Relationship Between Pattern Electroretinogram, Frequency-Domain OCT, and Automated Perimetry in Chronic Papilledema From Pseudotumor Cerebri Syndrome

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PURPOSE. We evaluated the ability of transient pattern electroretinogram (PERG) parameters to differentiate between eyes with visual field (VF) loss and resolved papilledema from pseudotumor cerebri syndrome (PTC) and controls, to compare PERG and optical coherence tomography (OCT) with regard to discrimination ability, and to assess the correlation between PERG, frequency domain OCT (FD-OCT), and VF measurements.

METHODS. The VFs and full-field stimulation PERGs based on 48 and 14-min checks were obtained from patients with PTC (n = 24, 38 eyes) and controls (n = 26, 34 eyes). In addition, FD-OCT peripapillary retinal nerve fiber layer (RNFL) and segmented macular layer measurements were obtained and correlation coefficients were determined.

RESULTS. Compared to controls, PERG N95 and P50+N95 amplitude measurements with 48-minute checks were significantly reduced in eyes with resolved papilledema from PTC. Both PERG N95 amplitude and OCT parameters were able to discriminate papilledema eyes from controls with a similar performance. Significant correlations, ranging from 0.25 (P < 0.05) to 0.43 (P < 0.01) were found between PERG amplitude values and OCT-measured macular ganglion cell layer thickness, RNFL thickness, and total retinal thickness. The PERG amplitude also was significantly associated with VF sensitivity loss with correlation coefficients ranging from 0.24 (P < 0.05) and 0.35 (P < 0.01).

CONCLUSIONS. The PERG measurements were able to detect neural loss in PTC eyes with resolved papilledema and were reasonably well correlated with OCT measurements and VF parameters. Thus, PERG may be a useful tool in the monitoring of retinal neural loss in eyes with active papilledema from PTC.

Keywords: optical coherence tomography, pattern electroretinogram, standard automated perimetry, pseudotumor cerebri, papilledema

C hronic papilledema is an important cause of progressive and permanent visual loss, mostly in patients with pseudotumor cerebri syndrome (PTC).1–3 A condition defined as raised intracranial pressure without localizing neurological findings, ventriculomegaly, or intracranial mass. The diagnosis of PTC currently is applied to patients with idiopathic intracranial hypertension (IIH) with no identifiable cause, or to patients with cerebral venous outflow system obstruction, or impairment.4–6 Visual field (VF) loss on standard automated perimetry (SAP), the main morbidity of PTC, occurs in up to 92% of patients.2 Although visual deficit is initially reversible, once retinal nerve fiber layer (RNFL) and retinal ganglion cell (RGC) atrophy develop, as it does in a large percentage of cases, VF loss is permanent.1,4,7

Medical treatment of PTC is based on dieting (if the patient is obese), the use of acetazolamide for reducing intracranial pressure, and anticoagulants for cranial sinus thrombosis. Surgical treatment with either optic nerve sheath fenestration or shunting procedures may be necessary when visual loss occurs despite medical treatment. As in other diseases of the anterior visual pathway, careful assessment of vision involves functional and structural evaluations of the neural elements of the eye.8 The VF loss, usually assessed by SAP, and visual acuity are the most commonly used parameters to quantify functional loss. Structural measurements, on the other hand, can be obtained with a number of technologies, the most common of which is optical coherence tomography (OCT), which has been shown to be an important tool to detect and quantify damage in a number of optic nerve diseases.6–13 Axonal loss usually is quantified with OCT based on circumpapillary (cp) RNFL or macular thickness measurements. However, although previous studies have shown that OCT-measured cpRNFL thickness can
be used to estimate the degree of papilledema. OCT quantification of RNFL loss in papilledema is difficult on OCT because the presence of optic disc edema prevents accurate estimation of axonal loss.

The neural integrity of the retina also may be objectively assessed by the pattern electroretinogram (PERG), an electro-physiological test that reflects the function of RGCs and other intraretinal cellular elements. Previous studies have documented reduced PERG amplitude parameters in eyes affected by optic neuritis (ON) or compressive optic neuropathies, but only one previous study evaluated the ability of this method to detect neural loss in IIH, and showed that it can detect subclinical abnormalities in early stage papilledema eyes. Since PERG parameters may be less affected than OCT measurements by the presence of optic disc and retinal edema, it is of interest to evaluate the efficiency of PERG in the detection of axonal loss in eyes with chronic papilledema.

The purpose of this study, therefore, was to evaluate the ability of PERG to distinguish normal controls from patients with resolved papilledema secondary to PTC, to compare PERG and FD-OCT with regard to discrimination ability, and to assess the correlation between PERG, OCT, and VF measurements using SAP.

**Patients and Methods**

**Subjects**

This was an observational, prospective cross-sectional study. Participants were recruited from the Neuro-ophthalmology service of the University of São Paulo Medical School. Approval from the Institutional Review Board Ethics Committee was obtained for the study. The study followed the principles of the Declaration of Helsinki and informed consent was obtained from all participants.

A total of 38 eyes with clinically resolved papilledema from 24 patients (22 women) diagnosed with PTC and 34 eyes from 26 normal controls (13 women) were evaluated. The PTC was diagnosed based on its definition as a syndrome of increased intracranial pressure without ventriculomegaly or a mass lesion, and with normal cerebrospinal fluid (CSF) composition. This includes patients with IIH and intracranial hypertension secondary to elevated intracranial venous pressure. In our sample, 21 patients had IIH and 3 had PTC secondary to cerebral venous thrombosis. The IIH was defined based on previously published criteria, with high CSF opening pressure (intracranial pressure > 25 cm H2O) measured by lumbar puncture at the time of diagnosis; normal magnetic resonance (MR) imaging and MR venography; normal CSF composition; and normal neurological findings except for papilledema and possible sixth cranial nerve palsy. In patients with cranial sinus thrombosis, the diagnosis was based on neuroimaging studies, including MR venography and/or cerebral angiography.

The other inclusion criteria for PTC patients were: clinically resolved papilledema, grade 0 according to the Frisen scale27 with stable VF defect for at least 6 months after clinical and/or surgical treatment; at least one CSF pressure measurement < 25 cm H2O after papilledema resolution; and abnormal VF defined as the presence of at least two contiguous test points, not including those directly above and below the blind spot, with a total deviation (TD plot) and a pattern deviation (PD plot) of one point with \( P < 0.5\% \) and one point with \( P < 2\% \). Patients with intracranial diseases other than cranial venous sinus thrombosis were excluded. The control group consisted...
of normal age-matched healthy volunteers recruited from among the hospital staff.

**VF Testing**

Subjects underwent a complete ophthalmic examination, including VF evaluation using SAP. VF, OCT, and PERG examinations were performed within a period of 2 weeks. Testing for VF was performed using the 24-2 SITA-Standard strategy (Humphrey Field Analyzer; Carl-Zeiss Meditec, Dublin, CA, USA) and a Goldmann size III stimulus on a 10 cd/m² (31.5 apostilb) background. Patients had to have reliable VF testing, defined as less than 30% fixation losses, false-positive, or false-negative responses. The ophthalmologic exclusion criteria were history of clinically apparent optic neuropathies other than papilledema, history of IOP elevation, clinical signs of glaucomatous optic neuropathy, retinal diseases, or optic disc anomalies.

**PERG Recordings**

Transient full-field PERG was recorded in accordance with the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) using the RETiscan System (Roland Consult, Wiesbaden, Germany). The checkerboard stimulus was generated by a 21-inch rectangular black-and-white flat screen monitor (CRT color monitor; Roland Consult) in a semi-dark, acoustically isolated room. The stimulus was generated on a pattern-reversing checkerboard subtending a visual angle of 23° (horizontal) × 17° (vertical) at a 1-m viewing distance. The black-and-white checks (measuring either 0.8° or 0.23°) had a mean luminance of 80 cd/m² and a contrast of 97%. The pattern reversed at a rate of 8.6 reversals per second (4.3 Hz), with an analysis time of 180 ms. Online artifact rejection was set at 100 µV and the bandpass of the amplifier was set to the range of 5 to 50 Hz.

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<table>
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<tbody>
<tr>
<td>Subjects</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Eyes studied</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>41.3 (10.3)</td>
<td>37.3 (8.9)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>2/22</td>
<td>13/13</td>
</tr>
<tr>
<td>MD, mean (SD) in dB</td>
<td>-8.87 (9.05)*</td>
<td>-0.70 (1.09)</td>
</tr>
<tr>
<td>CMD, mean (SD) in dB</td>
<td>-7.64 (9.29)*</td>
<td>-0.12 (1.07)</td>
</tr>
<tr>
<td>CMD, mean (SD) in 1/Lambert</td>
<td>0.47 (0.28)*</td>
<td>0.89 (0.22)</td>
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* P < 0.05 compared to controls, generalized estimated equations models.
Each patient’s refraction was optimally corrected for the monitor distance and stimulation was binocular. The subject was instructed to look at a 6-mm “X” fixation target at the center of the screen. Sweeps contaminated by eye blinks or gross eye movements were rejected automatically. Dawson-Trick-Litzkow (DTL) electrodes were used as active electrodes, while gold cup skin electrodes served as reference and ground electrodes at the ipsilateral canthus and on the forehead, respectively. The conjunctiva was anesthetized with tetracaine eye drops. No miotic or mydriatic drugs were used.

Two check sizes were used subtending 48 and 14 minutes of visual angle. The averaged response of 200 artifact-free reversals was recorded for each test with a minimum of two trials per presentation. Each averaged response required approximately 3 minutes to obtain. The results shown are the average of the two recordings. The P50 and N95 amplitudes and peak times were measured relative to baseline and stimulus onset. In addition, the overall amplitude, taken as the maximum peak-to-trough amplitude (P50+N95) was calculated for each response.

**OCT Examination**

The subjects underwent Frequency domain OCT (FD-OCT) scanning using a commercially available device (3D OCT-1000; Topcon Corp., Tokyo, Japan). The scanning protocol involved the acquisition of a 6×6 mm cube scan of the optic nerve head (ONH) and macula with a scan density of 512×128 pixels (Figs. 1A, 1B). Criteria for acceptable OCT images included the following: absence of large eye movements, defined as an abrupt shift completely disconnecting a large retinal vessel; consistent signal intensity level across the scan; and absence of black bands (caused by blinking). Average cpRNFL was automatically calculated by the software.

To evaluate macular thickness, the borders of each layer were determined by a computer algorithm and the results manually corrected when necessary.\(^1\)\(^2\)\(^3\)\(^4\) Five borders were determined: (1) the border between the vitreous and RNFL, (2) the border between the RNFL and retinal ganglion cell layer (RGCL), (3) the border between the inner plexiform layer (IPL)...
and the inner nuclear layer (INL), (4) the border between INL and outer plexiform layer (OPL), and (5) the border between Bruch’s membrane and the choroid. Because the boundary between the RGCL and the IPL can sometimes be hard to determine, we combined RGCL and IPL (RGCL+IPL) into a single measure. For each cube scan, we segmented 128 B-scans and obtained the thickness for each evaluated layer, including 4 separate measurements corresponding to the macular RNFL, RGCL+, INL, and total retinal thickness.

**Data Analysis and Statistics**

The PERG and FD-OCT parameters of papilledema and control eyes were compared by generalized estimating equation (GEE) models to compensate for intereye dependencies. Because eyes of the same individual were included, GEE models were used to adjust for within-patient intereye correlations. Receiver operating characteristic (ROC) curves were used to describe the ability of PERG and OCT parameters to discriminate eyes in different groups of individuals from controls. The method of DeLong et al. was used to compare the areas under the ROC curves (AROCs). To compare the diagnostic ability of OCT and PERG, we also investigated eyes labeled as normal or abnormal curves (AROCs). To compare the diagnostic ability of OCT and PERG, we also investigated eyes labeled as normal or abnormal curves (AROCs). To compare the diagnostic ability of OCT and PERG, we also investigated eyes labeled as normal or abnormal curves (AROCs). To compare the diagnostic ability of OCT and PERG, we also investigated eyes labeled as normal or abnormal curves (AROCs).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PTC</th>
<th>Controls</th>
<th>P Value</th>
<th>AROC (SE)</th>
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<tbody>
<tr>
<td>PERG 48 min arc</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Peak time, ms</td>
<td>P50 52.6 ± 8.7</td>
<td>P52.6 ± 2.2</td>
<td>0.95</td>
<td>0.59 (0.07)</td>
</tr>
<tr>
<td></td>
<td>N95 96.8 ± 8.4</td>
<td>92.6 ± 3.4</td>
<td>0.007*</td>
<td>0.04 (0.07)</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>P50 3.3 ± 1.5</td>
<td>4.0 ± 1.1</td>
<td>0.02*</td>
<td>0.65 (0.07)</td>
</tr>
<tr>
<td></td>
<td>N95 4.8 ± 2.0</td>
<td>6.2 ± 1.3</td>
<td>0.001*</td>
<td>0.73 (0.06)</td>
</tr>
<tr>
<td></td>
<td>P50+N95 8.1 ± 3.3</td>
<td>10.2 ± 2.3</td>
<td>0.002*</td>
<td>0.69 (0.06)</td>
</tr>
<tr>
<td>PERG 14 min arc</td>
<td></td>
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<tr>
<td>Peak time, ms</td>
<td>P50 56.4 ± 5.4</td>
<td>54.8 ± 3.8</td>
<td>0.15</td>
<td>0.65 (0.07)</td>
</tr>
<tr>
<td></td>
<td>N95 99.9 ± 10.0</td>
<td>97.5 ± 4.5</td>
<td>0.19</td>
<td>0.65 (0.07)</td>
</tr>
<tr>
<td>Amplitude, μV</td>
<td>P50 2.0 ± 1.2</td>
<td>2.5 ± 0.9</td>
<td>0.06</td>
<td>0.62 (0.07)</td>
</tr>
<tr>
<td></td>
<td>N95 2.9 ± 1.7</td>
<td>3.7 ± 1.2</td>
<td>0.02*</td>
<td>0.65 (0.07)</td>
</tr>
<tr>
<td></td>
<td>P50+N95 4.9 ± 2.7</td>
<td>6.2 ± 1.9</td>
<td>0.05*</td>
<td>0.65 (0.07)</td>
</tr>
<tr>
<td>OCT thickness</td>
<td>Macular, μm</td>
<td></td>
<td></td>
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<tr>
<td>RNFL 28.3 ± 10.3</td>
<td>39.9 ± 4.3</td>
<td>&lt;0.001*</td>
<td>0.86 (0.04)</td>
<td></td>
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<tr>
<td>RGCL+ 60.4 ± 9.4</td>
<td>70.4 ± 5.5</td>
<td>&lt;0.001*</td>
<td>0.79 (0.05)</td>
<td></td>
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<tr>
<td>INL 31.9 ± 2.5</td>
<td>31.2 ± 2.1</td>
<td>0.19</td>
<td>0.59 (0.07)</td>
<td></td>
</tr>
<tr>
<td>TR thickness 257.0 ± 19.1</td>
<td>294.3 ± 20.3</td>
<td>&lt;0.001*</td>
<td>0.89 (0.04)</td>
<td></td>
</tr>
<tr>
<td>OPT disc, μm</td>
<td>cpRNFL 107.8 ± 10.4</td>
<td>95.9 ± 16.0</td>
<td>&lt;0.001*</td>
<td>0.74 (0.06)</td>
</tr>
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*P values indicated. TR, total retinal.

**RESULTS**

Table 1 shows the demographic and visual function data for the 24 PTC patients (38 eyes studied) and 26 healthy controls (34 eyes studied). There was no significant difference between the groups regarding average age ($P = 0.15$). A total of 10 eyes of patients with PTC were not included, 4 due to poor visual acuity and 6 because VF was entirely normal. A total of 18 healthy controls had one eye randomly selected for the study, while 8 had both eyes included. When including one or both in controls, we tried to approximately match the proportion of unilateral or bilateral eyes studied in the group of patients with PTC. The PTC eyes had significantly reduced VF mean deviation (MD) and CMD when compared to controls (Table 1).

Figure 2 shows examples of PERG responses along with VF defects in different eyes studied. Figure 3 and Table 2 show PERG measurements of eyes from all the groups studied. With the 48’ check stimulus, the amplitude parameters P50, N95, and P50+N95 were significantly smaller in eyes of patients with PTC than in controls ($P = 0.007$). The N95 peak time also was significantly longer in PTC eyes compared to controls ($P = 0.007$). With the 14’ check stimulus, no significant difference was observed in P50 amplitude ($P = 0.06$), while N95 and P50+N95 were significantly smaller in eyes of patients with PTC than in controls ($P = 0.02$ and 0.05, respectively). No significant difference in peak time parameters was found between the two groups of subjects ($P = 0.15$ and 0.19).

Table 2 also shows OCT parameters in patients and controls. In the macula, total retinal thickness, RNFL thickness, and RGCL+ layer values were significantly reduced in PTC eyes compared to controls ($P < 0.001$). No significant difference in INL measurements was found between the two groups. The cpRNFL thickness measurements were significantly smaller in PTC eyes than in controls ($P < 0.001$).

Table 2 also contains the AROC values corresponding to the observed PERG amplitudes and OCT thickness values. The PERG amplitudes (48’ check stimulus) and OCT thickness values were able to differentiate PTC eyes from controls. When analyzing PERG results, the highest AROC values were those of PERG amplitude measurements (48’ check stimulus) of N95 and P50+N95 (AROC = 0.73 and 0.69). With regard to OCT
results, the highest AROC values were those from measurements of total macular retinal thickness and macular RNFL measurements (AROC = 0.89 and 0.86). The AROC of OCT-measured total macular thickness was significantly greater than that of PERG N95 (√ 0.017) and P50+N95 (√ 0.004). The AROC of OCT-measured macular RNFL was significantly greater than that of PERG P50+N95 (√ 0.01). No significant difference was found between the AROC of macular RNFL thickness and the AROC of PERG N95 (√ 0.053).

Figure 4 shows the proportion of abnormal eyes based on the normative average estimated using the 10th percentile of controls as the lower limit of normal.
patients with axonal loss in resolved chronic papilledema, we defined the cutoff point as 10th percentile of normal values for the best-performing PERG and OCT parameters. These cutoffs are shown as dashed lines in Figure 4. For a specificity of 90%, the best discrimination of abnormality (sensitivity) was observed for PERG N95 amplitude with 48": checks (abnormal in 19 of 38 eyes, 50.0%), followed by PERG P50+N95 amplitude with 48": checks (abnormal in 16 of 38 eyes, 42.1%) and PERG P50+N95 amplitude with 14" checks (abnormal in 15 of 38 eyes, 39.5%). With OCT, macular RNFL and RGCL+ provided the best discrimination of abnormality (abnormal in 21 of 38 eyes in both cases, 55.3%) followed by total retinal thickness (abnormal in 18 of 38 eyes, 47.4%). No significant difference was observed between the best-performing PERG and OCT parameters for discriminating controls from resolved papilledema eyes (P > 0.05, McNemar’s test).

Table 3 shows the relationship between PERG parameters, OCT measurements, and VF sensitivity loss on the central 16 VF test points. A significant correlation was observed between most PERG and OCT measures. The best correlations were observed between N95 amplitude with 48" check stimulus and OCT thickness corresponding to macular RNFL (R = 0.43) and RGCL+ thickness (R = 0.41), followed by P50+N95 amplitude with 48" check stimulus and OCT-measured macular RNFL thickness (R = 0.40). The N95 and P50+N95 amplitude with 48" and 14" check size correlated significantly with VF sensitivity loss. Significant correlations also were observed between most PERG amplitude parameters and VF sensitivity loss on the central 16 VF test points, Figure 5 shows the results of the linear regression analysis for the best-performing relationships between PERG amplitude and OCT thickness, and between PERG amplitude and VF sensitivity loss. PERG amplitude parameters were better correlated with OCT thickness (Fig. 5, right) than with VF sensitivity loss (Fig. 5, left).

**DISCUSSION**

Average PERG amplitudes were lower in eyes with chronic papilledema from PTC syndrome than in normal controls. In particular, average N95 and P50+N95 amplitude parameters were significantly reduced in the group of patients with chronic papilledema when compared to controls, matching results of previous studies suggesting that PERG, on average, is able to detect RGC and/or other intraretinal cellular elements loss in different types of optic neuropathies. In our study, amplitude reduction was observed mostly when the 48" check size was used. This is in accordance with previous studies and the recommendations of the ISCEV protocol, which suggest using 0.8" (48") checks for optimal PERG amplitudes. With regard to latency, with the exception of N95 peak time using 48" check stimulus, no significant differences were found between patients and the controls, matching the findings of most previous studies evaluating PERG in optic nerve diseases.

Papilledema is a major cause of progressive and permanent visual and retinal neural loss, especially in patients with PTC. Although visual loss is initially reversible in papilledema eyes, once RNFL and RGC atrophy develops, permanent VF loss occurs in a large percentage of eyes. Estimating the amount of retinal neural loss would be of great interest during treatment of the PTC syndrome, mainly in patients who achieve only partial control of the disease and incomplete resolution of papilledema. When medical treatment fail, in controlling the disease, surgery may be necessary. However, the decision of continuing medical treatment or performing surgery can be difficult to make in some cases and usually is based on VF analyses. The VF assessment in itself provides no indication of whether vision can be recovered; rather, recovery is dependent on the amount of existing axonal loss. Therefore, adding the evaluation of RGC integrity to VF monitoring is highly desirable during treatment of papilledema due to PTC. The reduced PERG amplitude parameters observed in the present sample suggests that the technology may be a useful adjunct to VF monitoring in this scenario. Our findings are in agreement with the study of Falsini et al. that using steady-state PERG, found abnormalities in 77% of eyes with early onset papilledema from IIIH.

The second purpose of our study was to investigate the correlation of PERG findings with VF and OCT measures. Previous studies have found significant correlations between PERG amplitude parameters and OCT-measured cpRNFL thickness or average macular volume in patients with multiple sclerosis. Hokazono et al. recently found a significant correlation between N95 amplitudes and macular parameters, particularly between N95 and macular RGCL+ or cpRNFL thickness measurements in patients affected with multiple sclerosis or neuromyelitis optica. In the current study we also found significant correlations between most PERG amplitude parameters and OCT measurements, mostly N95 or P50+N95 PERG amplitude with 48" check stimulus, macular RGCL+, and RNFL thickness and cpRNFL thickness. The strong
correlation between PERG amplitude and RGCL+ and RNFL thickness is in agreement with the most widely accepted concept regarding the origin of PERG responses in the retina. A significant, although only moderate correlation also was found between PERG amplitude and VF sensitivity loss (Table 3).

Previous studies have evaluated the use of OCT in patients with papilledema, mostly to quantify the degree of optic disc edema and to monitor treatment efficacy. The use of OCT for quantifying retinal neuronal loss in eyes with papilledema, however, has some limitations since the presence of optic disc edema artificially increases OCT-measured cpRNFL thickness and prevents accurate estimation of peripapillary axonal loss. While the assessment of neuronal loss based on macular thickness measurements is less affected by the presence of disc edema, retinal complications may occur (e.g., macular edema, internal limiting membrane folds, hemorrhage, and even subretinal neovascular membrane), which prevent accurate quantification of macular thickness and macular RNFL or RGC layer thickness. Thus, since PERG response presumably is less affected by optic disc and retinal edema than OCT data, it is important to continue exploring PERG technologies capable of quantifying the neural integrity of the retina.

While we believe PERG could be useful to estimate axonal loss even in eyes with optic disc edema, to better evaluate its relationship with OCT and VF on SAP, we purposely chose to study eyes with resolved papilledema, and permanent (irreversible) structural and functional visual loss. In our study, PERG amplitude measurements proved to be able to differentiate between normal and papilledema eyes. Although the ROC curve analysis showed PERG parameters to be slightly less effective than OCT measurements in discriminating between eyes with papilledema and controls, the diagnostic ability of the two technologies was, in fact, very similar. Furthermore, when the assessment of the discrimination power was based...
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on the number of eyes with abnormal results below the value corresponding to the lower 10th percentile of normal, no significant difference was found between the two methods (Fig. 4).

While further studies using PERG in patients with active papilledema are necessary, the finding in this study of reduced PERG amplitude parameters in such eyes, and significant correlations between PERG and OCT and VF measurements suggests the technology may be useful in the monitoring of visual function in patients with pseudotumor cerebri syndrome.

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