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ORIGINAL ARTICLE

Vestibular Evoked Myogenic Potential Findings in Multiple Sclerosis☆

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KEYWORDS
Vestibular evoked myogenic potentials;
Vestibular tests;
Multiple sclerosis;
Demyelinating diseases

Abstract
Introduction: Multiple sclerosis is an inflammatory disease involving the occurrence of demyelinating, chronic neurodegenerative lesions in the central nervous system. We studied vestibular evoked myogenic potentials (VEMPs) in this pathology, to allow us to evaluate the saccule, inferior vestibular nerve and vestibular-spinal pathway non-invasively.
Methods: There were 23 patients diagnosed with multiple sclerosis who underwent VEMP recordings, comparing our results with a control group consisting of 35 healthy subjects. We registered p13 and n23 wave latencies, interaural amplitude difference and asymmetry ratio between both ears. Subjects also underwent an otoscopy and audiometric examination.
Results: The prolongation of p13 and n23 wave latencies was the most notable characteristic, with a mean p13 wave latency of 19.53 ms and a mean latency of 30.06 ms for n23. In contrast, the asymmetry index showed no significant differences with our control group.
Conclusions: In case of multiple sclerosis, the prolongation of the p13 and n23 VEMP wave latencies is a feature that has been attributed to slowing of conduction by demyelination of the vestibular-spinal pathway. In this regard, alteration of the response or lack thereof in these potentials has a locator value of injury to the lower brainstem.

PALABRAS CLAVE
Potenciales vestibulares miogénicos evocados;
Pruebas vestibulares;
Esclerosis múltiple;
Enfermedades desmielinizantes

Hallazgos de potenciales vestibulares miogénicos evocados en la esclerosis múltiple

Resumen
Introducción: La esclerosis múltiple es una enfermedad consistente en la aparición de lesiones desmielinizantes, neurodegenerativas y crónicas del sistema nervioso central. Se propone en esta enfermedad, estudiar los potenciales vestibulares miogénicos evocados, que nos van a permitir evaluar de forma no invasiva el sáculo, el nervio vestibular inferior y la vía vestíbulo-espinal.

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Métodos: Presentamos 23 pacientes diagnosticados de esclerosis múltiple a los que se les realizaron los potenciales vestibulares miogénicos evocados, comparando resultados con nuestro grupo control, integrado por 35 sujetos sanos. Se registró la latencia de las ondas p13 y n23, la diferencia interaural de amplitud y el índice de asimetría entre ambos oídos. También se llevó a cabo una exploración de otoscopia y audiometría.
Resultados: La prolongación de las latencias de las ondas p13 y n23 es la característica a destacar, con una media en la onda p13 de 19,53 ms y 30,06 ms para la n23. El índice de asimetría, por el contrario, no mostraba diferencias estadísticamente significativas con nuestro grupo control.
Conclusiones: En el caso de la esclerosis múltiple, la prolongación de la latencia de las ondas p13 y n23 de los potenciales vestibulares miogénicos evocados es una característica que se ha atribuido a un enlentecimiento de la conducción por la desmielinización de la vía vestíbulo-espinal. En este sentido, la alteración de la respuesta o ausencia de la misma en estos potenciales tiene un carácter localizador de la lesión a nivel de troncoencéfalo inferior.

Introduction

Multiple sclerosis (MS) is a disease consisting of the appearance of chronic neurodegenerative demyelinating lesions in the central nervous system. At present the causes that provoke it are unknown, although various autoimmune mechanisms are known to be involved. The hypothesis has been proposed that MS can be produced by a combination of several genetic and environmental factors; these include possible viral infections or others factors in childhood or during pregnancy that might prepare the immune system for a later abnormal reaction.[1,2] In a normal state, there is a barrier between the central nervous system and blood flow, called the blood–brain barrier, which is formed when endothelial cells cover the walls of the blood vessels. For unknown causes, this barrier does not work well in patients with MS and auto-reactive T-cells are capable of crossing it. When they do, they recognise healthy parts of the central nervous system as foreign and attack them. From that moment on, lymphocytes and macrophages destroy the central nervous system myelin, a fatty substance that covers the nerve cell axons and is essential for appropriate nerve transmission. At this point, the process of demyelination is triggered.

As for the epidemiology of this disease, we can indicate that in northern Europe 1 out of 1000 people suffer from MS. In central Europe it is the most common inflammatory disease of the central nervous system. In Spain the mean prevalence can be estimated at 40–50 cases per 100 000 inhabitants. The first symptoms generally present in humans when they are from 20 to 40 years old, rarely below the age of 15 or above that of 60. As with the majority of autoimmune diseases, it occurs twice as frequently in females than in males.[1]

In the majority of cases, MS begins with the acute onset of symptoms in a period of time that ranges from hours to days. This presentation is called exacerbation, attack or episode. Later on we speak of relapses. The first symptom is optic neuritis, followed by (in frequency) numbness and tingling in limbs.

There is currently no cure for MS. However, various drugs (interferons, immunosuppressants and monoclonal antibodies) have been found that are effective in its treatment, blocking the development of the disease and fighting against the symptoms.[3–5]

Diagnosing MS is a complex task. In fact, it can only be reliably diagnosed through post-mortem autopsy or biopsy, although there are specific non-invasive criteria to diagnose it with certainty. Proof of an extension of the lesions is necessary, both in time and in physical space in the central nervous system. That is, there should be at least 2 different lesions, verifiable through clinical symptoms or magnetic resonance; in addition, proof of new symptoms or lesions within 30 days is needed.[6] Spinal taps are used to obtain proof of the chronic inflammation of the central nervous system, indicated by the detection of oligoclonal bands in the cerebrospinal fluid. Studies on nerve conduction of the optic, sensory and motor nerves also provide evidence of the existence of the disease, given that the process of demyelination implies a reduction in the speed of conduction of nerve signals. Vestibular evoked myogenic potentials (VEMPs) are used to perform the study, with the expectation of an increase in p13 and n23 wave latencies to demonstrate the existence of demyelinating lesions in the vestibulospinal tract as a consequence of the slowing in the conduction of the nerve signal produced in MS.

As its name indicates, VEMP is a myogenic potential generated by a sound stimulus that allows us to explore non-invasively part of the vestibular sense organ (saccule and inferior vestibular nerve). Colebatch[7] explains the vestibular origin of this potential by a study showing that the biphasic myogenic waves (short latency) induced in the sternocleidomastoid muscle by loud sounds disappear in cases of vestibular neurectomy, but they are still obtained in cases of deafness. The lack of relation between these potentials and the semicircular canals is also known; if their function is annulled with streptomycin or a case of benign paroxysmal positional vertigo is involved, the VEMP remain the same. Moreover, in inner ear malformations that affect the cochlea and the semicircular canals but not the vestibule, VEMP are present. We could therefore state that VEMP are fundamentally generated by the ipsilateral afferents of the ear stimulated and that they depend on the integrity of the posterior labyrinth and the vestibular nerve. It key component p13-n23, defined as the positive-negative potential, is made up of an initial positive p13 wave (from 10 to 13 ms of

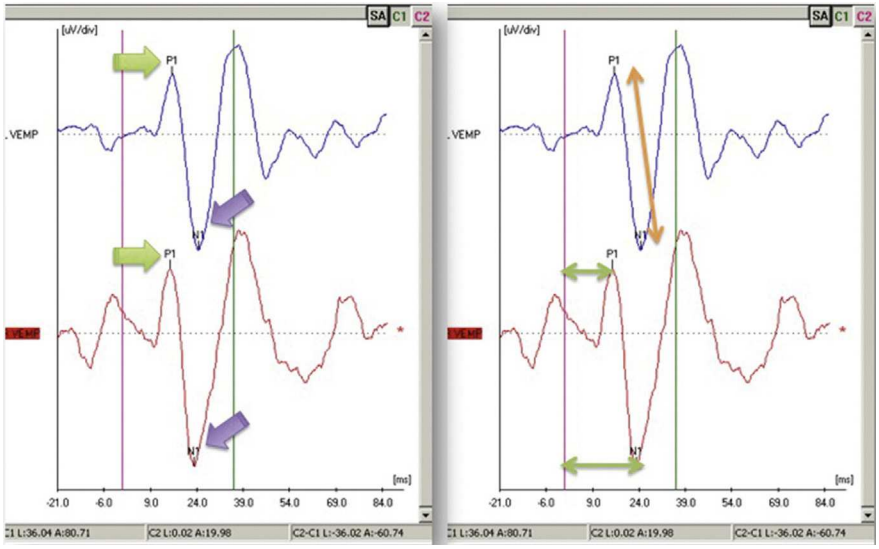

Figure 1 Record of vestibular evoked myogenic potentials. On the left, the p13 waves of the recording (indicated with green arrows) and the n23 waves (purple arrows). On the right, the inter-aural asymmetry of the amplitude (indicated with an orange arrow) and the inter-aural difference of the p13 and n23 wave latency (with green arrows).

latency), followed by another negative n23 wave (from 19 to 23 ms of latency).[8]

Methods

This was a retrospective study to compare the VEMP response obtained in a control group and in a group of patients diagnosed as having MS.

The control group consisted of 35 healthy subjects, lacking relevant serious antecedents. The ages ranged from 18 and 65, with a mean of 36 years. There were 17 females and 18 males.

In turn, the case group consisted of 23 patients. Of these, 13 presented the diagnosis of relapsing-remitting MS, while the remaining 10 were diagnosed with secondary-progressive form, with a mean follow-up of 12 years. The ways in which the disease presented clinically in our patients were as follows: paresthesia of upper and/or lower limbs (10 cases), loss of visual acuity (6 cases), diplopia (2 cases) and hemiparesis (2 cases); the rest of the patients had more non-specific onset forms. Patient age ranged from 30 to 65 years, with a mean of 47. The age at diagnosis varied from 23 and 51 years old, with a mean of 34. With respect to gender, there were 17 women and 6 men in the sample.

A general assessment, together with bilateral otoscopy and pure tone audiometry, was carried out on both groups. In addition, they all received VEMP testing. For this, 3 types of electrodes were placed: the ground electrode on the forehead,[9] active electrode in the middle third of the sternocleidomastoid muscle,[10,11] and reference electrode in the sternoclavicular joint or in the upper area of the sternum.[12] The patient sat down and turned the chin to the side opposite the stimulus, thereby tightening the sternocleidomastoid muscle.[9,13,14] The sound stimulus through intrachannel probe was a click, as it is easy to perform, symmetrical and reproducible, with an average of 200 presentations. The click used had an initial intensity of 100 dB, which was gradually lowered to 90, 80, 70... dB; it lasted 0.2 ms and its frequency was between 500 and 1000 Hz. Another fact to bear in mind is that the sound stimulus was always monoaural, given that a binaural stimulus (in spite of being more rapid) reduces the possibility of locating the side of the lesion due to obtaining crossed responses.[12,13] Considering all of this, the parameters of these potentials to be assessed were the presence or absence of response; p13 and n23 wave latency in milliseconds, a very constant parameter that increases in central lesions; and the asymmetry ratio that represented the level of imbalance in the vestibular responses, which is significant in central and peripheral vertigo. It should be noted that the inter-aural difference in amplitude that refers to the difference in intensity or amplitude that exists between the signal that arrives at one ear or the other was also evaluated; however, this is a more variable parameter, affected by multiple exogenous factors, which can be reduced in both middle ear disease and in central and peripheral lesions. Fig. 1 presents these parameters in one of our recordings of these potentials. With respect to statistical analysis, the programme used for data management was SPSS®. The statistical test chosen for comparing the various parameters between the 2 groups was Student's *t*-test, given that each of the variables involved in the study was normalized. The level of statistical significant selected was P=.05.

Results

It should be remembered that we had 2 sample groups, 1 consisting of 35 healthy subjects and another of 23 patients diagnosed with MS in its various clinical forms. The bilateral otoscopy was normal in cases and controls, with no middle or outer ear disease that could bias the study result being

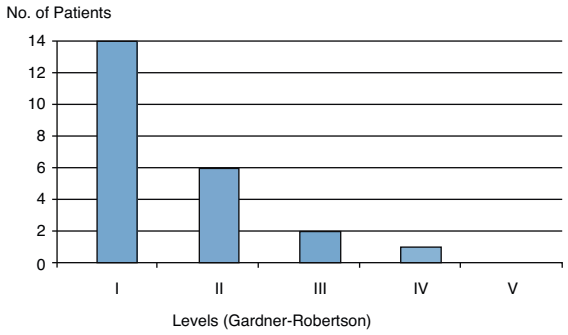

Figure 2 Hearing level recorded for pure tone audiometry of the 23 patients with multiple sclerosis, according to the Gardner–Robertson hearing scale, in which Class I corresponds to thresholds below 30 dB, Class II encompasses thresholds between 31 and 50 dB, Class III includes thresholds between 51 and 90 dB, Class IVcorresponds to thresholds between 91 and 100 dB and Class V is defined as deafness.

found. The pure tone audiometry showed levels of hearing compatible with normal hearing in the 35 healthy subjects, with hearing thresholds that did not exceed 25 dB for any individual. The situation was different in the MS group. There were 9 cases of different grades of sensorineural hearing loss, as can be seen in Fig. 2, while the 14 remaining patients presented normal hearing. No patient presented an air-bone gap in the audiometry, which would have suggested the existence of a transmission hearing loss that might have affected the result of the potential.

Now we turn to examining the VEMP results in the 2 groups. The mean value of p13 wave latency for the right ear in the patients diagnosed with MS was 19.05 ms, with a range from 9.6 to 31.04 ms; while that for the left ear was 20.01 ms, with a range between 11.26 and 29.17 ms. The mean overall p13 wave latency in the total sample of patients with MS was, consequently, 19.53 ms. If we compare this figure with that of the control group, in which the mean p13 wave latency for both ears was 11.88 ms, we can say that there is a statistically significant increase (P=.034) in the p13 wave latency in our patients with MS. In turn, the mean n23 wave latency in the group of patients was 28.97 ms for the right ear, with a range from 19.38 to 39.21 ms, and 31.15 ms for the left ear, with a range between 20.42 and 46.66 ms; the overall mean for both ears was 30.06 ms. Again, if we compare this result with that obtained in the control group (in which the mean latency was 19.22 ms for both ears), we find an increase in the n23 wave latency in patients with MS, with statistically significant validity (P=.041). Figs. 3 and 4 present the results of the latencies of these waves for all the members of the group of cases and of the control group.

Another parameter assessed was the asymmetry ratio. The average for this ratio in the group of patients with MS was 20.17%, with a range from 2% to 78%, while for the control group it was 13.63%. Both percentages lie within the values considered in the literature as normal; that is, they were below 30%. Fig. 5 describes the individual results for this ratio.

The inter-aural difference in amplitude was also evaluated in all the patients. However, the results obtained for this factor showed a clear disparity and were not taken into account in the statistical study. It must not be forgotten that this is a more variable parameter, being affected by multiple exogenous factors and it could be reduced in both middle ear disease and in central and peripheral lesions.

We can state that we did not find any relationship between the clinical state of the patient and the degree of alteration in the VEMP responses. The patient's clinical status was assessed on the basis of 2 parameters: the type of symptoms during the attack and the degree of impairment. The second parameter was obtained using the disability status scale proposed by Kurtzke, which quantifies the affectation of 8 functional systems (visual, motor, sensory, cerebellar, bowel-bladder, sexual, mental and brainstem); however, it is very conditioned by the capacity to walk, which in turn also conditions the scores. No connection between the delay in the p13 and

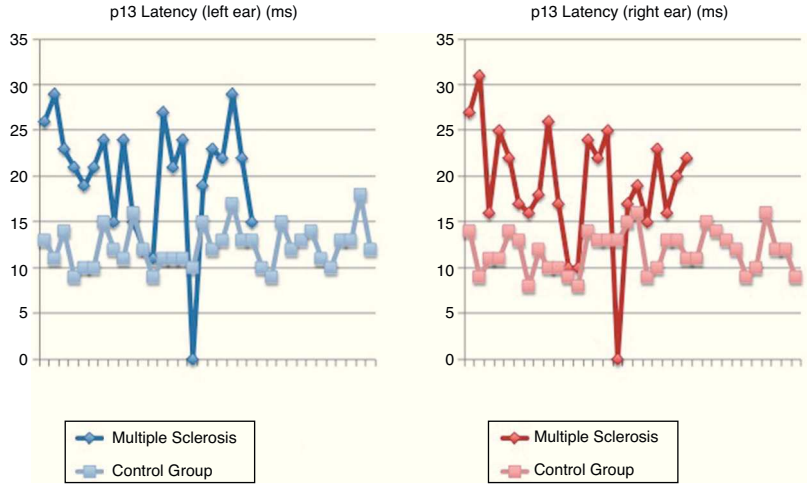

Figure 3 Latency in milliseconds of the p13 waves in the left and right ears of the patients diagnosed with multiple sclerosis and of the control group.

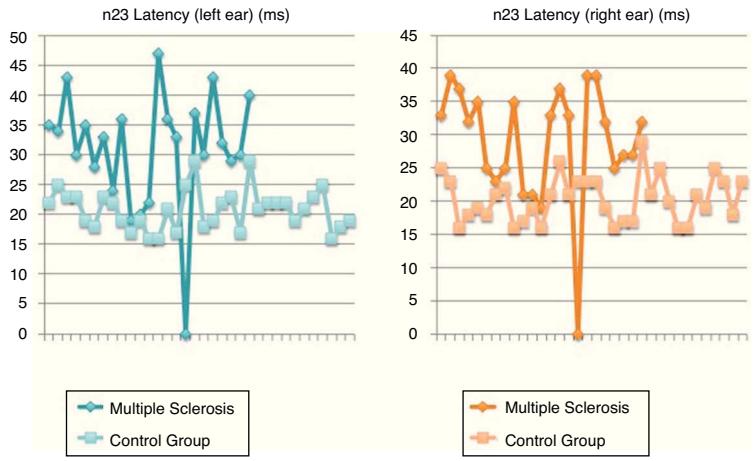

Figure 4 Latency in milliseconds of the n23 waves in the left and right ears of the patients diagnosed with multiple sclerosis and of the control group.

n23 wave latencies has been found with the number, size and extension of the demyelinating lesions found in the magnetic resonance tests that all patients had undergone.

Discussion

Multiple sclerosis is 1 of the diseases belonging to the group known as demyelinating diseases because they gradually produce attacks on the myelin sheaths of the axons, consequently affecting nerve conduction. At present, 4 different clinical forms of MS are recognised (commented earlier), among which the relapsing-recurring and the secondary-progressive forms are notable for being the most frequent in the population affected by this disease.[1,2] This fact also appears to be repeated in our sample of 23 patients, given that 57% have the relapsing-recurring variety and the remaining 43% have the secondary-progressive form. It is estimated that the percentage in which we can find the most aggressive clinical form (commonly known as primary-progressive) is only 10%.[1,2] However, our study sample of patients did not have any primary-progressive form or the benign variant. It is also stated that, as in the majority of diseases of autoimmune origin, MS affects women more, in a ratio of 2:1.[1,2,6] This was also true for our sample, with a representation of almost 74% for females against only 26% for males. There are various studies that have been carried out on this disease and in all of them the fact that the first symptoms generally appear between the ages of 20 and 40 years is mentioned[1,2,6]; our sample presented ages between 30 and 65 years at the moment of study, but if we go back to the moment of diagnosis, we find that this range is reduced, with ages from 23 to 51, and a mean of 34 years.

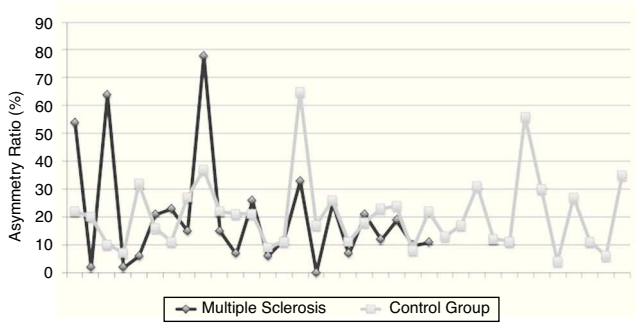

Figure 5 Asymmetry ratios in percent of the sample of patients with multiple sclerosis and of the control group.

Next, we focus on the objective of our study: corroborating if this process of demyelination that happens in MS could affect the vestibulospinal tract, and consequently trigger the slow-down of nerve conduction through this tract. To do so, we used VEMP, which allowed us to explore the saccule, inferior vestibular nerve and vestibulospinal tract. There are few articles in the literature about this, but the majority of those found state that there is an increase in p13 and n23 wave latency in these patients. Moreover, many of them dare to indicate that this prolongation of latencies is much more significant in the p13 wave than in the n23.[8,15–19] In our study we compared the p13 and n23 wave latencies in 2 groups, the one composed of 23 patients affected by MS and the other with 35 healthy subjects. The difference of latencies obtained between the 2 groups was evaluated, letting us state that there is a statistically significant increase in the p13 wave latency in patients with MS. We also find ourselves in a similar situation upon comparing the results obtained for the n23 wave latency, where statistical analysis using Student's *t*-test revealed a statistically significant prolongation of the n23 wave latency in the patients with MS. If we extrapolate our results from the patients with MS and compare them with the values defined in the literature as normal for the p13 and n23 wave latencies,[8,15,16] we can also say that this increased latency is corroborated in the group of cases. The physiopathological explanation of this phenomenon seems clear: in the case of MS, the prolongation of the p13 and n23 wave latencies in VEMP is a feature that has been attributed to a slowing down of the nerve signal conduction caused by the process of demyelination when this affects the vestibulospinal tract.

As for the asymmetry ratio, we repeat that this is a parameter that gives information about the level of imbalance in the vestibular responses. In the literature percentages lower than 30% are considered as falling within normal range for this ratio.[8,17–19] In contrast to what happens with the p13 and n23 wave latencies, we have not been able to confirm that this ration is always altered in patients with MS. In fact, in our sample of patients with MS, the average figure for this ratio was 20.17% and it was 13.63% in the control group. Independently of the fact that there is no statistical difference between these 2 percentages, we can state that in both cases the asymmetry ratio showed figures that, according to the literature, fall within the normal range.[8,15–18]

The data on amplitudes provide less information, without being able to reach a plausible conclusion. As we have indicated before, amplitude is one of the most variable VEMP parameters, it is influenced by many extrinsic factors and appears altered in both middle ear disease and in central and peripheral lesions.[15,16]

Lastly, it should be noted that the individuals having this disease can display a wide range of symptoms. Some of these, such as those previously mentioned in our sample, are of variable seriousness. Such symptoms can be classified according to the area of the nerve system affected as: those derived from damage to the optic nerve, derived from damage to the spinal cord and derived from brain damage.[6] In reference to this, the last data examined is the existence of a clinical and/or radiological correlation with these potentials. Some authors feel that there is not only concordance between these potentials and the clinical and radiological findings (which they put at approximately 60%), but that in up to 10% of cases the existence of an alteration in VEMP response indicates dysfunction at the level of the inferior brainstem in the patients having normal magnetic resonances and lacking specific clinical signs.[20] This is not the case in our study, where the patients with p13 and n23 wave latencies within the parameters of normality and with asymmetry ratios lower than 30% presented abundant signs and symptoms, with hemiparesis and paresthesia when the test was performed, as well as multiple extended lesions in the magnetic resonance imaging; while the patients with greatly altered potentials were completely asymptomatic when the test was performed and had few lesions in the imaging tests.

Conclusions

As a conclusion, we can say that in patients with MS in which demyelination has extended to the vestibulospinal tract, there is going to be a prolongation of the p13 and n23 wave latencies as a consequence of the reduction of the nerve signal conduction along this tract caused by the process of demyelination. In fact, this increase—statistically significant—in the p13 and n23 latencies is clear in the patients with MS in comparison to the control group. The presence of alteration of the response or its absence in the VEMP will serve as a factor placing the lesion at the level of the inferior brainstem, without providing any information as to the nature of this lesion. The affectation of both ears has also been confirmed in our study, as well as the absence of correlation between the results for the potentials and clinical signs or symptoms or the characteristic radiological alterations of MS. For all these reasons, these potentials are considered to constitute a good auxiliary method of diagnosis of the state of the vestibulospinal tracts in MS cases. They can even help to diagnose this disease in early stages.

Conflict of Interests

The authors have no conflicts of interests to declare.

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