Pattern-reversal electroretinograms for the diagnosis and management of disorders of the anterior visual pathway

Eletroretinograma de padrão reverso no diagnóstico e acompanhamento das afecções da via óptica anterior

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ABSTRACT

The pattern electroretinogram is an electrophysiological test that assesses the function of inner retinal layers, particularly the ganglion cells layer of retina, using a reversing checkerboard or grating pattern that produces no change in average luminance over time. The normal pattern electroretinogram is composed of a prominent positive component (P50) and a large later negative component (N95). Since structural damage that compromises the retinal ganglion cell layer can lead to pattern electroretinogram changes, particularly in the N95 amplitude, the test can be useful in the treatment of a number of anterior visual pathway diseases. In this article, we review the methods for recording pattern electroretinogram and its usefulness in the diagnosis and management of diseases including inflammatory, hereditary, ischemic and compressive lesions of the anterior visual pathway.

Keywords: Electroretinography/methods; Optic nerve injuries; Retina/physiopathology; Optic nerve diseases/diagnosis; Pattern recognition, visual; Vision Disorders/diagnosis; Visual Pathways/pathology

INTRODUCTION

Disorders of the anterior visual pathway are the most frequent and important diseases in neuro-ophthalmology and include compressive, inflammatory, ischemic, toxic, deficient, degenerate, and traumatic lesions. In such conditions, measurement of the degree of retinal and optic nerve structural impairment is of great importance in the diagnosis and management. The main structural change related to these diseases occurs in the retinal nerve fiber layer (RNFL), which is composed of axons of retinal ganglion cells (RGC). Thus, various methods have been used to morphologically and functionally evaluate this cell population. Optical coherence tomography (OCT), for example, is capable of measuring peripapillary retinal nerve fiber layer (RNFL) and macula thickness, thereby making it possible to quantify axonal injury in the retina. Axonal loss may also be measured by scanning laser polarimetry, although with a poorer performance in relation to OCT.

Another way of evaluating the RGC function is through electrophysiological tests, particularly the pattern-reversal electroretinogram (PERG). Although PERG was conceived in 1964, only recently has it had a greater application in relation to the quantification of neural loss for diseases of the optic nerve. However, the majority of PERG studies were performed in glaucoma patients. The purpose of this paper is to review the characteristics and techniques for obtaining PERG and review the abnormalities observed with this technology in the most important neuro-ophthalmological disorders of the anterior visual pathway, including hereditary, inflammatory, demyelinating, ischemic, and compressive lesions of optic chiasm nerves.

TYPES OF RESPONSE AND METHODS

PERG is an electrophysiological test that objectively evaluates the function of the central retina generated by a stimulus structure in the form of a checkerboard or bars, generally in black and white, that alternates with a regular frequency and a constant luminance. The response obtained by PERG expresses the function of the most internal retinal layers, particularly the RGC layer. According to the reversal frequency, two types of PERG can be obtained: stationary or transitory. When the stimulus presents less than <7 reversals/sec, PERG is said to be transient and the final wave obtained is composed
of three components: N35, a small negative component with a peak time occurring around 35 ms; P50, a prominent positive wave emerging around 50 ms and N95, a wide negative wave around 95 ms. (Figure 1) When a high reversal index is used, PERG is considered to be at a steady-state and the wave acquires a sinusoidal form(9).

When analyzing transient PERG results, the latencies and amplitudes of the P50 and N95 peaks are taken into account. The P50 amplitude is measured from the minimum point of the N35 valley to the P50 peak, and the N95 amplitude is measured from P50 peak to the minimum point of the N95 valley (Figure 1). In some patients, the N35 deflection is poorly defined. In these cases, the average N35 is used, which is obtained between the baseline at time zero and the beginning of the deflection of P50. The peak times (implicit time) are measured from the beginning of the stimulus to the maximum or minimum point of each wave, taking into account the ideal form of the wave. The peak times are erroneously called latencies because they refer to the time between the stimulus and the beginning of the deflection of the wave, not the maximum activity of the peak(11).

The response generated by the pattern-reversal stimulus has a small amplitude and varies considerably depending on the technique that is used. The International Society for Clinical Electrophysiology of Vision (ISCEV) has established parameters for examinations with the goal of reducing differences among laboratories, improving the appearance of the wave, making it possible to compared data obtained by different services.

The stimulus that is used varies in relation to size, luminance, contrast, and reversal index. The responses to lower stimuli have smaller amplitudes. Squares measuring 48° (0.8º) are recommended for clinical use, but the results of studies on the ideal square size are controversial and show that there is also a dependence on the area of the board. The luminance should always be constant and greater than 80 cd/m². The contrast between the black and white reversals should be maximized (close to 100%) and should never be less than 80%. The reversal index will determine the type of PERG obtained(11).

To perform the examination, three electrodes are used. The reference electrode should be fixed in the outer canthus the eye. The capture electrode (active) should remain in contact with the lower bulbar conjunctiva. At our service, we use a DTL (Dawson-Trick-Litzkow) type apparatus, which should be tangential to the inferior bulbar conjunctiva. At our service, we use a DTL (Dawson-Trick-Litzkow) type apparatus, which should be tangential to the inferior bulbar conjunctiva. The cell origin of PERG is still a matter of controversy. Hollander et al.(18) reported the extinction of PERG in cats after section of the optic nerve. The authors observed a progressive decrease in the amplitude of PERG response first at low spatial frequencies and later at high frequencies, up until complete response elimination four months later, yet the response to the electroretinogram (ERG) by flash remained. Concomitantly, retrograde degeneration of the RGC was demonstrated histologically. Thus, the authors suggested that the response origin evoked by the reversal pattern would be confined to the RGC. In another study, Harrison et al.(19) demonstrated an important reduction in the P50 amplitude, but without extinction of the wave, in a patient without light perception 30 months after resection of the optic nerve due to a glioma. That author then suggested that PERG could have an effect in the most external layers of the retina and does not reflect only the response in the RGC.

Benninger, Schuurmans(11) and Schuurmans, Benninger(20) studied the outcomes in humans of variations in the parameters of pattern stimulation in relation to temporal frequency, luminance, and contrast. These authors proposed that the P50 component depended, in part, on the luminance of the stimulus and would be generated by the most external layers of the retina. On the other hand, the N95 component demonstrated a strong correlation with the spatial frequency of the stimulus, may be related to variations in contrast, and may be generated by the RGC.

The hypothesis regarding different PERG wave component origins was subsequently corroborated by clinical observations made by Holder(21). In this study, the author observed that the P50 and N95 components could be selectively altered in retinal diseases and diseases of the optic nerve, respectively. In particular, the P50 component was shown to be altered in all patients with retinal and macular diseases. On the other hand, the N95 component was abnormal in 81% of patients with diseases of the optic nerve while the P50 component remained normal.

In seven patients examined with dominant optic atrophy, a condition characterized histopathologically by loss of RGC, Benninger et al. reported selective loss of the N95 amplitude and a normal P50 component(18). Subsequently, Holder et al.(22), reported a reduction of the N95 amplitude in 13 patients with such condition. Yet, in more advanced cases, there was also a reduction of P50 latency without an extinction of the component. This finding is in agreement with those of Harrison et al.(19) who reported a reduction of the P50 amplitude in a patient with surgical resection of the optic nerve.

Thus, PERG has proved to be important in the evaluation of diseases of the anterior visual pathway, particularly those in which there is a generalized loss of RNFL. Among these, glaucoma, compressive diseases of the optic chiasm, and demyelinating diseases stand out. Next, we will review the main studies that have used PERG for evaluating disorders of the anterior visual pathway.

**HEREDITARY OPTIC NEUROPATHIES**

The hereditary diseases that most commonly cause primary dysfunction of the RGC are: Leber’s hereditary optic neuropathy.
(LHON) and dominant optic atrophy (DOA). LHON is a disease that primarily affects men in the second and third decade of life, transmitted through a maternally inherited mitochondrial DNA mutation. This disease is characterized by subacute, painless, usually severe and initially monocular loss of visual acuity (VA). In addition, there is hyperemia of the optic disc with peripapillary telangiectasia and a ceccocentral defect of the visual field (VF). The other eye is affected within weeks or months after the first eye. The main characteristics of PERG in these patients is a marked acute reduction of the N95 component with preservation of the P50 component as demonstrated by Holder (17). The preferential involvement of the N95 component exhibits a strong correlation between this wave with the loss of RGC with preservation of the P50 component, which suggests a more external retinal origin and not only RGC involvement.

DOA is an autosomal dominant hereditary disease caused by a mutation in the OPA1 gene, located in the long arm of chromosome 3. This disease is associated with progressive visual loss, optic disc pallor, cecocentral VF defect and loss of color vision. Berninger et al. (18) reported electrophysiological abnormalities in seven patients with DOA. Three were severely impaired and demonstrated a reduction in the amplitude of the N95 component in addition to a reduction of P50 latency and amplitude. Yet, Holder et al. (19) observed a preferential reduction of the N95 component during initial phases of the disease and a reduction in the amplitude and latency of P50 at more advanced phases.

DEMYELINATING INJURIES OF THE OPTIC NERVE

Involvement of the anterior optic nerve is an important manifestation of multiple sclerosis (MS). MS is clinically characterized by episodes of focal involvement of the optic nerve, the brain parenchyma, and the spinal cord, with periods of exacerbation and remission that are separated both in time and locations of the lesion. MS preferentially affects female individuals at a ratio of nearly 2:1. Initial symptoms generally occur between 30 and 50 years of age, although children and elderly may also be affected.

Visual dysfunction occurs in 80% of patients with MS during the course of the disease. Although it may affect any part of the visual pathway, involvement predominantly occurs at the level of the optic nerve. Visual loss may be acute, insidious or even be asymptomatic. When acute, it manifests itself in the form of optic neuritis, characterized by unilateral visual acuity (VA) loss that evolves over a period of a few days, associated with periorcular pain, decrease in color vision, contrast sensitivity, a relative afferent pupillary defect, and predominantly central VF defects. Fundus eye examination may be normal when optic neuritis is retrobulbar or the disc margins may be blured in papillitis. VA loss ranges from subtle to absence of light perception. There is a tendency toward improvement in the VF and fields, while contrast sensitivity present a lesser tendency to recover (20).

For the acute, insidious, and asymptomatic forms, the characteristic pathological process in MS is inflammatory demyelination of the axons, which leads to atrophy of the optic nerve. Axonal loss is present particularly in chronic lesions and is responsible for the persistence of neurological deficiencies and visual dysfunction. Its assessment can be useful monitoring evolution of the disease.

Several authors have reported PERG abnormalities in patients with demyelinating neuritis because the exam is capable of detecting RGC dysfunction. Arden et al. (21) first reported a reduction in PERG amplitude parameters among patients affected by optic neuritis, suggesting retrograde axonal degeneration of RGC. The authors found evidence that PERG was generated by layers that were closer to the retina than those evaluated by multifocal electroretinogram. Serra et al. (22) reported a reduction in the PERG amplitude among patients affected by recurrent optic neuritis caused by MS. The amplitude measured by these authors was from the peak of the first positive wave, called a, to the trough of the second negative wave, called b. Thus, these authors did not obtain evidence of changes specific to each kind of wave, thereby not allowing characterization of the most common type of alteration in these cases. Similar results have been reported by other authors (23,24). On the other hand, Kirkham, Coupland (25) did not find differences between the PERG amplitudes in patients with MS related optic neuritis and normal controls and concluded that PERG did not satisfactorily reflect optic nerve dysfunction.

Holder (17), however, demonstrated specific abnormalities for each PERG wave in patients with optic nerve diseases including optic neuritis. He reported that 81% of patients with abnormal PERG from optic nerve disorders presented reduction in the N95 amplitude parameter while sparing the P50 component. In the same study, all patients with retinal or macular dysfunction invariably demonstrated P50 abnormalities. Thus, the author suggested that RGC loss from optic nerve diseases resulted in specific alterations of the N95 component of PERG. In another study, Holder (26) found that among optic neuritis patients with visual evoked potential abnormalities 40% demonstrated PERG abnormalities, 85% of them with isolated N95 amplitude reduction.

Berninger, Heidereider (27) described the PERG abnormalities among 20 patients affected by acute optic neuritis after remission of their disease. According to their report, there was a reduction in P50 amplitude in all patients and a reduction in the N95 amplitude in 18 patients during an acute episode of optic neuritis. After remission, there was recovery of the P50 component to normal levels, yet the reduction in N95 persisted.

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

Nonarteritic anterior ischemic optic neuropathy (NAION) is caused by a sudden and irreversible ischemic event that affects the optic nerve. NAION affects elderly patients, usually older than 50 years of age, and causes sudden visual loss and altitudinal VF defects. In addition to age, other risk factors associated with NAION include diabetes mellitus, hypertension, tobacco use, and crowded optic nerve.

There are few PERG studies in patients with NAION. Froehlich, Kaufman (28) and Atilla et al. (29) reported a N95 amplitude reduction and normal P50 amplitude and latency. Parisi et al. (30) described a reduction in the amplitude of the P50-N95 component in a patient with NAION and an increase in P50 latency. These authors suggested that the alterations may be the result of ischemic dysfunction in the retina. Insufficiency of the blood supply would probably also induce alterations in the layers anterior to the RGC, thereby causing retinal dysfunction and abnormalities in the P50 component of PERG.

COMPRESSIVE LESIONS OF THE ANTERIOR VISUAL PATHWAY

Compressive lesions of the anterior visual pathway are those that affect the optic nerve in its entirety and the optic chiasm. Compressive intraorbital lesions cause chronic and unilateral loss of visual acuity associated with edema of the ipsilateral optic nerve and frequently cause proptosis as well. Among these lesions, the tumors (gliomas and meningiomas of the optic nerve and orbital hemangiomas) and inflammatory lesions (orbital pseudotumor and ophthalmomopathy dysphoria) stand out. Even though these injuries cause compression of the optic nerve, the most common cause of visual loss associated with compression of the anterior optic nerve are chiasmal tumors, among which pituitary adenomas stand out. These types of tumors commonly lead to visual dysfunction in both eyes.
Among the visual functions impaired, the VF must be highlighted, both in the diagnosis and monitoring of the disease. The characteristic field defect with chiasmal disorders is bitemporal hemianopia, which may be complete or incomplete. Despite being important for the assessment of chiasmal disorders, the VF, by itself, does not permit, in a single examination, differentiation between an active chiasmal lesion (a tumor still compressing the optic chiasm) and a non-active lesion (which is a compression lesion that has already been treated). Patients with a field defect resulting from active compression of the optic pathway may demonstrate an improvement in visual dysfunction if they are properly treated. On the other hand, non-active defects do not improve despite clinical treatment or surgery. Information in regards to the reversibility or lack thereof of visual dysfunction is of fundamental importance from a clinical point of view, as it is an important factor when making a therapeutic decision. Thus, a structural evaluation of the RNFL and RGC becomes relevant. In addition, in chiasmal compressions, there is a predominant loss of nerve fibers originating in the nasal retina of both eyes resulting in atrophy along a band of the optic nerves, which is characteristic of this disease. This type of neural loss serves as an interesting model for correlations between structure and function.

Ruther et al. (32) evaluated 19 patients with previous active chiasmal compression 5 to 10 days after surgical resection of a tumor using steady-state and transitory PERG. For both techniques, there was a positive correlation between the amplitude of PERG and the visual results after surgery. The patients who demonstrated greater amplitudes prior to the operation remained stable or improved after the surgery leading the authors to suggest that PERG could still be useful for predicting visual prognosis following surgery.

In another study, Parmar et al. (34), also studied PERG as an indicator of visual prognosis during the preoperative evaluation of patients with active chiasmal compression. They reported an improvement in the VF in 65% of patients who demonstrated a normal N95/P50 index. Among patients who presented an abnormal N95/P50 index, only 27% had an improvement in their VF after decompression. The VF remained unaltered in 26% of the eyes with a normal N95/P50 index compared to 67% of those with an abnormal index. Thus, the authors suggest that PERG may be a valuable tool for assessing the prognosis in these patients.

In a previous study we demonstrated that PERG was useful for differentiating between patients with band atrophy of the optic nerve from normal controls (35). Band atrophy patients demonstrated P50 and N95 amplitudes that were significantly smaller than that of controls when there was a full-field stimulus. There was no significant difference for latency. In the same study, stimulation of the nasal and temporal hemifields was also performed. In both cases, there was a significant difference in the P50 and N95 amplitudes between patients and controls. The decrease in PERG amplitude that was obtained when the nasal sector of the retina was stimulated probably reflected axonal damage of such fibers prior to the surgical decompression.

We have also evaluated the relationship between OCT, PERG and standard automated perimetry (SAP) in eyes with temporal hemianopia from chiasmal compression (36). Forty-one eyes from 41 patients with permanent temporal VF defects from chiasmal compression and 41 healthy subjects underwent transient full-field and hemifield (temporal or nasal) stimulation PERG, SAP and time domain-OCT macular and RNFL thickness measurements. Deviation from normal VF sensitivity for the central 18° of VF was expressed in 1/Lambert units. PERG and OCT measurements were significantly lower in eyes with temporal hemianopia than in normal eyes. A significant correlation was found between VF sensitivity loss and full-field or nasal, but not temporal, hemifield PERG amplitude. Likewise a significant correlation was found between VF sensitivity loss and most OCT parameters. No significant correlation was observed between OCT and PERG parameters, except for nasal hemifield amplitude. A significant correlation was observed between several macular and RNFL thickness parameters. The study indicated that in patients with chiasmal compression, PERG amplitude and OCT thickness measurements were significantly related to VF loss, but not to each other. The conclusion was that OCT and PERG quantify neuronal loss differently, but both technologies are useful in understanding structure-function relationship in patients with chiasmal compression.

**PERSPECTIVES**

PERG has proven to be of important value for the evaluation of diseases that affect the anterior visual pathway. Abnormalities in the amplitude of the N95 component is strongly correlated with RGC dysfunction. On the other hand, the P50 component appears to reflect dysfunctions in the layers anterior to the RGC and are altered in macular and retinal diseases. N95 wave can therefore be useful for documenting and monitoring RGC abnormalities.

An important limitation of PERG in the study of visual pathway disorders, however, is the fact that normal responses can be obtained when small lesions focally affect the RGC and the RNFL. In these cases, full-field PERG may not show the exact location of retinal damage. A very important perspective was introduced recently after the incorporation of the multifocal analysis technique developed by Sutter and Tran (37). In their technique, multiple stimuli are presented simultaneously, thereby generating multiple responses in small areas of the central retina. The variation in luminance is independent for each area tested and the presentation of stimuli is modulated in a pseudo-random manner. Thus, it is possible to obtain a multifocal electroretinogram and, more recently, a multifocal PERG (mfPERG). The mfPERG combines a standard stimulus with constant luminance and a multifocal technique with the goal of identifying focal damage to the RGC.

Few studies have evaluated mfPERG for macular or optic nerve diseases. Two previous studies have shown that mfPERG is capable of identifying patients with RGC loss from glaucoma and can differentiate them from normal controls (38,39). Yet, in these studies, the authors did not find correlation between VF defects and PERG amplitude reduction. Kistoner et al. (40), evaluated the response of 15 patients with well defined glaucomatous and scotoma damage of the VF using mfPERG stimulation. There was a statistically significant reduction in the average amplitude for patients in relation to controls, but no differences in latencies were found. However, the reduction in the amplitudes did not correspond topographically to the location of the scotoma in patients with glaucoma. Stiefelmeier et al. (41), studied 23 patients with glaucoma in different stages of the disease. The authors reported reduced amplitudes using mfPERG in relation to normal controls, mainly in the central area. There was a correlation between the severity of the disease and amplitude reduction in the central area, yet there was no correlation with VF defects. It seems therefore that various factors can influence the correlation between reduced amplitudes measured by mfPERG and VF defects.

We recently studied a group of patients with band atrophy of the optic nerve and permanent temporal field loss due to prior compression of the chiasm due to pituitary adenomas (42). Twenty-three eyes of patients with band atrophy and 21 control eyes were studied in order to evaluate the ability of mfPERG to detect neural loss and assess the relationship between mfPERG and VF loss in eyes with chiasmal compression. Mean values of mfPERG amplitudes from the temporal hemifield and temporal quadrants were significantly lower in eyes with band atrophy than in controls. No significant difference was observed in nasal hemifield measurements. Significant correlations were found between VF relative sensitivity and mfPERG amplitude in different VF sectors. We concluded that...
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8. Ventura LM, Sorokac N, De Los Santos P, Feuer WJ, Porciatti V. The relationship between mfPERG amplitudes and the severity of VF defect suggests mfPERG can be used as an indicator of ganglion cell dysfunction and opens the perspective of use of such technology for quantification of localized neural loss in lesions of the anterior visual pathways. However, although promising for the future, mfPERG still needs more studies to evaluate its potential role in demonstrating dysfunctions located at the retinal ganglion cell layer and its correlation with visual field defect.


