Chapter 5

The Visual Evoked Potential in Idiopathic Inflammatory Demyelinating Diseases

Silvio Pessanha Neto, Luiz Carlos Pinto and
Regina Maria Papais Alvarenga

Additional information is available at the end of the chapter

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Abstract

Within the group of inflammatory idiopathic demyelinating diseases, there is a great number of diseases that have an initial attack in common, including visual. Multiple sclerosis (MS) is a chronic, demyelinating, immune-mediated disease, with considerably varying prevalence and incidence. Neuromyelitis optica (NMO), which until recently was considered a variant of MS, is currently considered an independent entity. However, it resembles MS, because it is an immune-mediated disease characterized by the simultaneous or sequential involvement in time of optic neuritis and extensive demyelinating myelitis. Fifty percent of patients with MS have isolated optic neuritis. However, the frequency of abnormalities ranges from 57 to 100% in visual evoked potential (VEP). Several studies have evaluated the clinical, evolutive, and demographic characteristics of idiopathic optic neuritis and demonstrated their differences among the cases related to MS and NMO. The most common changes in VEP studies in multiple sclerosis are as follows: increased interocular differential latency of P100 wave and the absolute increase in latency of P100 wave. New studies indicate that VEP pattern in NOM spectrum syndromes is different from that of MS.

Keywords: neuromyelitis optica, visual evoked potential, optic neuritis, multiple sclerosis, P100 wave

1. Introduction

Visual evoked potential (VEP), which has been known for more than 40 years, consists of electric signals mainly generated by the occipital cortex in response to visual stimulation. They are generally used to assist in the identification of pathologies that impair the visual pathways in any of its segments.

2. Technical aspects

2.1. Stimulation

In VEP studies, two types of stimulation, photostimulators and pattern reversal, are normally used. The most used photostimulators are the common photographic flash and goggles, which are used for swimming, or similar ones, in which each lens is replaced by a cloudy plate, with minute light bulbs installed in its internal face, for the luminous extremities to face each eye. These stimulators are connected and synchronized with the equipment system of stimulation, scanning, and promediation. Flash stimulation is not only the oldest one, used in clinical neurophysiology since the 40s, but also the most common method used during many years and until the beginning of the 70s to obtain VEP. The flash stimulates almost all the retina, mainly the peripheral one, because of its capacity to capture the variations of room luminosity. Depolarization waves provoked by stimuli radiate mainly to the pretectal zones and thalamic nuclei, ending up in lesser amount in the visual cortex, and in larger amount in the association areas, on the nonvisual cortex. When the flash is used, it is necessary that the contralateral eye is very well occluded, because the capture of potentials generated by the stimulation of the unexamined side can lead to false-negative results.

One of the main disadvantages in the responses obtained with this technique is its great variability, both among individuals and in the same patient; it can also vary according to the electroencephalographic activity at that moment. Therefore, flash stimulation was gradually replaced by more reliable methods, being reserved for the cases of patients with very low visual acuity, encephalopathies, and other pathologies.

In the case of goggles, the light bulbs or light emitting diodes (LEDs) on them are generally red, and each one has 3 mm of diameter. At each series of stimuli, the stimulator is adjusted so that one side of the goggles remains with the light off, occluding vision in one of the patient's eyes, while in the stimulated side the LEDs are on and are turned off with a frequency of 1–2 Hz. In each side, at least two series of 60–260 stimuli are applied.

Both flash and goggles stimulate the entire retina and provide results that are more qualitative than quantitative. However, they are very useful, because they can stimulate the retina even when the eyes are closed, as it occurs in the case of patients in coma, children or adults who do not want to cooperate [1, 2].

Currently, despite the utility of the photostimulators, the most commonly used visual stimulation is the pattern reversal that, as already mentioned, consists of a monitor in the screen of which there is an image with black and white squares, similar to a chessboard. During stimulation, the squares alternate their colors. The white ones become black, and the black ones become white, successively, at a frequency of 1–2 Hz. These constant inversions stimulate the macular area of the retina, more specifically the foveal zone, radiating to the lateral geniculate body, and then to the primary visual cortex, in area 17. However, for this, it is important that the patient keeps the look fixed on the center of the monitor screen [3].

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In the stimulation by the reversal pattern, the patient should remain seated in front of the monitor, with the eyes keeping a distance of 70 cm to 1 m from the screen. As the stimulation is monocular, the contralateral eye is kept occluded and at least two series of 60–260 stimuli in each side of the visual pathway are applied.

The distance between the patient's eye and the monitor, related to the size of the each reversal pattern square side, provides the visual angle used in the test. Despite the existence of tables, the simplest way to calculate the visual angle is to multiply the width of the square by 3450 and divide the result by the distance in millimeters between the screen and the patient's eyes. This way, the visual angle is obtained in minutes. To convert this unit to degrees, we simply divide the resulting value by 60 [4–6].

The visual angle used is very important, because it influences in the exam results. In adults, visual angles with 10–20 arcmin produce responses of higher amplitude. The visual angles of more than 15 min stimulate mainly the fovea, and those with more than 40 min stimulate more the parafoveal retina. The central visual field is the most responsible for P100 amplitude, because the central vision has greater cortical representation than the peripheral vision. Problems in the central vision can change P100 amplitude without modifying its latency. In the diagnostic routine, angles of 28–32 arcmin are more frequently used.

The equipment visual stimulation module allows the use of a reversal pattern, the squares of which can vary in size according to the examiner interest. In practice, they have options of squares of 0.5, 1.0, 2.0, or 5 cm of side. With this, depending on the clinical case and the patient's visual acuity, the series of stimuli can be repeated with the use of different visual angles.

There is a direct relation between the visual angle and the exam result. The smaller the squares, the more reliable the responses. However, in the patients with visual acuity deficit, the use of bigger squares is necessary, because even losing some precision, it is crucial that the patient visualizes and identifies the reversal pattern; otherwise, it will not be possible to capture responses, or falsely abnormal responses will be obtained [7–9]. Before undergoing a VEP study, the patient should have an ophthalmologic evaluation for measuring his/her visual acuity, aiming to rule out refractive defects [10].

The reversal pattern can be one of "full field," which is the most used, or of "half field." In the half-field pattern, the chessboard image fills only one of the halves of the monitor screen, with the other remaining entirely black. This allows selective stimulation of the nasal or temporal field of the retinas, serving both for the diagnosis and to inform if the lesion is prechiasmatic, chiasmatic, or retrochiasmatic [11].

Some authors have used colored reversal patterns, but the results have not been advantageous. There is also the "bar grating reversal pattern," known as gratings, which is little used and on which, instead of the squares, the monitor presents horizontal or vertical, white and black bars, which alternate colors consecutively too [12, 13].

In brief, because of its higher precision and sensitivity, the reversal pattern is the most commonly used. The flash and goggles are used in cases where it is supposed that the patient

is not looking at the center of the screen, in comatose patients, in surgical monitoring, or in children who have difficulty fixing attention on the monitor.

2.2. Capture

The most common assembly consists of the colocation of an active electrode in Oz, on the occipital cortex, with the reference in Fz, and the ground in the frontal area in Fpz. However, depending on the number of channels available, other assemblies can be made. In a second channel, for example, the active on Oz can be used, with the reference on Pz or Cz. Although being a capture type that is more used in half-field stimulations, the active electrodes can be fixed on points located 5 and 10 cm lateral to Oz, in known leads, such as R5, R10, L5, or L10, in which the letters "R" and "L" represent the right side and the left side, respectively.

The visual response is formed by three waves, which form the M-like image. The first deflection is N75, which is negative. It is followed by a positive, sharper, and deeper wave, with a mean latency of 100 ms, that it is the P100. The third wave, N145, is also negative as the first one. However, the most important response is P100, because it is the most defined and the one that has greater reproducibility in normal people. It represents the occipital cortex depolarization to the applied stimuli. The normal values for each one of these responses can vary in accordance with the laboratory and its equipment.

The first negative potential (N1) has a latency between 60 and 90 ms; the first positive potential (P100) has a latency of 85–120 ms, with an average value of 100 ms. The second negative potential (N2) varies from 125 to 155 ms.

The amplitude of the P100 response varies between 3 and 21 μV. The amplitude of the N1 and N2 responses is a little lower and usually measures less than 12 μV for N1 and less than 16 μV for N2. N1 and N2 responses vary a lot, and in some cases, they are not easy to be identified. In part, for this reason, maximum attention is usually given to P100 response, which is easy to obtain and reproduce in normal people, and has well-defined parameters.

P100 latency and the parameters of normality vary from a laboratory to another due to the technique used, the type of equipment, and the age of the examined people. In laboratories where a population of young patients predominates, the mean and maximum latencies accepted as normal will be lower than those obtained in laboratories where older patients predominate.

The ideal is that each examining physician determines his/her own normal values. For this, at least 30 normal and representative people should be examined. The results obtained should be analyzed, and a mean latency should be determined for the whole group. The normal parameters are obtained, adding two or three standard deviations to this average value. If this is not possible, then normal values published by authors of high credibility in the area can be used in a more practical way.

As previously cited, the inconsistency and variability of the N1 and N2 potentials discouraged most authors, and all the attention and importance was given to P100 response. Despite all this, Pavot believes that, although the N1 and N2 parameters are wider than those of P100,

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there are certain limits of normality. According to his experience, in certain pathological conditions, as, for example, in multiple sclerosis (MS), in some cases the manifestations appear with an increase of N2 latency, or with its disappearance [14].

In the interpretation of the exams, absolute P100 latency is valued, as well as the difference between P100 latencies in one side and the other (interocular latency) and also its amplitude, which is compared with that of the contralateral eye. A difference of amplitude higher than 50% between the two sides is significant.

2.3. Factors that interfere with the evoked visual responses

When performing VEP studies, it is extremely important to give much attention to some details that can affect the results. In addition to age, sex, visual acuity, and other physiological factors, the visual evoked potentials are also affected by technical parameters, such as electrode positioning; luminosity in the examination room; level of concentration of the patient, who has to keep the look persistently directed to the center of the screen of the stimulation monitor; visual angle; luminosity and brightness of the monitor screen; and type of stimulator; filters.

In reversal pattern stimulation, variations in the quality of the stimuli, such as brightness, luminosity, frequency, and size of the square, can affect the responses, changing the morphology, amplitude, and latencies of its components.

Brightness reduction increases latency and reduces P100 amplitude, in 15 ms and 18%, respectively, for each log unit that reduces luminosity. The reduction of the contrast, which can be calculated in percentage according to the difference of luminosity between the white and black squares, also affects P100, increasing its latency and reducing its amplitude.

As previously mentioned, the size of the square determines the visual angle used and has direct influence in the responses. The use of smaller squares makes the study more accurate, but in turn, its use will depend on the level of visual acuity of the patient, since they stimulate the fovea, and the refractive defects produce out-of-focus retinal images, increasing P100 latency. The larger squares with up to 5 cm of side are less affected by the visual acuity variations.

The electrodes should be well located, because positioning them on points that are out of those normally proposed result in absent, or dispersed, responses with potentials of modified shapes, low amplitude, and unreal latencies. Loose, badly fixed electrodes produce artifacts that make the identification of the potentials difficult.

Noise excess in the room can affect the patient's concentration capacity in the examination, making the look to deviate from the stimulator. During the examination, the examiner should ensure that the patient is kept awake all the time, and with the look focused on the center of the monitor screen. If the patient closes the eyes or deviates the look from the screen, the potential amplitude can lower and the latencies can increase, leading to false-positive results.

In cases of restless patients, with concentration difficulty, as it is common to occur in children and even in those cases when the examiner suspects that the patient is purposefully trying to interfere with the examination, a stimulation performed with special glasses or goggles is recommended.

Some authors recommend to avoid exam performance in the evening because at this time the patient is frequently tired, sleepy and it is more difficult to remain concentrated, and with the look fixed on the screen.

Special attention should be given to refractive errors, and to retinal diseases. Patients who wear glasses or contact lenses have to be alerted to take them on the day of the examination, because decreased visual acuity slightly reduces amplitude of the responses, and can also change their latency.

Age modifies P100 latency, following a variable curve that is descending in the two first decades of life, steady until the fifth or sixth decade, and crescent above 60 years. Women tend to have little shorter latencies than men. However, menopausal women can present a higher P100 latency than men in a similar age.

In healthy individuals, there is no evidence of P100 alterations caused by the same increase of temperature or even by exercises. However, the exercises can reduce P100 amplitude in multiple sclerosis patients with impairment of the visual pathways [15].

3. Criteria for the analysis of the visual evoked potentials

In the analysis of the visual responses obtained, the examiner should value the following parameters: absolute latency; interocular latency difference, or interocular differential latency; P100 response amplitude; interocular amplitude difference or interocular differential amplitude; and potential morphology.

3.1. Absolute latency

The examiner evaluates whether the latency of the potential obtained is within the normal range, that is, the normal average with more or less three standard deviations. A latency that exceeds the limits of normality, with the possibilities of technical errors discarded, indicates a defect of sensory conduction in the studied visual pathway.

3.2. Interocular differential latency

The parameter for this measure should be determined in each laboratory, but in general it varies from 5 to 8 ms. An interocular differential latency above these values is usually associated with pathologies. Many times this latency increase is the first manifestation of some diseases. In many cases of optic neuritis, the interocular latency change can be the only abnormality detected.

3.3. P100 response amplitude

P100 amplitude can vary in normal people, but an amplitude of 1–5 μV, or the absence of P100 generally means a pathological condition [16].

3.4. Interocular amplitude difference

There is much controversy on the limit of normality for the value of the amplitude difference between the responses obtained in the two eyes. When the stimulation for the "full-field reversal pattern" is used, some authors advocate that, to be abnormal, there must be an amplitude reduction of at least 80%, or total absence of P100. However, for most authors, a reduction of the differential amplitude between 50 and 75% or more indicates visual pathway impairment. In the stimulation of the hemifield, there is a consensus that an amplitude difference of more than 50% is abnormal.

3.5. Morphology

In a normal person, the P100 response has the format of a letter "V." An alteration in the potential shape or its disappearance represents an abnormality [16].

4. Clinical applications

Any pathology, regardless of its nature, which affects the ocular structures responsible for the reception of light and images, the visual pathway, or the cortex, can lead to changes in the visual evoked responses. In the pure retinal pathologies, as it occurs in the retinitis pigmentosa, the important changes in the ophthalmologic examination and in the electroretinogram are very striking and easy to be identified. On the other hand, it is important to remember that retinal responses take a long time to disappear in cases of brain death.

In the diseases affecting the receptors and the visual pathways, or the visual pathways and the cortex, frames with coincident or divergent findings can be observed in the VEP studies. The frames known as coincident are those in which no difference in the type of response obtained is observed, either with the use of the flash, or with the reversal pattern, that is, the responses are normal or abnormal in the two methods. In the frames with divergent findings, the neurophysiological abnormalities are manifested in only one of the techniques, with normal responses being observed in the other.

The visual evoked potentials are used in the investigation of neurological impairment, mainly in the suspicion of optic neuritis, multiple sclerosis, and compressive lesions affecting the visual pathways. Diseases affecting the optic nerve or causing its demyelination are the more frequently associated with changes of visual response latency. To understand the neurophysiological diagnosis, and the alterations caused by pathologies throughout the optic pathways, it is necessary to know these pathways anatomy [17, 18].

The visual pathways are formed from the retina, through the chaining of three types of neurons. The first receptor neurons, which are the cones and the rods, make synapsis with bipolar cells, and these ones with a third type of neuron, which are the ganglion cells. The ganglion cell axon junction forms the optic nerves, which take the visual impulses to the lateral geniculate bodies in the diencephalon, where they make synapses with neurons that go to the occipital cortex through the geniculocalcarine tract.

In its route to the geniculate bodies, the optic nerve fibers from the nasal portion of each retina cross to the opposite side on the level of the optic chiasm. Thus, from the chiasm, each optic tract consists of the optic fibers from the temporal retina on the same side and of the fibers that were formed in the contralateral nasal retina. This peculiarity of the optic pathways to cross part of their fibers in the chiasm, continuing as a mixed tract that has fibers of the retinal portion of the ipsilateral eye, and also of the contralateral eye, causes the most varied visual syndromes, depending on the location of the lesion.

5. CNS idiopathic inflammatory demyelinating diseases

Demyelinating optic neuritis represents the most frequent cause of transitory visual loss in young adults, affecting 2.6 men and 7.5 women per year, for each 100,000 inhabitants. The average age for its occurrence is 31 years. The optic pathway demyelination causes blocks or delays in the visual pathways conduction, with consequent alterations in the studies of visual evoked potentials. Demyelination precedes the inflammatory process, which is the real responsible for the reversibility of the picture. Thus, inflammation improvement contributes for the rapid visual improvement after a crisis. In addition, mainly in young people, remyelination is another important factor in the recovery of vision. However, when an axonal lesion and a more persistent demyelination occur, improvement is not usually complete.

Visual loss in optic neuritis can be preceded in some days by ocular pain in the affected side, which tends to resolve. This pain is possibly caused by the tension on the inflamed nerve. About 70% of the adults initially present with a unilateral picture, but in 30% it can affect both eyes. The visual loss can be sudden, progressing in a few hours, or can have a slower progression, taking some days to be installed. In 7% of the cases, this time is of 1–2 weeks.

The diagnosis of optic neuritis is one of exclusion, what makes the investigation of other diseases affecting the optic nerve, such as hereditary, metabolic, toxic, vascular, and compressive diseases, indispensable.

In the isolated demyelinating optic neuritis, the magnetic resonance reveals changes on the affected nerve in 84% of the cases. In 34% of the patients, the exam also shows changes in the asymptomatic side. In addition, 50–70% of these patients show multifocal demyelinating lesions in the corpus callosum and on the periventricular white substance or in other parts of the encephalon.

Within the group of the idiopathic inflammatory demyelinating diseases, there is a great number of pathologies that can have an initial outbreak in common, either visual, motor, sensitive, proprioceptive, cerebellar, medullary or of the brainstem, characterizing the so-called clinically isolated syndrome—CIS. It is only after the second outbreak and evaluation of the complementary exams that it is possible to establish or suggest the definitive diagnosis, such as MS. This aspect can sometimes confuse physicians who attend the patient and delay the treatment.

MS diagnosis is based on the identification, at history taking, of two acute episodes with a duration of at least 24 h, and evidence at the neurological examination of objective signs of functional system impairment, indicating inflammatory lesions located on different topographies in the CNS.

It was only in 1983 that complementary methods, such as magnetic resonance and evoked potentials, were introduced in the MS diagnosis criteria proposed by Poser, with the purpose to identify subclinic inflammatory lesions. In the last decade, MRI was used to confirm temporal and spatial dissemination of inflammatory lesions in the neuroaxis and then to anticipate the clinical diagnosis of MS. Currently, with a patient with monofocal or multifocal clinically isolated syndrome, the dissemination in the space can be demonstrated in the MRI through T2 hyperintense lesions, in at least two of the four regions of the CNS: periventricular, juxtacortical, infratentorial, and spinal. Temporal dissemination is proven by the presence of a new T2 lesion, or a contrast-enhancing lesion, when serial MRI scans are compared, or by the coexistence of asymptomatic contrast-enhancing or nonenhancing lesions in a single initial examination. These radiological criteria should only be applied to young patients, with strong clinical suspicion of MS characterized by the presence of clinical signs of acute CNS impairment, which presents with outbreaks, having a suggestive behavior of an inflammatory disease, and after ruling out all the diseases secondarily affecting the white substance. The application of these criteria aims to anticipate the clinical diagnosis and, consequently, the beginning of the treatment, since all the FDA-approved medicines from 1993 on for MS act in the initial phase of the disease, reducing inflammation and the annual rate of outbreaks [20].

MS is a chronic disease, with greatly variable prevalence and incidence, dependent on ethnicity and demographic region, with the highest indices being described in Caucasian populations living in regions of the North hemisphere, places of cold weather. In its more prevalent clinical form, there are outbreaks and remissions that affect individuals from 20 to 40 years of age, and with predominance in women. Currently, it is estimated that more than 300,000 Americans have a definite diagnosis of the disease and, because it affects young patients in full activity, it has strong sociocultural impact [21].

NOM, which was included among MS variants, is currently considered an independent condition. The historical description of this disease was a clinical, and anatomical and pathological case report in 1894, in France, by Eugene Devic. This condition was called Devic's disease, and during a century, the diagnosis was based on the identification of an acute, monophasic inflammatory disease, characterized by severe and bilateral ON, and transverse myelitis (TM), installed simultaneously or in a short interval of time. Only after the 1990s studies of independent series published in different western and eastern populations started to describe recurrent cases of NOM, where the index events occurred separately for a variable period of time, and were followed by new acute episodes, affecting the spinal cord and the optic nerve [22–24]. Only recently the presence of lesions in locations other than the spinal optic axis was accepted, with inflammatory lesions being demonstrated, although in lower frequency, in the brainstem and encephalon [23]. In Asian individuals, the selective and severe involvement of the optic nerves and spinal cord is very typical. In this region, this syndrome is classified as a variant of MS, defining two distinct subtypes: the opticospinal form (OSMS), which has characteristics that are similar to the remittent-recurrent form of western NOM, and the conventional form, which is similar to the classic MS, as it is described in western patients [25].

Currently, many works in the literature try to define the probability of an isolated and initial case of idiopathic optic neurite to progress, to keep its monophasic course, to be

associated with myelitis or with outbreaks that impair other areas of the CNS. Among several significant aspects, the main justifications for these studies regarding the progression risk are related to the patient's prognosis, and the possibility to search early therapies at the first signs of isolated idiopathic ON, since this can be the first symptom, not only of NOM, but also of MS.

The clinical and evolutive characteristics of idiopathic ON have been analyzed by the Optic Neuritis Study Group (1995). The most relevant predictive factor of MS development after 15 years was the presence of changes in the brain MRI in the occasion of a visual outbreak [26]. Other works tried to identify the main characteristics of the cases of NOM-related ON, evidencing that in this condition the visual involvement is generally more severe and bilateral [24].

In 2007, Wingerchuk et al. [27], from the Mayo Clinic, defined a group of conditions that were catalogued as syndromes of the NOM spectrum. These entities, although independent, are elements of the same group. They are as follows: neuromyelitis optica (NOM), extensive idiopathic myelitis, recurrent monocular optic neuritis (rON) or simultaneously bilateral optic neuritis (BON), Asian-type opticospinal multiple sclerosis (OSMS), optic neuritis, or extensive idiopathic myelitis associated with systemic autoimmune disease, optic neuritis, or idiopathic myelitis associated with typical brain lesions of NOM (hypothalamus, corpus callosum, and periventricular region) or lesions in the brainstem.

6. VEP in idiopathic inflammatory demyelinating diseases

Since 1972, the pattern of visual response abnormalities of patients with ON, obtained with this method, has been studied [28], with the MS-related VEP characteristics of the optic neuritis being well-defined. However, there are few articles in the literature discussing the VEP pattern in NOM. Currently, MS pattern is frequently used to analyze the VEP of patients with NOM, configuring an interpretation bias.

The most common changes in the VEP studies in MS, in descending order of prevalence and importance, are as follows: the absolute increase of P100 wave latency, this wave morphology changes, and finally the absence of response. Frederiksen and Petrera [29] followed patients in the acute phase of ON since the beginning of the symptoms, with performance of VEP, repeating it in subsequent months. Among these patients, 35.5% had the definite diagnosis of MS, and had, according to the authors, a significant relation with delays of P100 wave latency in the VEP. They also observed subclinical changes of the optic nerve, with the presence of abnormal VEP in asymptomatic eyes.

Several studies emphasize VEP sensitivity in the evaluation of ON in patients with demyelinating diseases, even overcoming the optical coherence tomography, as Naismith et al. showed in 2009 [30]. At that time, the authors evaluated patients with different diagnosis related to the demyelinating diseases (CIS, MS, and NOM) that had at least one episode of ON in the last six months and tried to compare VEP sensitivity to the optical coherence tomography,

in the evaluation of clinical and subclinical ON. VEP showed higher sensitivity both in the evaluation of clinically identified ON (81% vs. 60%, $p = 0.002$), and in the cases of evaluation of asymptomatic eyes.

In the study by Matthews et al. [29], a total of 223 individuals were evaluated, with 186 with a diagnosis of MS and 37 healthy controls. In this study, the sample was submitted to VEP, to evaluate the differences in the pattern of responses to this exam, considering the groups of definite, probable, possible MS, and the control group. It showed that while all controls had VEP responses within normal range, the group with definite MS had a higher percentage of change when compared to the other groups. It was also observed that the main characteristic of the VEP that was changed was P100 wave latency in these patients.

Frederiksen and Petrera [31] followed patients in the acute phase of ON since the beginning of symptoms, with performance of VEP, and its repetition in subsequent months. Among these patients, 35.5% had definite diagnosis of MS, and had, according to the authors, a significant relation with delays of P100 wave latency in the VEP. They also observed subclinical changes of the optic nerve, with the presence of abnormal VEP in asymptomatic eyes.

In order to enhance the sensitivity for the detection of optic nerve affections with the use of VEP, and to analyze its effectiveness in the early evaluation of patients with suggestive pictures of ON and MS, Davidson et al. in 2004 [32] examined 124 individuals with VEP using two different intensities of contrast. Although they observed a higher number of abnormal VEP with reduced contrast, when they followed the outcome they noticed that they were false positives.

Considering that NOM is a pathology that is different from MS, and its strong relation with the presence of anti-AQP4 serum antibodies, Watanabe et al., in 2009 [33], decided to study the abnormalities of the findings of evoked potentials of patients with definite diagnosis of MS, and the presence of positivity for anti-QP4. In this study, they observe that in the anti-QP4-negative MS group the delay in the latency of the P100 wave is evident, following the literature. However, the anti-QP4-positive group presents a higher percentage of patients with absence of this wave, revealing a more severe lesion ($p = 0.003$). They also conclude that the antibody positivity, and the absence of response, showed significant relation with a more serious progression of visual impairment (OR = 35.432%, $p < 0.001$).

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Neto et al., in 2013, conducted a study where 19 patients, with NOM diagnosis, with 74% being Afro-Brazilians, underwent VEP study. Of the 38 eyes examined, 18 (47.37%) showed no visual evocable response. Of the 20 eyes (52.63%) where VEP responses were detected, 18 (90%) had P100 wave latency within normal range, while only 2 (10%) had increase of the

latency of this wave. Regarding P100 wave amplitude, 11 of the 20 eyes (65%) that generated visual responses had values below that considered normal in the study. Seven (35%) had amplitudes ≥ 5.8 μV, being considered normal. In 65% of the 20 eyes where the visual response was evocable, a reduction of the P100 wave amplitude was found, with normal latency [34].

Ringelstein et al., in 2014, reproduced the study by Neto et al., and analyzed the medical records of 43 Caucasian patients with NOM diagnosis, and compared the findings of their VEP with those of 81 healthy patients. The authors find reduced amplitude in 12.3%, long latencies in 41.9%, and absence of response in 14% of NOM eyes, suggesting that VEP in NOM would have a heterogeneous standard. However, the frequencies of amplitude reduction and the absence of response are greater than those observed in all the studies of patients with MS. In the article, they suggest that the difference in sample results, compared to the study by Neto et al. could be explained by ethnic issues that distinguish the populations studied [19]. In addition, in the study by Ringelstein et al., the reference value for amplitude normality is lower than that used by Neto et al., being 3.0 and 5.8 μV, respectively [35].

In 2015, Chirapapaisan et al. evaluated hospital medical records of patients being investigated for MS, with no definite diagnosis. VEP was analyzed, along with the confirmation of the subsequent diagnosis of MS through McDonald diagnostic criteria (2005). Twelve of the 35 patients (34%) converted to MS, and 23 (66%) did not have diagnostic confirmation. P100 Latencies and differences of interocular latency were longer in the clinically definitive MS (CDMS) than in non-CDMS patients ($p = 0.002$, 0.001, respectively). All patients of the group that converted to MS had P100 latencies higher than 102ms, the average of the patients with no diagnosis of MS, thus providing 100% of sensitivity. No patient developed MS with P100 latency <102 ms. Brain lesions in the magnetic resonance were significantly associated with CDMS development ($p = 0.001$). Therefore, the previsibility to develop CDMS was higher when the P100 latency delay and the brain lesions of magnetic resonance were concomitantly present [36].

In the last decade, recurrent ON, not associated with MS and NOM, was classified according to its clinical presentation in recurrent isolated form (RION) and chronic recurrent (CRION) form [37]. In CRION and RION, ON is more severe than in MS, leading to severe, bilateral visual impairment that can cause amaurosis. However, while a high prevalence of anti-AQP4 antibody positivity is observed in NOM, in CRION 95% of the patients present negativity for anti-AQP4 [38]. In all syndromes cited, the OCT reveals significant reduction of the fiber layers of the temporal and nasal retina.

7. Conclusions

We can conclude that VEP has recently been sufficiently studied and shows differences between the classic pattern of MS and that of NOM, where the responses are more heterogeneous, and the reduction of P100 wave amplitude and the absence of response are more prevalent [34], but data in the literature are lacking about the VEP pattern in RION, CRION, syndromes of the NOM spectrum, and OSMS of MS.

Author details

Silvio Pessanha Neto[1,2,3]*, Luiz Carlos Pinto[3] and Regina Maria Papais Alvarenga[2]

*Address all correspondence to: silvio.neto@estacio.br

1 Estacio de Sa University, Rio de Janeiro, Brazil

2 Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

3 Luiz Carlos Pinto Clinical Neurophysiology Center, Rio de Janeiro, Brazil

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