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Pattern Electroretinogram Abnormality and Glaucoma

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Abstract

Purpose—To determine the existence of retinal ganglion cell dysfunction and associated risk factors in glaucoma suspects with increased optic disc cupping and normal visual field.

Design—Cross-sectional, observational study.

Participants—Two hundred glaucoma suspect (GS) patients were identified based on optic disc abnormalities (vertical cup-to-disc ratios [C/D]>0.5; vertical C/D asymmetry ≥ 0.2 ; disc hemorrhages; notching) in association with known glaucoma risk factors (positive family history, African American descent, increased intraocular pressure [IOP]), but normal visual fields. Forty-two patients had early manifest glaucoma (EMG). Sixteen normal black subjects were added to update previous pattern electroretinogram (PERG) normative data and to establish a normal control (NC) group with a racial breakdown comparable with that of the study groups.

Methods—Pattern electroretinograms were recorded simultaneously from both eyes using skin electrodes and automated analysis; visual fields were monitored with standard white-on-white automated perimetry (SAP) central 24-2 program; vertical C/D was evaluated by an independent reader from stereo disc photographs; and univariate and multivariate statistical analysis between PERG and other outcome measures was evaluated.

Main Outcome Measures—Pattern electroretinogram amplitude (μV), phase (π rad), and interocular asymmetry in amplitude and phase (%); and SAP mean deviation (MD; decibels), vertical C/D, age (years), IOP (mmHg), and race (black vs. nonblack).

Results—The PERG results were abnormal in at least 1 of the outcome measures in 52% of GS patients and 69% of EMG patients. The PERG amplitude was correlated weakly with both MD ($P < 0.01$) and vertical C/D ($P = 0.05$). The correlation between PERG amplitude and MD and C/D was stronger ($P < 0.001$) for interocular differences rather than absolute measures. Interocular PERG amplitude asymmetry increased with severity of disease (EMG>GS>NC; $P < 0.01$). The PERG amplitude decline with age was steeper in patients with a more negative MD ($P < 0.01$) and in patients with a more negative MD and a larger vertical C/D ($P = 0.06$). Black race (but not family history) was associated with lower PERG amplitude ($P > 0.005$) in GS and EMG patients, but not in normal controls ($P = 0.44$).

Conclusions—The correlation between PERG abnormality and known risk factors for glaucoma indicates that PERG has a predictive potential for the development or progression of the disease, or both.

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Dr Porciatti has a patent pending application (no. PCT/US03/03155) on the technique for pattern electroretinogram recording.

In primary eye care, it is common to encounter patients with increased optic disk cupping and normal visual fields in association with other risk factors for glaucoma. When standard automated perimetry (SAP) and intraocular pressures (IOP) are normal, the clinician is left in a quandary of whether this represents physiologic cupping or preperimetric glaucoma. Management of these patients would benefit from a technique with sufficient sensitivity and specificity to detect early glaucoma.

The pattern electroretinogram (PERG) is an electrophysiological technique that has been used to evaluate the function of retinal ganglion cells in humans and experimental animals.^{1–3} The PERG is altered in glaucoma^{4–13} and in many cases of ocular hypertension (OHT),^{14–17} and has been shown to be as successful as short wavelength automated perimetry and frequency doubling technology in detecting glaucomatous eyes as well as identifying those with future progression before SAP.^{18,19}

The purpose of this study was to determine the existence of retinal ganglion cell (RGC) dysfunction using the PERG and to evaluate the association between PERG abnormalities and known risk factors for glaucoma in a large population of patients with suspicion of glaucoma. A smaller population of patients with early manifest glaucoma also was tested for comparison. To facilitate the PERG technique, we developed a noninvasive paradigm for PERG recording. The method overcomes some of the limitations of current techniques using corneal electrodes, reported by some laboratories as too variable and too dependent on both operator skill and patient compliance.^{20–22} This paradigm is fast and automated, and the responses, recorded with skin electrodes, have good signal-to-noise ratio and reproducibility.²³

Preliminary results of this study have been reported previously in abstract form [Ventura LM, Porciatti V, Parrish RK. Over 50% of glaucoma suspects with increased disk cupping and normal visual field have abnormal function of retinal ganglion cells (RGC). Presented at: AAO Annual Meeting, October 20, 2002; Orlando, Florida. Ventura LM, Porciatti V, Feuer W, Ishida, K, Parrish RK. Correlation between intereye differences in pattern ERG (PERG) and risk factors for glaucoma in glaucoma suspects. Presented at: AAO Annual Meeting, November 15, 2003; Anaheim, California].

Patients and Methods

Patients

Two hundred glaucoma suspect (GS) patients and 42 patients with early manifest glaucoma (EMG) participated in the study. The mean age of the entire group of patients was 57 ± 13 years (median, 57 years). Black patients comprised 52 of the total 242-person population (21%; GS, $n = 40$; EMG, $n = 12$). Eligibility was determined through a detailed medical and ocular history and a comprehensive eye examination. Eye examination included best-corrected visual acuity (BCVA), refraction at distance and near, IOP with Goldmann applanation tonometry, corneal pachymetry, gonioscopy, dilated fundus examination, stereophotographs of the optic disc, and a Humphrey perimeter central 24-2 program (SAP). Vertical cup-to-disc (C/D) ratios were evaluated from stereo photographs of the optic disc by 1 independent observer (KI). Clinical and demographic information were obtained as specified in the Ocular Hypertension Treatment Study (OHTS) design.²⁴ Subjects met the following inclusion criteria: (1) for GS patients,²⁵ $BCVA \geq 20/20$, normal SAP according to the OHTS criteria²⁴ (reliability $< 33\%$ on all indices, normality $> 5\%$ on all global indices in 2 consecutive sessions 6 months apart), and glaucomatous optic disc appearance (vertical C/D > 0.5 ; vertical C/D asymmetry ≥ 0.2 , localized thinning of the disc, splinter disc hemorrhages) or increased IOP (> 21 mmHg); (2) for EMG patients, $BCVA \geq 20/20$, abnormal SAP or progression of optic disc abnormalities according to the OHTS criteria, or both.²⁴ For the normal control (NC) group, we updated previously published data²³ to include a larger number (14%) of blacks to approximate the racial

breakdown of the study group. The NC group was a mixed population of 114 individuals (67 white, 24 Hispanic, 5 Asian American, 2 Indian American, 16 African American) of both genders (55% male) and of different ages (range, 22–85 years; mean, 46.4 ± 18.2 years). Subjects were free from systemic or ocular diseases as assessed by routine ophthalmologic examination and had BCVA of 20/20 or better.

For all subjects, exclusion criteria were the presence of ocular or systemic disease that may cause nonspecific PERG abnormality, such as age-related macular degeneration, diabetes, Parkinson's disease, and multiple sclerosis. Patients with previous intraocular surgery, except for uncomplicated cataract extraction, were excluded. Patients with high myopia (>5 diopters) also were excluded because the electroretinogram may be reduced nonspecifically in high myopia.²⁶ Thirteen of 200 GS patients (6%) and 18 of 42 EMG patients (43%) used various topical glaucoma medications.

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miami (IRB 01/036B, IRB 01/365B). Informed written consent was obtained by all subjects after the nature of the test and possible risks were explained in detail.

Pattern Electoretinogram Recording

The PERG was recorded in a manner recently described.²³ The testing strategy is incorporated in a commercially available system (Glaide; Lace Elettronica, Pisa, Italy). The PERG was simultaneously recorded from both eyes by means of skin electrodes on the lower eyelids (reference ipsilateral temple, common ground central forehead). The spatiotemporal characteristics of the stimulus have been optimized to yield the highest amplitude in control subjects²⁷ and the maximum amplitude reduction in glaucoma.^{10,14,15,28,29} The pattern stimulus consisted of horizontal gratings (1.7 cycles/degree, 25° circular field, 95% contrast, 40 candelas/m² mean luminance), reversed in counterphase at 8.14 Hz (16.28 reversals/second). Signals were band pass filtered (1–30 Hz), amplified (100,000 fold), and averaged (at least 600 sweeps in blocks of 300 sweeps). Subjects were fitted with the appropriate correction for a viewing distance of 30 cm and were instructed to fixate on a target at the center of stimulus. Subjects did not receive dilating drops and were allowed to blink freely. Sweeps contaminated by eye blinks or gross eye movements were rejected automatically over a threshold voltage of 25 μ V. The PERG waveforms were evaluated automatically in the frequency domain by discrete Fourier transform (DFT) to isolate the component at the reversal frequency (16.28 Hz). Other frequencies, such as those originating from eye muscles and electroencephalogram activity, were rejected. A noise waveform was obtained simultaneously by multiplying alternate sweeps by +1 and -1 (thereby canceling out the PERG and leaving the background activity), and the 16.28-Hz component was analyzed and measured by DFT. Under these experimental conditions, the PERG waveforms recorded in individual eyes were not contaminated by the responses originating from the contralateral eyes, as with some corneal electrodes.^{30,31} The recording time was approximately 3 minutes for both eyes simultaneously. An example of PERG waveforms recorded simultaneously in both eyes of a control subject, and corresponding DFT filtering is shown (Fig 1). Because the PERG was recorded in response to relatively fast alternating gratings, the response waveforms typically were steady state with a sinusoidal-like waveform and a frequency corresponding to the reversal rate. Automated DFT analysis of the PERG waveforms allows isolation and reconstruction of the harmonic component at the contrast-reversal rate (16.28 Hz), and computation of its amplitude in microvolts and phase in π rad.

Statistical Analysis

Comparison of Pattern Electretinogram Amplitude and Phase between the Normal Control Group and Glaucoma Suspect and Early Manifest Glaucoma Patients

As previously reported,²³ the PERG amplitude and phase decrease with age in normal subjects. The regression of amplitude with age is linear on log–log coordinates, whereas that of phase with age is linear on linear scales. The equations of the regression lines were: $\log(\text{amplitude}) = 0.632 - 0.389 \times \log(\text{age})$ and $\text{phase} = 1.99 - 0.0032 \times \text{age}$. The regression relationships were used to derive the age-specific amplitude and phase. To determine the extent to which the PERG amplitude and phase differ from normal, we expressed data as deviations from age-specific normal values in decibels (dB): $10 \times (\log_{10} [\text{measured}] - \log_{10} [\text{expected}])$. Deviations from age-specific values were determined for GS and EMG patients and were compared with those of the normal controls with analysis of variance. Only 1 eye per subject (left eye) was included in the analysis to avoid inclusion of the correlated data from two eyes of the same patient.

Comparison of Interocular Asymmetry in Pattern Electretinogram Amplitude and Phase between the Normal Control Group and Glaucoma Suspect and Early Manifest Glaucoma Patients

In both patients and controls, % interocular asymmetries in PERG amplitude have been expressed according to the equation: $\% \text{ asymmetry} = |\text{right eye} - \text{left eye}| / (\text{right eye} + \text{left eye}) \times 100$. Interocular asymmetries were compared among NC, GS, and EMG groups with an analysis of variance.

Correlation between Pattern Electretinogram Amplitude and Phase Deviations from Age-Specific Normal Control Values with Vertical Cup-to-Disc Ratio and Mean Deviation

Mean deviation was chosen among different SAP parameters because, similar to the PERG, it is an integrated measure of visual function and depends on optical opacities. In this analysis, PERG amplitude and phase, C/D, and mean deviation (MD) were averaged for the two eyes of each participant. The strength of correlation was assessed in GS, EMG, and both groups combined with Pearson's correlation coefficient.

Correlation between the Signed Pattern Electretinogram Interocular Differences (Right Eye – Left Eye) and Corresponding Asymmetries in Mean Deviation and Vertical Cup-to-Disc Ratio

The strength of correlation was assessed in GS patients, EMG patients, and both groups combined with Pearson's correlation coefficient.

Correlation between Mean Deviation and Vertical Cup-to-Disc Ratio and Correlations of Signed Interocular Differences between Mean Deviation and Vertical Cup-to-Disc Ratio

These measures were compared with analog measures between PERG and C/D (see above).

Multivariate Analysis between Pattern Electretinogram and Decade of Age, Family History of Glaucoma, African Ancestry, Mean Deviation, Vertical Cup-to-Disc Ratio, and Intraocular Pressure

Multiple regression, using the method of generalized estimating equations³² to account for the correlation between the two eyes of each subject, was used to conduct this analysis.

Results

Comparison between Pattern Electretinogram of Patients and Control Subjects

The PERG amplitude and phase decreased with aging in normal subjects (Fig 2).²³ The thick lines represent the regressions of amplitude or phase as a function of age of the NC group, and the thin lines represent the corresponding 95% tolerance limits. Normal controls of black race

were not significantly different from nonblacks with respect to PERG amplitude ($P = 0.43$, analysis of covariance adjusting for age) or PERG phase ($P = 0.44$). After adjusting for age, the mean PERG amplitude of black controls was slightly reduced by $0.05 \mu\text{V}$ as compared with nonblack controls (95% confidence limit, -0.08 to $+0.18$; difference with nonblacks controls not significant). Because there was no statistically significant difference in the decline of PERG amplitude with aging ($P = 0.17$) between black and nonblack NC subjects, all normal participants' data were combined.

Note in Figure 2 that numerous eyes of both GS and EMG patients have an amplitude and phase smaller than the 95% tolerance limits of the NC group, and that the frequency of abnormalities seems to be greater for older patients. In GS patients, 91 of 400 eyes (23%) had abnormal results for amplitude, 48 of 400 eyes (12%) had abnormal results for phase, and 25 of 400 eyes (6%) had abnormal results for both amplitude and phase. In EMG patients, 31 of 84 eyes (37%) had abnormal results for amplitude, 14 of 84 eyes (17%) had abnormal results for phase, and 7 of 84 eyes (8%) had abnormal results for both amplitude and phase. Statistical analysis of data presented in Figure 2 show that amplitude deviations from normal increase significantly with age ($P < 0.001$, 2-way ANOVA) and with increasing level of pathologic characteristics, in that $\text{EMG} > \text{GS} > \text{NC}$ ($P < 0.05$, Tukey test). There is also a significant interaction between age and pathologic features ($P < 0.001$). That is, the increasing deviation from normal with age is larger in EMG than in GS patients. Average deviations in the 3 groups of subjects are summarized in Figure 3. The average phase is not significantly different between the groups.

Comparison between Pattern Electrophoretogram Interocular Asymmetry of Patients and Control Subjects

Differences in PERG amplitude and phase between the two eyes (interocular asymmetry) may represent an important additional criterion in the evaluation of changes in RGC function.^{33, 34} If glaucoma progresses asymmetrically,³⁵ then the amount of PERG amplitude and phase asymmetry may be larger than normal even before the absolute values of PERG amplitude and phase exceed the tolerance limits of NC subjects.

In the scattergrams (Fig 4), PERG amplitude and phase of right eyes are plotted as a function of corresponding values of the left eyes. As previously shown,²³ normal controls have a limited degree of PERG interocular asymmetry in amplitude ($12.0 \pm 9.6\%$) and phase ($2 \pm 1.4\%$). Thin lines represent the 95% tolerance interval for amplitude (Fig 4A, C) and phase (Fig 4B, D) asymmetries of normal subjects. Three percent of normal subjects slightly exceeded the 95% confidence interval for amplitude asymmetry and 1% did so for phase asymmetry. Among GS patients 14.1% had an abnormal (outside the 95% tolerance intervals of normal subjects) interocular asymmetry in amplitude (Fig 4A), 8.5% had abnormal interocular asymmetry in phase (Fig 4B), and 4.5% had abnormal interocular asymmetry for both amplitude and phase (Fig 4A, B). In EMG patients, interocular asymmetry in amplitude was abnormal in 14.5% of patients (Fig 4C), interocular asymmetry in phase was abnormal in 9.5% of patients (Fig 4D), and 2.4% of patients had abnormal interocular asymmetry for both amplitude and phase (Fig 4C, D).

The average interocular asymmetries in PERG amplitude for the NC group and GS and EMG patients are plotted in Figure 5. The average PERG amplitude asymmetry increased with increasing severity of the disease ($P < 0.001$, analysis of variance). Asymmetry in both GS (20.5%) and EMG patients (28.7%) was larger than that of the NC group (12.7%; $P < 0.05$, Tukey test). Amplitude asymmetry was larger in EMG than in GS patients ($P < 0.05$, Tukey test). There was no significant interaction between age and pathologic features (GS and EMG patients, $P = 0.7$). Unlike amplitude asymmetry, the average PERG phase asymmetries were not significantly different from controls in GS and EMG patients.

Correlation between Pattern Electroretinogram and Mean Deviation and between Pattern Electroretinogram and Vertical Cup-to-Disc Ratio

We compared PERG deviation from normal with MD and vertical C/D ratio. The PERG amplitude and phase deviations from age-predicted averages are expressed in decibel units to normalize the scale with MD. The PERG amplitude deviations are plotted either against corresponding MDs (Fig 6A) or against corresponding vertical C/D ratios (Fig 6B). The PERG amplitude deviation from normal tends to increase with both increasing MD and increasing vertical C/D ratio (Table 1). Specifically, the correlation between PERG amplitude and MD is moderate for EMG patients ($r = 0.514$; $P = 0.003$), weaker for the entire patient population (GS plus EMG, $r = 0.252$; $P < 0.001$), and is not significant for GS patients. In many GS patients, the PERG amplitude deviation is larger than -2 dB (lower tolerance limit of normal controls) despite normal MD. Some GS patients, however, have MDs larger than -2 dB with normal PERG amplitudes. The correlation between PERG amplitude deviation and vertical C/D ratio is of borderline significance in the entire patient population (GS plus EMG, $r = -0.134$; $P = 0.055$), but not in individual subgroups. In contrast to PERG amplitude, no significant correlations were found between PERG phase and either MD or vertical C/D ratio.

Correlation between Pattern Electroretinogram Interocular Asymmetries and Corresponding Asymmetries in Mean Deviation and Vertical Cup-to-Disc Ratio

Signed interocular differences (right eye–left eye in decibels) in PERG amplitude are plotted against either corresponding interocular differences in MD or vertical C/D ratio (Fig 7). The results of the statistical comparison are summarized in Table 2. The correlations between PERG amplitude asymmetry and corresponding asymmetries in both MD and vertical C/D ratio are highly significant in all patient groups. The correlations are stronger for EMG patients than for GS patients (Table 2).

Comparison of the Correlation between Mean Deviation with Vertical Cup-to-Disc Ratio versus Pattern Electroretinogram with Vertical Cup-to-Disc Ratio

Tables 1 and 2 present the correlations of PERG amplitudes and PERG interocular asymmetries with MD and vertical C/D ratio. These may be compared with correlations between MD and vertical C/D ratio (Table 3). The correlation of MD with vertical C/D ratio is weaker than the correlation between PERG and cupping for all groups (Table 3).

Multivariate Analysis of the Association between Pattern Electroretinogram Deviations from Normal and Risk Factors for Glaucoma

To determine if known risk factors for glaucoma are associated with PERG amplitudes, a general linear model was fitted with PERG amplitude as the dependent variable and decade of age, family history of glaucoma, African ancestry, MD, vertical C/D ratio, and IOP as the independent variables.³² The results are summarized in Table 4. Older age was strongly associated with reduced PERG amplitude. Glaucomatous black patients comprised 52 of the 242-person total population (21%; GS, $n = 40$; EMG, $n = 12$) and had significantly lower PERG amplitudes compared with white patients (cumulated white and Hispanic patients). Our patient sample included 40% of subjects with a positive family history for glaucoma. Reduced PERG amplitude was significantly associated with both MD and vertical C/D ratio. After adjusting for the effects of MD and vertical C/D ratio, PERG reduction in EMG patients was not significantly different from that in GS patients. This result indicates that the PERG amplitude differences between GS and EMG patients found in the univariate analysis of data displayed in Figure 3 can be explained largely by differences in MD and vertical C/D ratio between these 2 groups of patients. Family factors and moderate IOP increase were not significantly associated with lower PERG amplitude. Finally, the PERG reduction in the right eyes was not different from that of the left eyes.

To understand more fully the relationship between PERG, age, and the standard measures of functional and structural deficits in glaucoma, we fitted 2 separate sets of models with interaction terms (MD $\times$ age and vertical C/D ratio $\times$ age). The interaction of age and MD was significant ($P = 0.003$), and the interaction with vertical C/D ratio was of borderline significance ($P = 0.064$; Fig 8). The PERG amplitude decreases with increasing age in all groups, but the effect is more pronounced in eyes with increasing MD (Fig 8A). The slope of PERG amplitude with age is steeper in patients with pronounced field defects and larger cups than in patients with smaller field defects and smaller cups. That is, the worse the field loss and the greater the cupping, the faster the loss of PERG amplitude with aging.

Discussion

We designed this study to determine the prevalence of PERG abnormalities in patients with glaucomatous cupping and normal SAP and to assess the correlation of PERG abnormalities with risk factors for open-angle glaucoma. The goal was to evaluate the predictive potential of the PERG for the early diagnosis of glaucoma. The PERG results were abnormal in at least 1 of the outcome measures (amplitude, phase, interocular asymmetry in amplitude, and phase) in 52% of GS patients and in 69% of EMG patients. Glaucoma suspects have nonpathologic SAP, but have glaucomatous cupping often associated with 1 or more risk factors for open-angle glaucoma. An abnormal PERG in GS, significantly correlated with increased cupping, suggests that PERG may detect associated glaucomatous neuropathy before the development of SAP losses.

The PERG abnormalities found in our patient sample most likely are associated with dysfunction of retinal ganglion cells themselves, of the circuitry of the inner retina impinging on retinal ganglion cells, or both. The PERG abnormalities were unlikely to be the result of optical degradation of the patterned stimulus such as defocus or substantial cataract formation, or of nonglaucomatous retinal changes. All patients had normal visual acuity and were corrected suitably for the viewing distance. Cataractous changes allowed were of the nuclear sclerotic type and were limited to a mild grade. Patients with high axial myopia or with diseases that may cause retinal dysfunction were excluded from our study.

The high frequency of PERG abnormalities in GS patients suggests that these patients do not have so-called physiologic cupping, but rather have retinal dysfunction that requires closer follow-up. Although suspicion may be heightened further, PERG abnormality in a GS patient does not necessarily determine that that patient has or will have glaucoma. The sensitivity and specificity of PERG abnormalities for identifying GS patients in whom reproducible visual field defects will develop can be established only with long-term follow-up studies. Nonetheless, a few pilot PERG studies have demonstrated that patients in whom glaucomatous visual field defects developed later also had abnormal PERG results at baseline^{12,36–38} or had progressive PERG changes before visual field defects developed.¹⁹ In addressing the question of why a few of our patients who had an MD worse than -2 dB would have a normal PERG amplitude, one should realize that PERG and visual field probe different parts of the visual field and different aspects of visual function. The PERG is a suprathreshold mass response of central RGCs and may be less sensitive than the SAP to an early focal defect if most of the RGCs are healthy. Conversely, the PERG may be more sensitive than SAP to detect a generalized dysfunction of the central retina with high RGC density and redundancy. Therefore, the ability to detect glaucomatous neuropathy in GS eyes is improved substantially by the combined use of these 2 methods.¹⁹

Screening a large population of patients allowed us to perform a multivariate analysis of the associations between PERG abnormalities and known risk factors for glaucoma. After correction for all independent variables, black patients had significantly smaller PERG

amplitudes than nonblack patients. By contrast, the PERG of normal black subjects was not significantly different from that of nonblack NC subjects. This is the first study to demonstrate an association between black race and reduced PERG amplitude in early glaucoma. This result is consistent with epidemiologic studies that show the incidence of glaucoma to be higher in the black population compared with the white population.^{39–41}

Family history of primary open-angle glaucoma (POAG), an established risk factor for POAG,⁴² was not significantly associated with PERG abnormalities in our study. Neither did the recent OHTS study⁴³ report family history as a significant risk factor for progression from ocular hypertension to POAG.

Moderate IOP increase was not associated with PERG reduction. This may seem somehow surprising, because it is known that the PERG amplitude is reduced in ocular hypertension patients.¹⁴ However, only 8% of our patient sample had a moderately increased IOP; therefore, no conclusion can be drawn regarding the correlation between PERG and increased IOP.

This study clearly shows that PERG amplitude deviations from normal increase with advancing age in GS and EMG patients. The PERG amplitude decline with age is steeper in patients with worsening MD. In addition, the PERG amplitude seems to decrease to a greater extent with age in patients with larger MD and vertical C/D ratio. That is, PERG amplitudes are reduced even more than what would be expected based on summing the individual effects of age and MD or vertical C/D ratio. The age effect was comparable in GS and EMG patients. This suggests that the progression of glaucoma may be accelerated for older patients with greater cupping and with greater degrees of field loss.

The moderate correlations between PERG abnormalities and risk factors for POAG in GS patients indicate that the PERG may have a predictive potential for the development of glaucoma. Screening with PERG merits further investigation, because our results show that a high proportion of patients with glaucomatous cupping and other risk factors display PERG abnormalities. The ease of this technique makes it suitable for mass screenings of populations at risk for glaucoma. The noninvasive PERG, therefore, may represent a complement to SAP for the detection and monitoring of the early stages of glaucoma.

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Figure 1.

Representative examples of pattern electroretinogram (PERG) waveforms (black lines) recorded simultaneously in both eyes of a 50-year-old normal subject. The response component at the contrast-reversal frequency, automatically isolated by digital Fourier transform (DFT) analysis (gray sinusoidal lines), is superimposed to the PERG waveforms. The PERG amplitude is evaluated as one half of peak-to-trough amplitude of the sinusoidal component (right eye, 0.91 microvolts [μV]; left eye, 0.99 μV), and the PERG phase is evaluated relative to the reversal period (right eye, 1.94 π rad; left eye, 2.03 π rad). ms/div = milliseconds per division.

Figure 2.

Scattergrams of (A, C) pattern electroretinogram (PERG) amplitude and (B, D) phase as a function of age in glaucoma suspect (GS) patients (upper panels, open symbols) and early manifest glaucoma (EMG) patients (lower panels, filled symbols). Scattergrams also display the average amplitude (thick lines) and 95% tolerance limits (thin lines) of amplitude and phase of normal controls. PI rad = π rads; uV = microvolts.

Figure 3.

Average pattern electroretinogram (PERG) amplitude deviation plus standard error of the mean from age-predicted normal average. The deviation of normal controls (NC) is not different from zero. Both glaucoma suspect (GS) patients and early manifest glaucoma (EMG) patients have a significantly larger deviation from age-predicted normal. The deviation is significantly larger for EMG than GS patients.

Figure 4.

Interocular asymmetries in (A, C) pattern electroretinogram (PERG) amplitude and (B, D) phase in glaucoma suspect (GS) patients (upper panels, open symbols) and early manifest glaucoma (EMG) patients (lower panels, filled symbols). Thin lines represent the 95% confidence interval of asymmetries in amplitudes and phases of age-matched normal controls. Note the excessive interocular asymmetry of several patients. PI rad = π rads; uV = microvolts.

Figure 5.

Average interocular asymmetry (plus standard error of the mean) of pattern electroretinogram (PERG) amplitude. Both glaucoma suspect (GS) patients and early manifest glaucoma (EMG) patients have a significantly larger interocular asymmetry than normal controls (NC). The asymmetry is significantly larger for EMG than GS patients.

Figure 6.

Pattern electroretinogram (PERG) amplitude deviation from normal average as a function of (A, C) standard automated perimetry mean deviation (MD) and (B, D) vertical cup-to-disc ratio (C/D) in glaucoma suspect (GS) patients (upper panels, open symbols) and early manifest glaucoma (EMG) patients (lower panels, filled symbols). dB = decibels.

Figure 7.

Interocular differences (right eye – left eye) in pattern electroretinogram (PERG) amplitude deviation from normal as a function of (A, C) corresponding interocular differences in mean deviation (MD) and (B, D) interocular differences in vertical cup-to-disc ratio (C/D) in glaucoma suspect (GS) patients (upper panels, open symbols) and early manifest glaucoma (EMG) patients (lower panels, filled symbols). HVF = Humphrey visual field.

Figure 8.

Models of pattern electroretinogram (PERG) amplitude decline with age including interaction terms (**A**) mean deviation (MD) and (**B**) MD plus cup-to-disc ratio (C/D). Note in (**A**) that the PERG amplitude decline with age is progressively steeper with increasing MD. Note in (**B**) that the PERG amplitude decline with age also depends on the amount of disc cupping. μV = microvolts.

Table 1

Correlations of Pattern Electrophoretogram Amplitude with Mean Deviation index of Standard Automated Perimetry and vertical Cup-to-Disc ratio

Group	Pattern Electrophoretogram versus Mean Deviation index of Standard Automated Perimetry	Pattern Electrophoretogram versus vertical Cup-to-Disc ratio
GS + EMG	$r = 0.252$ ($P < 0.001$)	$r = -0.134$ ($P = 0.055$)
GS	$r = 0.106$ ($P = 0.165$, n.s.)	$r = -0.079$ ($P = 0.302$ n.s.)
EMG	$r = 0.514$ ($P = 0.003$)	$r = -0.015$ ($P = 0.936$ n.s.)

C/D = vertical cup-to-disc ratio; EMG = early manifest glaucoma; GS = glaucoma suspects; MD = mean deviation index of standard automated perimetry; n.s. = not significant.

Table 2

Correlations of Pattern Electretinogram Amplitude Interocular Asymmetry with Interocular Asymmetry in Mean Deviation index of Standard Automated Perimetry and vertical Cup-to-Disc ratio

Group	Pattern Electretinogram Asymmetry versus Mean deviation index of Standard Automated Perimetry Asymmetry	Pattern Electretinogram Asymmetry versus vertical Cup-to-Disc ratio Asymmetry
GS + EMG	$r = 0.284$ ($P < 0.001$)	$r = -0.264$ ($P = 0.001$)
GS	$r = 0.177$ ($P = 0.020$)	$r = -0.231$ ($P = 0.002$)
EMG	$r = 0.476$ ($P = 0.006$)	$r = -0.369$ ($P = 0.038$)

C/D = vertical cup-to-disc ratio; EMG = early manifest glaucoma; GS = glaucoma suspects; MD = mean deviation index of standard automated perimetry.

Table 3

Correlations between Mean Deviation index of Standard Automated Perimetry and vertical Cup-to-Disc ratio

Group	Mean Deviation index of Standard Automated Perimetry versus vertical Cup-to-Disc ratio	Mean Deviation index of Standard Automated Perimetry Asymmetry versus vertical Cup-to-Disc ratio Asymmetry
GS + EMG	$r = -0.074$ ($P = 0.104$ n.s.)	$r = -0.196$ ($P = 0.002$)
GS	$r = 0.0433$ ($P = 0.39$ n.s.)	$r = -0.124$ ($P = 0.083$ n.s.)
EMG	$r = -0.0007$ ($P = 0.949$ n.s.)	$r = -0.312$ ($P = 0.044$)

C/D = vertical cup-to-disc ratio; EMG = early manifest glaucoma; GS = glaucoma suspect; MD = mean deviation index of standard automated perimetry; n.s. = not significant.

Table 4

Summary of Multiple Regression Model Results

Variable	Coefficient $\pm$ Standard Error of the Mean	P Value	Interpretation
Decade of age	-0.086 ± 0.012	<0.001	Amplitude decreases by approximately $0.1 \mu\text{V}$ per decade of age
Family history	-0.024 ± 0.033	0.46	Not significant after adjusting for the other variables
Black race	-0.111 ± 0.037	0.003	Glaucomatous blacks have amplitudes reduced by approximately $0.1 \mu\text{V}$ compared with nonblacks
EMG vs. GS	-0.058 ± 0.037	0.11	Not significant after adjusting for the other variables
Left eye vs. right eye	-0.011 ± 0.013	0.43	Not significant
C/D	-0.158 ± 0.079	0.032	PERG amplitude is reduced by approximately $0.15 \mu\text{V}$ for each 0.1 increase in C/D
MD	0.022 ± 0.006	<0.001	PERG amplitude decreases by approximately $0.2 \mu\text{V}$ with each decibel of mean deviation
IOP	0.002 ± 0.004	0.71	Not significant after adjusting for the other variables

C/D = vertical cup-to-disc ratio; EMG = early manifest glaucoma; GS = glaucoma suspects; IOP = intraocular pressure; MD = mean deviation index of standard automated perimetry; PERG = pattern electroretinogram.