Electrophysiological assessment of visual function in patients with non-arteritic ischaemic optic neuropathy

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Background and purpose: Our study aims to evaluate retinal function and neural conduction in post-retinal visual pathways of patients with non-arteritic ischaemic optic neuropathy (NION). *Methods:* Twenty patients (mean age: 63.7 ± 5.96 year) with NION and 20 age-similar control subjects were enrolled. Simultaneous recording of pattern electroretinograms (PERGs) and visual evoked potentials (VEPs), and Log of minimum angle resolution (MAR) visual acuity (VA) were assessed in NION patients and controls. *Results:* Significantly (ANOVA, $P < 0.01$) abnormal PERG and VEP responses, delayed retinocortical time (RCT, difference between VEP P100 and PERG P50 implicit times), and reduced VA were found in NION patients with respect to control subjects. The delay in RCT was not significantly (Pearson's test, $P > 0.01$) correlated with the PERG impairment. The reduction in VA was significantly (Pearson's test, $P < 0.01$) correlated to the increase in VEP P100 implicit time and RCT, whereas no correlations ($P > 0.01$) were found with PERG abnormalities. *Conclusions:* Non-arteritic ischaemic optic neuropathy patients with a reduction in VA may present two different, unrelated impairments: a dysfunction of the inner retinal layer (abnormal PERG) and abnormal post-retinal neural conduction (abnormal VEP and RCT). The reduction in VA seems to be related to the post-retinal impairment and seems to be independent from the retinal dysfunction.

Introduction

Non-arteritic anterior ischaemic optic neuropathy (NION) is a neuro-ophthalmologic condition that induces a loss in visual acuity (VA) and visual field [1]. It is determined by a sudden and irreversible ischaemic event affecting the intra-ocular optic nerve. Although generally painless, an average of 10% of NION patients report ocular pain or headache as ancillary symptoms [2]. NION typically occurs after the age of 50 [3,4] and usually tends to be unilateral, although bilaterally affected subjects were also observed after surgical procedures [5,6]. Numerous conditions seem to be associated with NION, such as diabetes [7], hypertension, other cardiovascular risk factors [7,8], and tobacco smoking [9].

The exact pathogenesis of NION is still not completely understood. An insufficient vascular blood supply of the intrascleral portion of the optic nerve as well as 'crowding' of the optic disc is presumed [10].

However, further evidence is needed to define whether the lesion remains limited to a part of the optic nerve or whether it also involves selective ganglion cells loss after retrograde degeneration. Indeed, it was hypothesized that 'crowding' of the optic disc produces intracellular axonal swelling secondary to mechanical obstruction of axoplasmic flow, particularly at the cribriform plate, resulting in additional ganglion cell death [10].

Histopathologic studies in eyes with ischaemic optic neuropathy documented retinal ganglion cell (RGC) loss and optic nerve gliosis, but these studies lack clinical data to define the diagnosis of idiopathic NION [11,12]. For this reason, electrophysiological tests could aid in the characterization of the pathophysiological mechanisms of NION, as they allow the *in vivo* exploration and dissection of different structures contributing to neural conduction in the visual pathways. In particular, the simultaneous recording of visual evoked potentials (VEP) and pattern electroretinograms (PERG) allows the analysis of the bioelectrical activity of the visual cortex and of the RGCs with their fibers, and allows to derive an index of neural conduction in post-retinal visual pathways (retinocortical time, RCT) [13].

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Unfortunately, the few neurophysiological studies performed with VEPs and/or PERGs are limited by the small number of subjects [14], by unreported and imprecise clinical data [15], or by the fact that patients were examined and data were recorded too soon after loss of vision [16].

Therefore in our study, we investigated retinal function and neural conduction in post-retinal visual pathways of patients affected by idiopathic NION at least 6 months after the acute episode using simultaneous recording of VEPs and PERGs.

Methods

Patients

Twenty patients affected by NION in one eye only (mean age: 63.7 ± 5.96 year, 20 NION eyes) and twenty age-similar control subjects (mean age 62.8 ± 6.54 years) took part in our study.

The diagnosis of NION was made on the basis of the following criteria [9,17]:

1 onset after the age of 50 years;
2 episode of sudden, painless, unilateral visual loss associated to afferent pupil defect and/or acquired dischromatopsia; the fellow eye was normal with no evidence of optic nerve or ocular disease;
3 detection of an optic disc edema and absence of signs suggesting a branch or central retinal artery occlusion using indirect ophthalmoscopy [slit-lamp biomicroscopy with a + 90 diopters no-contact lens (Volk Optical, Mentor, OH, USA)];
4 visual field defects on Goldman perimetry (see below);
5 normal intra-ocular pressure and no abnormalities of the anterior segment in both eyes at slit lamp examination.

Exclusion criteria were signs, symptoms or laboratory findings suggesting giant cell arteritis, including: age >70 years, headache, abnormal temporal artery on physical examination, fever (temperature ≥38°C), jaw claudication, high inflammatory response such as increased values of erythrocyte sedimentation rate, C-reactive protein and platelet count, and high immunoglobulin serum levels (high α-2 globulin) [18].

Other exclusion criteria for both NION patients and control subjects were presence of moderate to dense lens opacities or maculopathy which are known to affect PERGs [19], implanted intra-ocular lens, presence of corneal opacities, previous history of refractive surgery, glaucoma or ocular hypertension, intra-ocular inflammation such as anterior or posterior uveitis, retinal detachment or laser treatment for peripheral retinal diseases, ocular trauma, diabetes, and other systemic or neurological diseases.

Visual status and electrophysiological examinations in NION patients were assessed at least 6 months after diagnosis. Informed consent was obtained from each patient enrolled in this study and the research followed the tenets of the Declaration of Helsinki. The study was previously approved by the local Ethics Committee.

Visual status evaluation

Best-corrected VA was assessed by modified Early Treatment Diabetic Retinopathy Study (ETDRS) Table (Lighthouse Low Vision Products, Long Island City, NY, USA); VA was expressed in logMAR values obtained at the distance of 4, 2, 1, and 0.5 m.

Visual field was assessed by Goldmann perimetry using I-2e, I-4e, and V-4e targets regularly, although occasionally other targets including I-1e or those in between I-4e and V-4e were used if it was felt that they would provide additional information for the evaluation of visual status. Quantitative and qualitative changes of Goldmann visual field plotted perimetry were evaluated by the 'counting dots' method (CDM) originally described by Esterman [20]. It has been reported that this procedure may be considered a reliable method to quantify visual filed defects in NION [21].

Electrophysiological examinations

Simultaneous PERG and VEP recordings were carried out in both control subjects and in NION patients at baseline. Follow-up recordings were subsequently obtained in NION patients after 60, 120, 240, and 360 days, according to the above reported testing schedule.

The simultaneous recording of PERGs and VEPs using high (80%) contrast 15′ checkerboard stimuli reversed at the rate of two reversals per second were obtained following a previously published protocol [22,23].

For all VEPs and PERGs, implicit time and peak amplitude of each wave were measured directly on the displayed records by means of a pair of cursors. The simultaneous recording of VEPs and PERGs allows us to derive RCT, defined as the difference between VEP P100 and PERG P50 peak latencies [24].

Statistics

Differences in PERG and VEP responses and VA values between groups (Control eyes, NION eyes) were evaluated by ANOVA. Pearson's correlation was used to correlate VA values and all electrophysiological

parameters to correlate PERG and VEP values to RCT and to correlate PERG values to visual field defects ('counting dots' method). PERG and VEP implicit times and amplitudes and RCT data underwent logarithmic transformation to better approximate a normal distribution. In all analyses, a *P*-value less than 0.01 was considered statistically significant.

Results

Examples of the simultaneous recording of VEPs and PERGs performed in one control eye and in one NION eye are displayed in Fig. 1. Mean data and statistical analyses are presented in Table 1. NION eyes showed a significant ($P < 0.01$) reduction in VA when compared with control eyes. Visual field defects observed in NION patients were: inferior nasal sector defects in 6/20 (30%) NION eyes; generalized constriction of the entire isopter in 4/20 (20%) NION eyes; scotomas in the central 30° fields in 4/20 (20%) NION eyes; inferior altitudinal defects in 3/20 (15%) NION eyes; superior altitudinal defects in 1/20 (5%) NION eyes; nasal step in 1/20 (5%) NION eyes; and inferior arcuate defect in 1/20 (5%) NION eyes. Non-significant correlations were observed between visual field defects and PERG parameters (P50 implicit times vs. CDM values, $r = 0.368$, $P = 0.0978$; P50-N95 amplitudes vs. CDM values: $r = 0.402$, $P = 0.0781$).

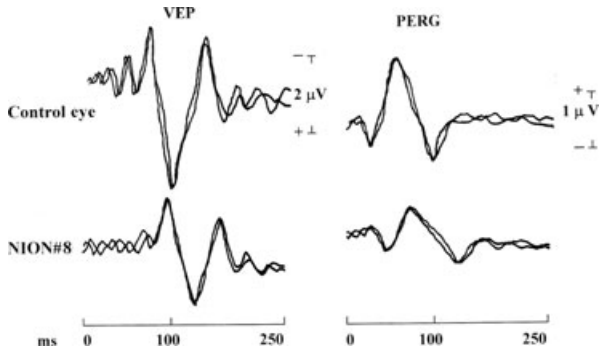

Figure 1 Layout of simultaneous visual evoked potentials (VEP) and pattern electroretinograms (PERG) recordings in a control subject and in one patient with nonarteritic ischaemic optic neuropathy (NION8). VEP and PERG implicit times were increased and amplitudes were reduced with respect to the control eye.

Pattern electroretinograms P50 and VEP P100 implicit times and PERG P50-N95 and VEP N75-P100 amplitudes were, respectively, significantly ($P < 0.01$) delayed and reduced ($P < 0.01$) in NION eyes when compared with controls. In addition, NION eyes showed significantly ($P < 0.01$) delayed RCT when compared with control eyes.

Individual PERG P50 implicit time and P50-N95 amplitude values observed in NION eyes are plotted as a function of the corresponding values of RCT in Fig. 2. Non-significant correlations ($P > 0.01$) were observed between RCT and these electrophysiological parameters of retinal function.

Individual PERG P50 implicit time, PERG P50-N95 amplitude, and RCT and VEP P100 implicit time values observed in NION eyes were plotted as a function of the corresponding values of logMAR VA in Fig. 3. The reduction in VA was significantly ($P < 0.01$) correlated to the increase in VEP P100 implicit time and in RCT, whereas no correlations ($P > 0.01$) were found with abnormal PERG parameters.

Discussion

Our study was designed to evaluate retinal and visual cortical responses 6 months after an episode of NION using simultaneous recordings of VEPs and PERGs. Our NION patients showed, together with a significant loss of visual acuity, reduced amplitudes and delayed implicit times of PERG recordings compared with controls. It is well known that PERGs reflect the bioelectrical activity of the innermost retinal layers associated with RGC function [25]. Thus, PERGs represent an important tool for detecting and monitoring the onset and progression of RGC dysfunction. The delay in implicit time and the reduction in amplitude of PERG responses observed in our patients are similar to

Table 1 Mean values ± 1 SD of visual acuity and electrophysiological parameters observed in control subjects (C) and in patients with nonarteritic ischaemic optic neuropathy

Group	*n*	Age (years)	Visual acuity (logMAR)	PERGP50 Implicit time (ms)	PERG P50-N95 Amplitude (μV)	VEP P100 Implicit time (ms)	VEP N75-P100 Amplitude (μV)	RCT (ms)
Controls	20	62.8 ± 6.54	0.040 ± 0.05	53.78 ± 1.76	1.65 ± 0.18	106.72 ± 4.24	5.06 ± 1.08	52.94 ± 3.78
NION	20	63.7 ± 5.96	0.565 ± 0.16	72.40 ± 4.55	0.95 ± 0.21	141.45 ± 8.58	3.33 ± 0.97	69.05 ± 8.02
A vs. Cf (1,38)		0.21, $P = 0.652$	176.5, $P < 0.001$	291.3, $P < 0.001$	128.1, $P < 0.001$	262.9, $P < 0.001$	28.41, $P < 0.001$	66.03, $P < 0.001$

PERG, pattern electroretinograms; VEP, visual evoked potentials; RCT, retinocortical time; MAR, minimum angle resolution; *n*, number of eyes tested; A vs Cf, one-way analysis of variance vs. control eyes.

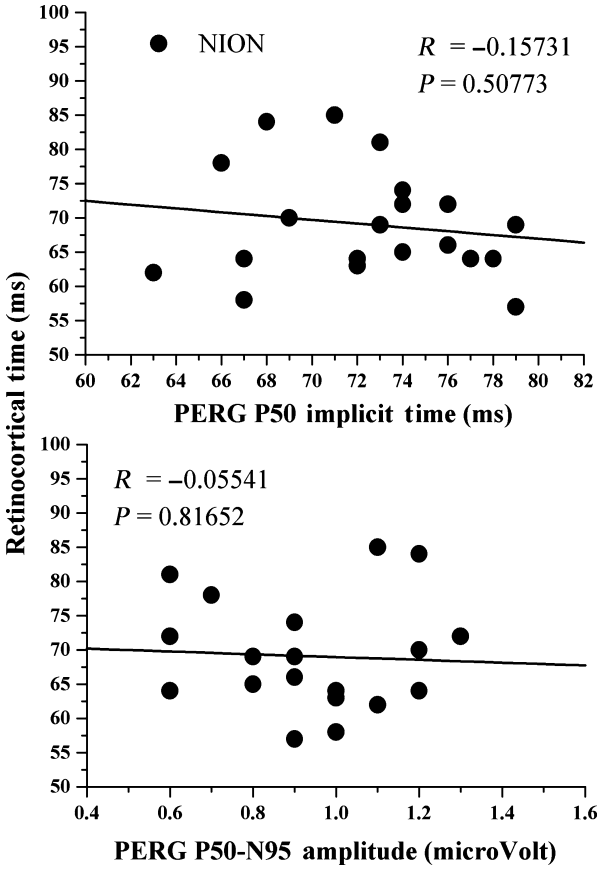

Figure 2 Individual pattern electroretinograms (PERG) P50 implicit time values and PERG P50-N95 amplitude values plotted against retinocortical time (difference between visual evoked potentials P100 and PERG P50 implicit times) in patients with nonarteritic ischaemic optic neuropathy (NION). Pearson's test was used for regression analysis and correlations.

those observed in other diseases that are known to affect the inner retina [22,26–28].

Neurophysiological assessment of the integrity of the visual system in NION is a poorly studied argument, so it is difficult to correlate our results to previous findings. However, Froehlich and Kaufman [16] and Atilla *et al.* [15] found a normal PERG P50 latency and amplitude, with a reduced N95 peak amplitude. Unfortunately, Froehlich and Kaufman performed the recordings too soon after loss of vision, when the retrograde degeneration phenomena had not yet started [16]. Atilla *et al.* on the other hand, did not discriminate between the arteritic and the non-arteritic forms of anterior ischaemic optic neuropathy [15] In addition, their results could also be biased by the relative large (73.2 min of arc) [15] or medium (30 min of arc) [16] check size employed as visual stimuli, which might be contaminated by a substantial luminance component. In another recent paper, patients affected by NION were electrophysiologically studied, revealing normal PERG P50 implicit times and reduced N35-P50 and P50-N95 amplitude [14]. However, several limitations affect this study: small sample size, binocular visual stimulation, medium check size (30 min of arc), and affected and unaffected eye values were pooled together in the same group [14].

In contrast to the experimental conditions described in the abovementioned papers, we used a smaller check size (15 min of arc) with a higher dominant spatial frequency known to preferentially stimulate the macular region [29], and only affected eyes were included in the statistics.

Pattern electroretinograms P50 implicit time and P50-N95 amplitude, both impaired in our studied eyes, are thought to originate from the innermost retinal layers (ganglion cells and their fibers), although a contribution of pre-ganglionic elements cannot be excluded [30]. In the absence of other retinal and/or neurological diseases, we can hypothesize that our PERG abnormalities could be ascribed to two different factors.

The first factor could be an ischaemic-related dysfunction of both pre-ganglionic elements and ganglion cells, probably because of the insufficient vascular blood supply at the optic nerve head level, also able to induce changes of retinal function. Our hypothesis is supported by animal models in which experimental ischaemia was induced. In fact, after transient ischaemic injury, morphometric changes and electrophysiological impairment were found and involved not only the optic nerve but also the retinal structures with a significant loss of the elements constituting the innermost retinal layers (ganglion cell and their fibers) [31–33].

The second factor could be related to a retrograde degenerative process involving the innermost retinal layers (ganglion cell axons and cell bodies) after the impairment of post-retinal visual pathways (see below), with a mechanism similar to that occurring in other optic nerve pathologies (e.g., multiple sclerosis) [22]. Thus, electrophysiological assessments of our NION patients were performed at least 6 months after the acute episode, which represents sufficient time to induce the phenomenon of retrograde degeneration [34].

Nevertheless, the lack of correlation between PERG abnormalities and the delay in RCT (see below) led us to believe that in our NION eyes, the retinal dysfunction could be independent from the impaired neural conduction along post-retinal visual pathways.

We also found a lack of correlation between the reduction in VA and PERG abnormalities in our NION patients. This suggests that the observed changes in VA cannot be exclusively ascribed to the retinal dysfunction.

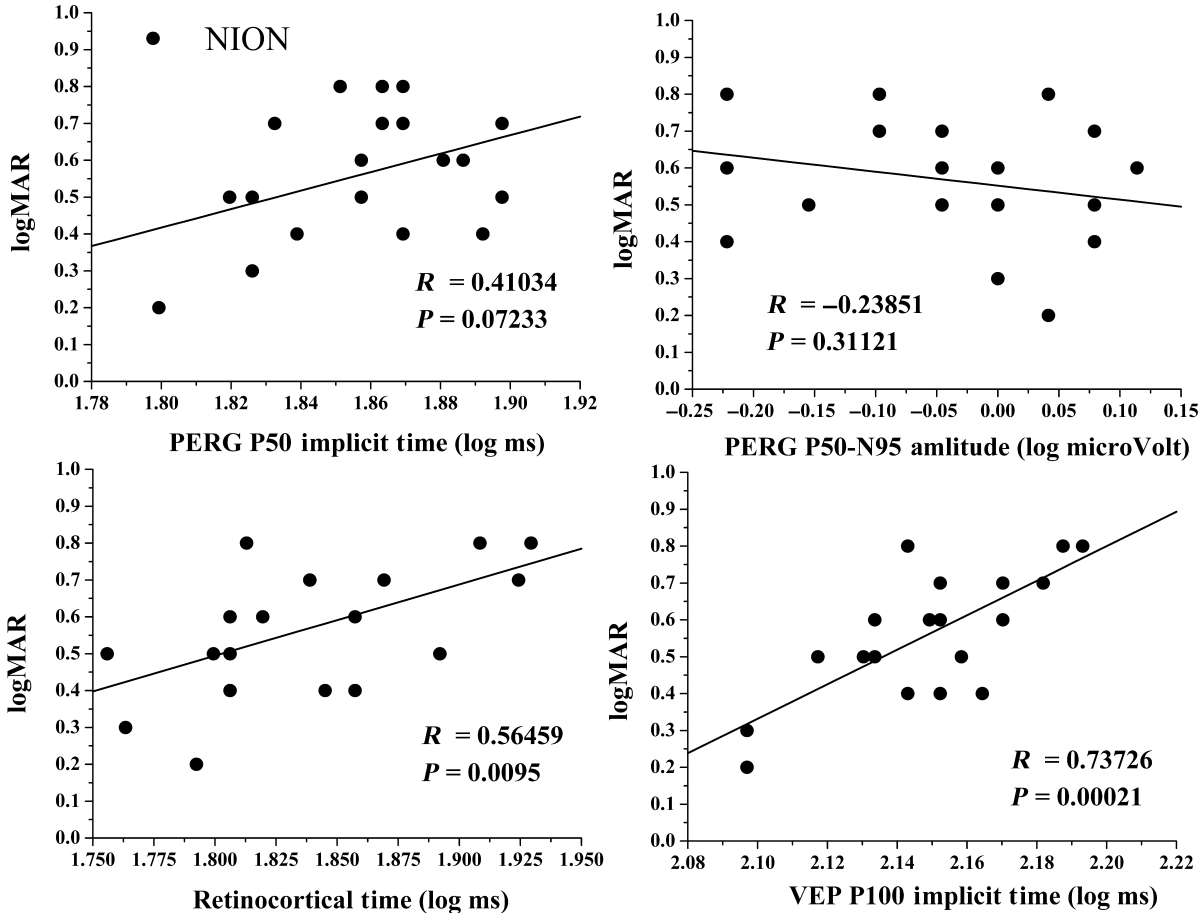

Figure 3 Individual pattern electroretinograms (PERG) P50 implicit time log values, PERG P50-N95 amplitude log values retinocortical time log values and visual evoked potentials (VEPs) P100 implicit time log values plotted against logarithm of minimum angle resolution (logMAR) values in patients with nonarteritic ischaemic optic neuropathy (NION). Pearson's test was used for regression analysis and correlations.

In line with PERG abnormalities, we found that NION patients showed delayed VEP implicit times and reduced amplitudes, and an increase in RCT. As previously discussed, RCT cannot be considered as a real transit-time between the retina and visual cortex, but an electrophysiological index of post-retinal neural conduction [13,22].

Our VEP results are consistent with previous findings reporting delayed VEP responses in NION eyes [15,35], whereas other studies suggested normal VEP implicit times but a reduction in amplitude [36–38]. There is no evidence in the literature regarding RCT in NION.

Visual evoked potentials and RCT abnormalities reveal the presence of a delayed neural conduction along the entire post-retinal visual pathways, including the optic nerve. The microvascular failure involving the optic nerve in NION is widely discussed by Hayreh in several published works [1,9,39].

Our electrophysiological findings may be supported by both human and animal models. Brigell [40] found a loss in VEP amplitude after NION, observing a decreased ability of the human optic nerve to transmit electrical signals. Moreover, as seen in an already mentioned study, Bernstein *et al*. [31] found that VEP responses were always reduced after acutely induced NION, with a permanent degradation of normal optic nerve electrical activity.

The lack of correlation between RCT and PERG abnormalities suggests that neural conduction along post-retinal visual pathways of NION eyes is delayed independently from the impairment of the inner retinal layers (ganglion cells and their fibers).

The reduction in VA of NION eyes is correlated to VEP abnormalities. This led us to believe that psychophysical (VA) and electrophysiological (VEP and RCT) visual cortical responses and the observed changes in

VA in NION eyes could be ascribed to a dysfunction occurring along the post-retinal visual pathways.

In conclusion, our NION patients with a reduction in VA may present two different, unrelated impairments: a dysfunction of the inner retinal layer (abnormal PERG) and abnormal post-retinal neural conduction (abnormal VEP and RCT). The reduction in VA seems to be related to the post-retinal impairment and is independent from the retinal dysfunction.

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