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The PERG in diabetic glaucoma suspects with no evidence of retinopathy

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Abstract

Objective—To better understand the role of diabetes mellitus on retinal ganglion cell (RGC) function of glaucoma suspects.

Methods—Eighteen diabetic glaucoma suspects (GSD) without retinopathy (type-2, n=16, type-1, n=2) and 156 age-matched glaucoma suspects without diabetes (GS) were tested with steady-state PERG (PERGLA paradigm, Ophthalmology 2004;111:161) as surrogate measure of RGC function. Results were compared with previously published data of 48 similarly aged normal controls (NC). All subjects (NC, GS, GSD) had small refractive errors and corrected visual acuity $\geq 20/25$.

Results—The mean PERG amplitude of both GS and GSD was significantly ($P<0.01$) smaller than that of age-matched NC. The mean PERG amplitude of GSD patients was significantly ($P<0.05$) smaller than that of GS accounting for individual differences in age, visual acuity, visual field defect and IOP. The mean PERG phase did not differ between GS and GSD.

Conclusions—In agreement with previous studies, our results show that on average, GS have reduced PERG amplitude compared to NC. PERG amplitude is further reduced in GSD compared with non-diabetic GS with otherwise comparable ophthalmologic and systemic conditions.

Keywords

retinal ganglion cell function; pattern electroretinogram; glaucoma; diabetes

Introduction

The pattern electroretinogram (PERG) represents a well-established surrogate measure of retinal ganglion cell (RGC) function in glaucoma (see for review refs 1–3). The PERG may be altered even before significant perimetric defects in patients with either ocular hypertension (OHT) (eg, 4–6) or suspicion of glaucoma (GS) due to optic disk abnormalities and other risk factors for glaucoma (eg, 7,8). The PERG signal may also be reduced in non-retinopathic, type-1 diabetes,^{9–13} as well as in non-retinopathic, type-2 diabetes associated with OHT.¹⁴ Since older subjects have increased susceptibility to both glaucoma and diabetes,¹⁵ it is important to consider that the presence of diabetes can alter the interpretation of PERG in the detection of early glaucoma.¹⁴

We have further investigated the influence of diabetes on the PERG of GS patients. Over the past years, we have tested a large group (n ~ 350) of glaucoma suspects (GS) with the steady-state PERG (PERGLA paradigm¹⁶) with the aim of detecting early progression of disease.⁸

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Conflict of interest: Vittorio Porciatti, Lace Elettronica, Italy.

17,18 A group of enrolled GS patients subsequently reported to have diabetes mellitus, predominantly type 2, non associated with retinopathy. We have compared the PERG of glaucoma suspects with diabetes (GSD) with that of another group of glaucoma suspects without diabetes (GS) controlling for differences in age, IOP, visual field, optic disk cupping, and central corneal thickness.

Methods

Subjects

One-hundred-seventy-four patients with suspicion of glaucoma (GS) participated in the study. Eighteen of them (GSD) had well-controlled diabetes (insulin-dependent, n=2 non-insulin dependent, n=16). For both GS and GSD patients, the presence and type of diabetes, as well as the current status of treatment, relied solely on self report. In GSD patients, diabetes duration was: between 1–5 years, n=13; between 5–10 years, n=2; between 10–20 years, n=3. All subjects underwent a detailed medical and ocular history and a comprehensive eye examination performed by one experienced ophthalmologist (LV). Eye examination included Best Corrected Visual Acuity (BCVA), refraction at distance and near, IOP with Goldmann applanation tonometry, corneal pachymetry, gonioscopy, dilated fundus examination with a 78 D indirect lens at slit lamp biomicroscope, stereophotographs of the optic disc, and a Humphrey Perimeter Central 24-2 program (SAP SITA standard). None of the GS and GSD patients had ophthalmoscopic evidence of retinopathy. 19 Subjects met the following inclusion criteria: 20 BCVA $\geq$ 20/25, normal SAP according to the OHTS criteria 19 (reliability $<33\%$ on all indices, normality $>5\%$ on all global indices in two consecutive sessions 6 months apart), and glaucomatous optic disc appearance (vertical C/D > 0.5 , C/D asymmetry ≥ 0.2 , localized thinning of the disc, splinter disc hemorrhages) or increased IOP (> 21 mm Hg). The majority of patients had early nuclear sclerosis of the lens (GS: 58%, GSD: 56%). For all subjects, exclusion criteria were the presence of ocular alterations (age-related macular degeneration, microangiopathy) and systemic disease other than diabetes that can cause PERG alterations (Parkinson's disease, and multiple sclerosis). 21,22 Subjects with high myopia (> 5 D) were also excluded because the ERG may be non-specifically reduced in high myopia. 23 Patients with previous intraocular surgery, except for uncomplicated cataract extraction, were excluded. Twenty-seven of GS (14%) and 2/18 GSD (11%) used various topical IOP-lowering medications. Characteristics of the patients and eyes used in the study appear in Table I. Previously published data for a population of 113 normal controls (NC) were also used,⁸ selecting those with age >50 years (n=48) to correspond to the age of patients. The age range of NC was 50–85 years, mean 63.9 (9.1).

The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miami. Informed written consent was obtained by all subjects after the nature of the test and possible risks were explained in detail.

PERG recording

The PERG was simultaneously recorded from both eyes according to the PERGLA paradigm, whose details have been previously described.¹⁶ In brief, skin electrodes were taped on the lower eyelids (active) and on the ipsilateral temples (reference). Subjects were fitted with the appropriate add for a viewing distance of 30 cm (distance of the visual stimulus); all of them reached J1+ Jeager acuity. Subjects were instructed to fixate on a target at the center of the stimulus; they did not receive dilating drops and were allowed to blink freely. The pattern visual stimulus consisted of horizontal gratings (1.7 cy/deg, 25 deg diameter circular field, 98% contrast, 40 cd/m² mean luminance), reversing in counterphase at 8.14 Hz (16.28 reversals/s). The pattern stimulus was generated on a CRT display (65 Hz refresh rate, not interlaced) placed at the bottom of a ganzfeld bowl having a background luminance of 3 cd/

m2. Electrical signals were band-pass filtered (1–30 Hz), amplified (100,000 fold), and averaged (600 sweeps in two successive blocks of 330 sweeps, each block requiring about 1½ minutes of acquisition time). The first 30 sweeps of each block were automatically rejected to eliminate response transients and allow steady-state conditions. During signal acquisition, sweeps contaminated by eye blinks or gross eye movements were automatically rejected over a threshold voltage of 25 μ V. Since the PERG was recorded in response to relatively fast alternating gratings, the response waveforms were typically sinusoidal-like, with a temporal period corresponding to the reversal rate. PERG waveforms were automatically analyzed in the frequency domain by Discrete Fourier Transform (DFT) to isolate the harmonic component at the contrast-reversal rate (16.28 Hz), and compute its amplitude in μ V and phase in π rad. At the contrast-reversal frequency of 16.28 Hz, a phase shift of 0.1 π rad corresponds to 3.1 ms change in latency. Decreasing phase values indicate latency delays. The PERGLA testing protocol is incorporated in a commercially available system (Glaide, Lince Elettronica, Rome, Italy).

Statistics

One eye per subject was selected for analysis (OD in all but one subject for which it was not eligible and the left eye was used). PERG amplitude data were log transformed to approximate normal distribution.¹⁶ Differences in mean PERG amplitude and phase between GS and GSD and normal controls were assessed with analysis of covariance accounting for the known effect of age on PERG. Post-hoc, pairwise multiple comparisons (Least Significant Difference) were used to test significant ($P<0.05$) differences among groups. The potential influence of other variables that might independently affect PERG amplitude and phase (age, IOP, SAP-MD, SAP-PSD, CCT, and vertical C/D ratio) in addition to the presence of diabetes was evaluated with forward stepwise multiple regression.

Results

The PERG amplitude and phase are known to physiologically decrease with increasing age. To understand whether PERG age-dependence differed among subjects groups, individual PERG amplitude and phase data have been plotted as a function of subjects' age (Fig. 1). In GS patients, log PERG amplitude decreased with increasing age ($R^2 = 0.131$, $P<0.001$) in a fashion similar to but with higher correlation than in NC ($R^2 = 0.087$, $P<0.001$). In GSD patients the slope of the log PERG amplitude with age was not significantly different from zero ($R^2 = 0.005$, $P=0.76$). There was a statistically significant ($P<0.004$) difference in log PERG amplitude between GS and GSD patients, and a significant interaction between diabetes and age. Statistically adjusting regressions for individual differences in visual acuity did not change the results. PERG phase significantly (R^2 : NC=0.226, GS=0.113, GSD=0.269, $P<0.001$) decreased with age in all subject groups with approximately similar slope. Regression lines of GS and GSD patients virtually overlapped and both were shifted downwards compared to NC by about 0.1 π rad (~ 3 ms delay in latency).

Mean Log PERG amplitudes and phases for each subject group are summarized in Fig. 2. Data represented in Fig. 2 have been adjusted to the group average age of 62 years; adjustment accounted for the interaction of age and diabetes status. The mean log PERG amplitude was significantly different among groups (ANOVA, $P<0.001$). Pairwise multiple comparisons showed that NC had mean log PERG amplitude larger than that of either GS or GSD patients ($P<0.05$). GS patients had larger amplitude than GSD patients ($P<0.05$). The mean PERG phase was significantly different among groups (ANOVA, $P=0.004$). Pairwise multiple comparisons showed that NC had larger PERG phase compared to either that GS or GSD ($P<0.05$). However, the PERG phase of GSD patients was not significantly different from that of GS patients.

In addition to age, PERG amplitude and phase are known to be correlated with a number of variables including IOP, C/D, and visual field defects.^{2,3} While the two patient groups were reasonably well age-matched, small differences in relevant variables between patient groups may represent confounding factors for detection of a significant effect of diabetes. Log PERG amplitude and PERG phase data have been submitted to forward stepwise multiple regression analysis to identify variables that may independently affect PERG amplitude and phase. Of the potential factors presented in table 1, after accounting for the effect of age only SAP-MD, slope (SE) = 0.028 (0.001) per unit of MD, was statistically significantly associated with log amplitude. The inclusion of SAP, IOP and VA in the model did not eliminate either the effect of diabetes ($p=0.026$) or the age*diabetes interaction ($p=0.050$). None of the potential variables other than age was significantly associated with phase. Neither log amplitude or phase was correlated with years since onset of diabetes among GSD ($p=0.15$, 0.67 , respectively).

Discussion

The PERG signal has been previously shown to be reduced in OHT and in GS¹⁻³ as well as in patients with non-retinopathic diabetes.⁹⁻¹³ The association of diabetes and OHT further reduces the signal compared to OHT alone.¹⁴ Our results indicate that glaucoma suspects with non-retinopathic diabetes also have significantly lower PERG signal compared to GS patients without diabetes; the effect is significant after accounting for interindividual differences in age, IOP, visual field defects, disk cupping, central corneal thickness, and visual acuity. Thus, the presence of diabetes appears to have a deleterious effect on inner retinal function independently of the association with ocular hypertension or suspicion of glaucoma due to optic disk abnormalities. Screening for diabetes may be needed before drawing conclusions from PERG results in GS patients.¹⁴

A pertinent question is to what extent a reduced PERG signal in GSD represents an index of detrimental influence on the future progression of glaucomatous disease. The PERG depends on the structural and functional integrity of RGC.^{24,25,26} The level of PERG signal is related to the number and/or vitality of inner retinal neurons — including normal connectivity or gain relationships between them — contributing to the recorded electrical signal (see ref 29 for discussion). In ocular hypertension and glaucoma, the level of PERG signal becomes progressively smaller with increasing severity and/or duration of disease.^{30,31} In non-retinopathic, type-1 diabetes the PERG signal is also significantly correlated with age at onset and duration of disease.^{13,32} Thus, the electrical responsiveness of RGCs — and/or the inner retinal circuitry impinging on them — appears to be negatively impacted by both glaucoma and diabetes and is associated with severity/duration of both conditions. Our results suggest that the known adverse effects of glaucoma on RGC responsiveness³³ combined with those of diabetes would result in PERG signal of smaller amplitude compared to GS patients without diabetes. It is unlikely that the additional reduction of PERG signal measured in GSD patients, compared to GS patients, is due to non-neural (optical) factors resulting from suboptimal dioptric correction (defocus) or presence of early cataract that may deteriorate the visual acuity and contrast of the pattern stimulus.²⁹ Both GS and GSD had a BCVA of $\geq 20/25$ and were carefully refracted for the viewing distance to achieve Jaeger J1+ acuity. Early lens alterations occurred in comparable proportions in GS and GSD patients. Statistical analysis also accounted for the role of difference of visual acuity among patients.

Interestingly, the difference in PERG amplitude between GS and GSD appeared to be relatively larger at young ages compared to older ages. A possible explanation for this age-dependent difference would be that once the PERG signal is very reduced (as in younger GSD) the limited dynamic range of the response does not allow further reduction of the signal with increasing age (floor effect: for discussion see 34). The floor effect is expected to play lesser role in GS.

This interaction between diabetes and age may represent a relevant issue for glaucoma progression and probably deserves further investigation.

Despite a significant difference between mean PERG amplitude of GS and GSD, distribution of data in the lower range of amplitudes overlaps in the two groups (compare fig. 1B with Fig. 1C). This implies that it will be impossible in individual patients to distinguish between glaucoma- and diabetes dependent reduction of PERG signal. The inability to distinguish between co-morbid conditions represents a current limitation of the PERG technique. Further investigation is needed to dissect out PERG amplitude reduction due to glaucoma from that due to diabetes. Another limitation of this study is that GSD subjects were classified based on self reporting rather than objective medically defined criteria. Some GS patients may have diabetes and insulin resistance and not be aware of their metabolic status. However, imprecise classification due to self-reporting should blur the difference between GS and GSD. Despite this limitation, our results show that the difference in PERG signal between GS and GSD is very significant.

In conclusion, our results show GSD without retinopathy display, on average, further reduction of PERG amplitude compared to GS without diabetes who had otherwise similar ophthalmologic and systemic conditions. Based on the level of PERG signal, the presence of diabetes appears to be associated with reduced RGC function in GS, implying a detrimental influence of diabetes on the development of glaucoma. Diabetes affects many psychophysical and electrophysiological tests (see ref.¹⁴ for review). The inner retina appears uniquely vulnerable to the metabolic stress of diabetes due to the combination of high metabolic demand and minimal vascular supply that limit its compensatory ability.³⁵ Experimental evidence in rat glaucoma models shows that diabetes may increase the susceptibility of RGCs resulting in increased apoptosis and altered glial reactivity.³⁶ Prospective studies will establish whether excessive PERG alterations in patients with early glaucoma and diabetes, compared to PERG alterations in patients with early glaucoma but without diabetes, predict an increased rate of glaucoma progression.

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Figure 1.

Log PERG amplitude (A, B, C) and PERG phase (D, E, F) as a function of age for different subjects' groups. Normal controls: open circles; Glaucoma suspects: open triangles; Glaucoma suspects with diabetes: open squares. In each panel, linear regression lines and 95% confidence intervals are shown.

Figure 2.

Age-adjusted mean Log PERG amplitude (A) and phase (B) for normal controls (open circles, NC), glaucoma suspects (open triangles, GS) and glaucoma suspects with diabetes (open squares, GSD). Due to the interaction between diabetes and age with amplitude, the size of inter-group differences depends on the age to which the data were adjusted. For analysis, group means were adjusted to the overall average of 62 years.

Table I

Summary of characteristics of patients and eyes.

Mean (SD)	GS N=155	GSD N=18	P-value *
Age (years) [Range]	62.2 (7.8) [50–82]	61.4 (8.8) [50–79]	0.67
Snellen Denominator	20.3 (2.0)	20.9 (2.0)	0.19
SAP-MD (dB)	−0.48 (1.12)	−0.87 (1.56)	0.21
IOP (mm Hg)	15.5 (2.7)	17.6 (3.9)	0.004
CCT (μm)	540.2 (32.1)	536.6 (47.0)	0.72
vC/D	0.54 (0.15)	0.49 (0.12)	0.28

* two-sample 2 tailed Student's t-test