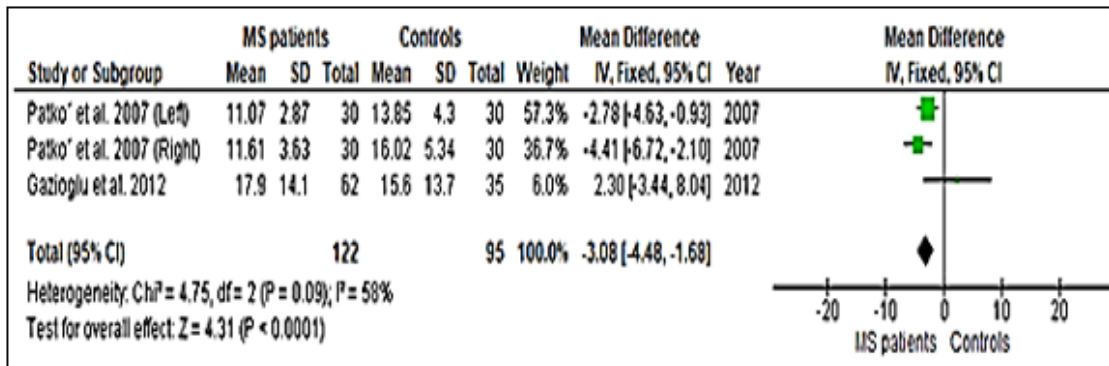
V. Amplitude in cVEMP and oVEMP (Figure 6)

Figure (A) showed a significant difference in amplitude asymmetry

ratio in cVEMP between MS patients and healthy controls with a P value < 0.0001 indicating that amplitude asymmetry ratio in cVEMP can be reliable for detecting lesions in the vestibular pathway. The pooled studies were heterogenous ($I^2 = 58\%$, $P = 0.09$) **Figure (B)** showed that the amplitude asymmetry ratio in oVEMP showed no

significant difference between MS patients and healthy controls with a P value = 0.43 indicating that amplitude asymmetry ratio in oVEMP cannot be reliable for MS diagnosis .The pooled heterogeneity of the included studies could not be assessed due to limited number of the included studies.

(A) Forest plot of mean difference (MD) in Amplitude in cVEMP



(B) Forest plot of mean difference (MD) in Amplitude in oVEMP

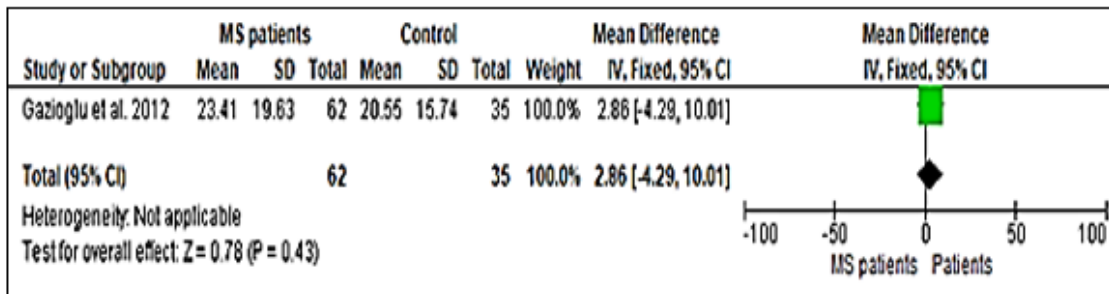


Figure (6): Amplitude in cVEMP and oVEMP

Discussion

The central nervous system is affected by multiple sclerosis, a degenerative condition. Multiple sclerosis is thought by many researchers to be an autoimmune disorder⁽¹⁾. The vestibular system of the ear can be affected by MS in a few different ways: peripherally, centrally, or both⁽¹³⁾. The utricle and saccule are otolith organs of the inner

ear, and VEMP is a neurophysiological diagnostic tool used to measure their function.⁽⁷⁾ This study aimed to assess the evidence on the role of VEMPs in diagnosis of multiple sclerosis as a tool to detect lesions in the vestibular pathways in the patients of MS. This meta-analysis found a statistically significant difference in the latency of P13 in cVEMP between MS patients and controls by analyzing the included

studies. This meta-analysis confirms previous research findings (Eleftheriadou et al., 2009- Parsa et al., 2015- Patko et al., 2007- Alpini et al., 2004- Gazioglu et al., 2012- Oh et al., 2016) that found that delayed latency of P13 is the most frequent abnormality in MS patients⁽¹⁴⁻¹⁹⁾.

Similarly, Delphi et al. 2021 found that MS patients' VEMP responses to 500 Hz tone bursts were collected; analysis revealed that MS patients' cVEMP P13 latencies were substantially longer than those of healthy controls⁽²⁰⁾.

Mean P1 wave latency in the brain stem involvement group was considerably longer than controls in a study including 40 MS patients and 40 controls that used cVEMP. They reasoned that cVEMP may be used to diagnose and monitor MS patients even if MRI did not reveal any demyelinating brainstem lesions.⁽²¹⁾

Consistent with these findings, Dabbous et al. 2021 reported that the Lt cVEMP P13 latency of MS patients was significantly ($p < 0.05$) longer than that of healthy controls⁽²²⁾.

Rather than injuries affecting neurons in the vestibular nucleus, demyelination of the afferent axons at the root entry zone or the axons of vestibulo-spinal tract may be responsible for the VEMP delay.⁽²³⁾

According to this meta-analysis, the latency of N23 in cVEMP has no positive significant results in diagnosis of MS lesions in the vestibular system with a P value = 0.31 indicating that latency of N23 in cVEMP cannot be reliable for detecting lesions in the vestibular pathway.

Our findings are consistent with those of Gazioglu et al. (2012), who also

observed no significant changes between MS patients and control subjects with regards to cVEMP mean N23 latencies⁽¹⁸⁾.

This meta-analysis contradicts a 2020 study by Hamed et al. that found substantial differences between MS patients and healthy controls in P13 latency and N23 latency on both the right and left sides⁽²⁴⁾.

This current study found that there was a statistically significant difference in the latency of N1 and P1 in oVEMP between MS patients and healthy controls with a P value < 0.0001 indicating that VEMP can be useful in diagnosis of MS.

The latency of N1 and P1 in oVEMP in MS patients with and without infratentorial lesions was considerably delayed compared to normal controls ($P = 0.001$), as was the case in our investigation⁽¹⁵⁾.

However, Gabelic et al. 2013 discovered the opposite, reporting a significantly longer delay of N1 response in the group of MS compared with controls. P1 latency of oVEMP did not achieve statistical significance⁽²⁵⁾.

According to the P13-N23 interpeak latency in cVEMP and N1-P1 interpeak latency in oVEMP in this meta-analysis, there is no significant difference in both, indicating that the interpeak latency has no positive results between MS patients and healthy controls. The pooled heterogeneity of the included studies could not be assessed due to limited number of the included studies. Interpeak latencies P13-N23 were consistently seen to be within acceptable ranges, which is consistent with the findings of the 2004 study by Alpini et al⁽¹⁷⁾.

No statistically significant findings were found in the included trials for MS patients when comparing the interaural latency difference P13 and N23 in cVEMP. Similarly, Parsa et al. 2015 discovered that the mean latency of P13 and N23 in cVEMP in MS patients showed no significant difference between the right and left sides ($P > 0.05$)⁽¹⁵⁾.

In addition, Delphi et al. 2021 reported that MS patients' cVEMP findings exhibited no statistically significant variations in the mean latency and amplitude of P13 and N23 on the right and left sides⁽²⁰⁾.

In the current study, regarding the interaural latency difference N1 and P1 in oVEMP, the analysis of the included studies showed a statistically significant difference between MS patients and controls. The pooled heterogeneity of the included studies could not be assessed due to limited number of the included studies.

In contrast to our findings, Parsa et al. 2015 discovered that in oVEMP, MS patients did not show any significant changes between the mean latency of N1 and P1 in the right and left sides ($P > 0.05$)⁽¹⁵⁾.

This meta-analysis showed significant positive results in the amplitude asymmetry ratio in cVEMP between MS patients and healthy individuals. On the other hand, the amplitude asymmetry ratio in oVEMP showed no significant difference between MS patients and healthy group.

Consistent with the findings of Delphi et al. 2021, the amplitude of P13 and N23 was considerably lower in MS patients than in control persons⁽²⁰⁾.

We found that the mean amplitude of p1-n1 was lower in MS cases compared to controls, although this difference was not statistically significant, echoing the findings of Guven et al⁽²⁶⁾. Interaural amplitude difference ratio (IAAD) > 36.55 percent in the cVEMP and > 36.1 percent in the oVEMP was declared abnormal in a study comparing MS patients to healthy controls (Dabbous et al, 2021).⁽²²⁾

Dabbous et al 2021, regarding the amplitude asymmetry ratio in cVEMP and oVEMP there was no statistically significant difference in the patients of MS compared to the healthy group⁽²²⁾.

The subject's failure to maintain a tonic contraction of the SCM muscle for a few seconds may contribute to the observed amplitude variation. Therefore, it is recommended that the amplitude should not be utilized as a tool to characterize the normal or pathological status of VEMPs⁽²⁷⁾.

In this meta-analysis, we analyzed the association between VEMP response and MRI brain finding (brain stem lesion) in MS patients. Patients with normal VEMP response have significantly lower brain stem lesions than those with abnormal VEMP results. VEMP abnormalities suggest a lesion in the vestibular pathways or in the vestibular nuclei, but it cannot determine a specific location of the lesion.

Di Stadio et al. 2019 found a statistically significant (P less than 0.05) correlation between VEMP modification (decreased amplitude or longer latency) and the existence of WMHs in the vestibular central pathways⁽¹³⁾.

Abd El Mageed et al. found a correlation between MRI-detected

brainstem lesions and positive VEMP results. Cervical VEMP and ocular VEMP latency and amplitude were significantly different between the control and MS patients ($P < 0.001$).⁽²⁸⁾

We further analyzed the association between VEMP responses and vestibular symptoms. We found that patients with normal VEMP response have significantly lower vestibular symptoms than those with abnormal VEMP results.

Likewise, Guven et al. 2014 discovered that VEMP abnormalities (delayed latency or no response) were more common in patients with vestibular symptoms than in those without MS ($P < 0.02$).⁽²⁶⁾ In addition, Gabelic et al. 2015 found that there was a statistically significant increase in the prevalence of VEMP anomalies among MS patients with clinical symptoms of brain stem involvement compared to patients without such signs and healthy controls⁽²⁵⁾.

Even though there was no substantial link with clinical or MRI findings, a high incidence of abnormalities in VEMP testing, specifically oVEMP tests, was identified in MS patients by Gazioglu et al. in 2012⁽¹⁸⁾. Eighty percent of patients with aberrant cVEMP (increased latencies of P13-N23) have a verified brainstem lesion in the MRI scan, as found by Hamed et al. in 2020.⁽²⁴⁾ These results were in line with Versino⁽²⁹⁾ and Patkó⁽³⁰⁾. They discovered that among MS patients, 40% and 31.4% had aberrant VEMP recordings.

If there is no cVEMP response, it could be because of axonal degeneration or significant myelin sheath injury⁽²³⁾.

When comparing VEMP anomalies to the existence of brainstem symptoms,

brainstem signs, or MRI lesions in Multiple Sclerosis (MS) patients, Sangu et al. 2022 found no significant correlation ($p > 0.05$). Brainstem MRI was normal in 38% of the MS group, whereas masseter VEMP (mVEMP), cVEMP, and oVEMP abnormalities were present in 82.4%, 64.7%, and 52.94% of the MS group, respectively. In the MS population, mVEMP appears to be the most useful of the three kinds of VEMP in detecting silent brainstem impairment that cannot be detected by clinical or MRI examinations⁽³¹⁾.

Conclusion

VEMP results alone are not sufficient for diagnosing multiple sclerosis (MS). They can serve as a supplementary tool in evaluating MS patients, as they are capable of identifying lesions in the vestibular system. However, VEMPs cannot pinpoint the precise location of these lesions.

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