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Beta-zone parapapillary atrophy and multifocal visual evoked potentials in eyes with glaucomatous optic neuropathy

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Abstract

We investigated changes in multifocal visual evoked potential (mfVEP) responses due to beta-zone parapapillary atrophy (β PPA). Patients with glaucomatous optic neuropathy (GON) with or without standard achromatic perimetry (SAP) abnormalities were referred for mfVEP testing during a 2-year period. Eyes with good quality optic disc stereophotographs and reliable SAP results were included. The mfVEP monocular mean latency delays (ms) and amplitudes (SNR) were analyzed. Age, SAP mean deviation (MD), pattern standard deviation (PSD), and spherical equivalent (SE) were analyzed in the multivariate model. Generalized estimated equations were used for comparisons between groups after adjusting for inter-eye associations. Of 394 eyes of 200 patients, 223 (57%) had β PPA. The β PPA eyes were older (59.6 ± 13.7 vs. 56.5 ± 13.7 year, $P = 0.02$), more myopic (-4.0 ± 3.5 vs. -1.3 ± 3.5 D, $P < 0.01$), and had poorer SAP scores (MD: -4.9 ± 5.2 vs. -2.6 ± 5.2 dB, $P < 0.01$; PSD: 4.3 ± 2.9 vs. 2.5 ± 3.0 dB, $P < 0.01$). By univariate analysis, mean latencies were longer in β PPA eyes (6.1 ± 5.3 vs. 4.0 ± 5.5 ms, $P < 0.01$). After adjusting for differences in SE, age, and SAP MD, there was no significant difference between the two groups ($P = 0.09$). β PPA eyes had lower amplitude log SNR (0.49 ± 0.16 vs. 0.56 ± 0.15 , $P < 0.01$), which lost significance ($P = 0.51$) after adjusting for MD and PSD. Although eyes with β PPA had significantly lower amplitudes and prolonged latencies than eyes without β PPA, these differences were attributable to differences in SAP severity, age, and refractive error. Thus, β PPA does not appear to be an independent factor affecting mfVEP responses in eyes with GON.

Keywords

Parapapillary atrophy; Visual evoked potentials; Glaucoma; Perimetry

Introduction

Parapapillary atrophy (PPA) is a prominent glaucoma feature [1, 2] and was initially described over 100 years ago [3–7]. Jonas et al. [4–8] defined two distinct zones of PPA based upon histological findings: (1) beta-zone, which is located adjacent to the optic nerve head and corresponds to an area of absence of retinal pigment epithelium (RPE) and photoreceptors and (2) alpha-zone, corresponding to an outermost zone, contiguous with beta-zone if both are present, characterized histologically by the progressive thinning and loss of the RPE and photoreceptors. Alpha-zone PPA occurs commonly in normal eyes, while beta-zone PPA (β PPA) is more prevalent in eyes with moderate to severe glaucoma [8]. β PPA may increase in size with progressive disc cupping [9–11] and is a risk factor for future visual field (VF) loss [12–17].

The multifocal visual evoked potential (mfVEP) is an objective functional test, which has been used to study glaucomatous loss of function [18–26]. In general, the reduction in amplitude has been used to identify functional loss due to glaucoma [18, 24], although both amplitude and latency may be affected [24, 27, 28]. Previous studies have reported a significant association between β PPA and VF abnormalities using standard achromatic perimetry (SAP) [29, 30]. There is a positive correlation between the area of β PPA and the severity of the VF global indices (mean deviation, MD and the corrected pattern standard deviation, CPSD) [29].

Given that mfVEP responses are affected by the presence and severity of glaucomatous damage and that β PPA is associated with the location and depth of SAP abnormalities, we hypothesized that β PPA is a confounding factor that may affect mfVEP responses. In particular, we hypothesize that (1) mfVEP abnormalities may be correlated with the presence and size of β PPA and (2) β PPA may be an independent factor associated with poorer mfVEP responses (i.e., decreased amplitude and/or increased latency). The present study aimed to test these hypotheses.

Patient and methods

This was a prospective study approved by the New York Eye and Ear Infirmary and Columbia University Institutional Review Boards. Written informed consent was obtained from all subjects, and the study followed the tenets of the Declaration of Helsinki. The patients enrolled were referred for mfVEP testing between August 1, 2007 and July 31, 2009 as part of an ongoing study investigating structural and functional tests in glaucoma patients and suspects.

Glaucoma was defined by the presence of GON associated with abnormal standard achromatic perimetry (SAP, Humphrey Visual Field Analyzer II, 24-2 SITA-Standard strategy, Carl Zeiss Meditec, Inc., Dublin, CA) results. A glaucoma suspect was defined as someone with optic disc abnormalities suggestive of glaucoma, but with a normal SAP result. GON was defined as focal or diffuse neuroretinal rim or nerve fiber layer loss, vertical cup-to-disc ratio >0.6 or an inter-eye asymmetry >0.2 . SAP abnormality was defined as a glaucoma hemifield test (GHT) outside normal limits or a pattern standard deviation (PSD) with $P < 0.05$ on two consecutive exams. All VF tests used for determination of SAP abnormality had reliability indices better than 20% fixation losses, false-positive responses, or false-negative responses.

To determine the presence of β PPA, two glaucoma specialists masked from all clinical data reviewed optic disc stereophotographs. Parapapillary atrophy was defined as an inner crescent of chorioretinal atrophy with visible sclera and choroidal vessels (β PPA) and an outer irregular area of hypo- and hyperpigmentation (alpha-zone PPA) [8]. In this study, only the presence of β PPA in photographs was reported and used in the analyses. Any disagreement between the two reviewers was adjudicated by a third investigator. For photographs in which β PPA was present, the reviewers measured its area in clock hours (1–12), as well as whether the area of largest β PPA was present “superior” or “inferior” to the disc. The location of largest β PPA area was determined using the method described by Park et al. [31]. In particular, the optic disc is bisected by drawing a line between the 2:30 and 8:30 clock hours on the optic nerve head to account for the position of the fovea, which is usually 2–6° below the optic disc. The investigators determined which half of the bisected disc (superior or inferior) was adjacent to the region of largest β PPA. Cases where the location of largest β PPA was inconclusive were called “symmetric”.

The multifocal visual evoked potential technique

The mfVEP stimulus, recording procedures, and analysis have been explained previously [22–28, 32–36] and are described here in brief.

The mfVEP stimulus (Fig. 1) consists of a dartboard array: VERIS Dart Board 60 with Pattern, Electro-diagnostic Imaging, Inc. (EDI, San Mateo, CA). It contains 60 sectors, each with 16 checks: 8 white (200 cd/m²) and 8 black (>1 cd/m²). At the viewing distance of 32 cm, the dartboard subtends 45° in diameter, with the central 12 sectors falling within the central 5.2° (diameter). The stimulus array was presented on a black-and-white monitor (Model M20DCD2RE, Richardson Electronics Ltd, La Fox, IL) and driven at a frame rate of 75 Hz. At each frame change, each sector had a 0.5 probability of reversing in contrast or staying the same, determined by the software's pseudorandom sequence.

Five gold cup electrodes were used; a ground electrode was placed on the forehead, a reference electrode was placed on the inion, another electrode was placed 4 cm above the inion, and an electrode was placed 4 cm lateral and 1 cm above the inion on either side. The midline channel consisted of the reference electrode and the electrode placed directly above the inion. Two other channels consisted of the reference electrode and the electrodes placed 4 cm lateral and one 1 cm above the inion on either side. The records were filtered with a high-frequency cutoff at 100 Hz and a low-frequency cutoff at 3 Hz (one half amplitude; Grass Instruments preamplifier P511J, Quincy, MA) and were sampled at 1,200 Hz (every 0.83 ms). Two monocular 7 min recordings were obtained for each eye, in an ABBA fashion, in a single session, beginning with the right eye, with the non-recording eye occluded.

The mfVEP analysis involved the following. The two runs for each channel were averaged and then further analyzed using a program written in commercial software (MatLab; The MathWorks Inc., Natick, MA). For the monocular analysis, each of the 60 "best" responses (i.e., from the channel with the largest signal-to-noise ratio (SNR)) was compared (cross-correlated) to normative responses generated from a group of 100 healthy control subjects to obtain a difference in latency in milliseconds as previously described [24]. The mean and median difference of these values was calculated for each eye. For the monocular analysis of amplitudes, we obtained the log SNR from the monocular best channel for each eye at each trace as previously described [24].

Examples of mfVEP responses, together with latency and amplitude probability plots obtained from a patient with open-angle glaucoma, are shown in Fig. 2. Each point in the plot corresponds to one of the 60 sectors on the dartboard display. Black points indicate that the response latency was within normal limits, gray points indicate that the response did not meet the minimum SNR criterion for analysis, and colored spots indicate that the response was significantly delayed at either the 5% level (>1.96 SD, desaturated color) or 1% level (>2.58 SD, saturated color). The right eye is indicated by blue and the left eye is indicated by red.

Displayed above each probability plot (see Fig. 2a) is the mean and median of the differences in latency for each of the patient's responses compared to the normative responses. We also calculated the total number of abnormal points (saturated + desaturated squares) for each mfVEP hemifield [33, 34]. The percentage of sectors with abnormal responses (latencies and amplitudes) out of the number of all sectors with measurable

responses was calculated. That is, sectors with responses with SNR below a criterion level were excluded for latency analysis [34, 35].

Examples of monocular amplitude plots are shown in Fig. 2b, comparing the amplitudes of the mfVEP responses in each of the sixty sectors tested in each eye to normal amplitude values obtained from a group of “normal” subjects. Black squares indicate that the amplitude response was within normal limits, gray boxes indicate that the response did not meet the minimum SNR criterion for analysis, and colored boxes indicate that the amplitude response was significantly lower at either the 5% level (> 1.96 SD, desaturated color) or 1% level (> 2.58 SD, saturated color). Similar to latency probability plots, the right eye is indicated by blue and the left eye is indicated by red.

Clinical data

Patient age, gender, ethnicity, and type of glaucoma were recorded. Mean deviation (MD) and pattern standard deviation (PSD) from the SAP VF tests performed closest to the date of the mfVEP test were also analyzed. Refractive error spherical equivalent (SE) was recorded.

Statistical analysis

T tests for independent samples were used to determine whether there were differences in clinical characteristics, as well as mean amplitude and latency values between eyes with and without β PPA. Linear regression analysis was performed to test the association between β PPA and mfVEP responses (amplitude and latency). A generalized linear model (analysis of covariance, ANCOVA) was used to adjust for potential differences between groups that could also affect mfVEP latency. To determine whether β PPA width measured in clock hours was associated with disease severity and mfVEP responses, we split the eyes into groups based on number of PPA clock hours (1–3, 4–5, 6–12) and constructed linear regression models (GEE) with the 1–3 clock hours group as the reference group. Thus, each β PPA clock hour group is interpreted as the average increase/decrease in the outcome (MD, PSD, mfVEP amplitude and latency), compared to the group with only 1–3 clock hours β PPA. If both eyes of the same subject met our inclusion criteria, both were entered in the analyses and a generalized estimating equation (GEE) was used to adjust for potential inter-eye associations. The agreement between the hemifield with the greatest mfVEP abnormality was compared to the hemidisc with the largest β PPA using a kappa statistic.

Statistical significance was defined as $P < 0.05$, and all tests were two-sided. Computerized analyses were performed using Stata 11/IC (StataCorp LP, College Station, TX, USA).

Results

The average $\pm$ SD time interval between the mfVEP and SAP VF tests was 4.5 ± 6 months. Of the 394 eyes (200 patients) enrolled, 223 (56.6%) eyes had β PPA based on photograph review. Of those, 114 (51.1%) had more β PPA inferiorly and 35 (15.7%) had symmetric β PPA. Based upon the monocular analysis, a slightly larger percentage of eyes showed more sectors with reduced mfVEP amplitudes in the superior hemifield (38%) compared to the inferior field (28%), with 34% having an equal number in both hemifields. A larger percentage of eyes showed more sectors with increased latencies in the inferior hemifield

(56%) compared to the superior hemifield (35%), with 9% of the eyes having an equal number in both hemifields. Regarding VF results in patients with glaucoma, the superior SAP hemifield had more abnormal points at $P < 0.5\%$ in the pattern deviation plot than did the inferior hemifield (6.4 ± 5.0 vs. 4.6 ± 3.8 , $P = 0.02$, paired t test).

Table 1 compares clinical data between eyes with and without β PPA. The β PPA eyes (56%) were older (59 ± 13 vs. 56 ± 13 year, $P = 0.02$), more myopic (-4 ± 3 vs. -1 ± 2 D, $P < 0.01$), and had worse VF indices (MD: -5 ± 5 vs. -2 ± 3 dB, $P < 0.01$; PSD: 4 ± 3 vs. 2 ± 2 dB, $P < 0.01$).

Univariate analysis revealed lower amplitudes in β PPA eyes compared to eyes without β PPA (log SNR 0.49 ± 0.16 vs. 0.56 ± 0.15 , $P < 0.01$). In the multivariate analysis, after adjusting for differences in MD and PSD, there was no significant difference between the two groups ($P = 0.51$).

Univariate analysis revealed that mean latencies were longer in β PPA eyes than those eyes without β PPA (6.1 ± 5.3 vs. 4.0 ± 5.5 ms, $P < 0.01$). In the multivariate analysis, after adjusting for differences in refractive error, age, and VF MD, there was no significant difference between the two groups ($P = 0.09$). When refractive error was excluded from the multivariate model, the presence of β PPA retained statistical significance ($P = 0.009$) (Table 2).

For discs with β PPA predominant in one region (i.e., superior or inferior, not symmetric), we evaluated whether the hemidisc with more extensive β PPA (superior or inferior) predicted the hemifield with the greater number of sectors showing increased latency. The kappa test demonstrated that hemidiscs with larger β PPA area showed poor agreement with hemifields with increased latency (kappa = -0.03). Hemidiscs with larger β PPA area showed better agreement with hemifields with reduced amplitude (kappa = 0.16) (Table 3). β PPA width in clock hours significantly correlated with VF severity (MD and PSD) and mfVEP latency (mean and median values), even after adjusting for age and refractive error (Table 4).

Discussion

We hypothesized a possible association between abnormal mfVEP responses (amplitude and latency) and presence of β PPA and that this association may be an independent factor that affects the interpretation of mfVEP results. Even though these hypotheses were partly confirmed in our study, the inclusion of other clinical covariates (refractive error, VF severity, and age) in the model revealed that β PPA is not independently associated with latency and amplitude abnormalities. This was also confirmed in our intraeye analysis, looking at hemifields/hemidiscs in the same eye, which has the advantage of removing the confounding effect of ocular (disease severity, refractive error) and systemic (age) variables in the analyses.

The association between β PPA and myopia, VF severity, and aging has been previously described [8, 37–39] and was confirmed in our study population. Kawano et al. [37] showed that β PPA area as measured with confocal laser ophthalmoscopy (CLO) significantly

correlated with axial length. These findings were further confirmed by Xu et al. [38, 39] in a population-based study showing that eyes with high myopia had larger β PPA. The strong association between myopia and PPA was particularly relevant to our findings, as the removal of refractive error from the multivariate model resulted in a significant association between β PPA and increased latency/reduced amplitudes.

Also, the association between aging and the prevalence, incidence, and risk of glaucoma progression has been reported [40–43]. Likewise, the area of β PPA measured morphometrically is significantly correlated with glaucoma patients' age [44]. By examining histological specimens, Curcio et al. [45] considered PPA an age-related degeneration of the RPE and Bruch's membrane complex resembling that found in age-related macular degeneration. This suggests that β PPA may be a surrogate feature of the aging optic nerve, which may thus increase its susceptibility to glaucomatous damage and progression. Burgoyne and Downs [46] have proposed that the susceptibility of the optic nerve to glaucomatous injury may be largely explained by progressive biomechanical and histological changes of the optic nerve complex, which are due to a combination of aging and IOP-related stress.

In summary, when interpreting results of mfVEP in eyes with β PPA, one should not attribute the observed amplitude and latency abnormalities exclusively to the presence of β PPA, but rather to myopia, older age, and severity of VF damage, which usually follow β PPA. Therefore, β PPA is not an independent factor associated with abnormal mfVEP responses in eyes with GON.

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Fig. 1.
The mfVEP stimulus (VERIS Dart Board 60 with Pattern, Electro-diagnostic Imaging, Inc.
(EDI, San Mateo, CA))

Fig. 2.

a mfVEP monocular latency plots. In the latency probability plots, each tested sector of the retina tested is represented by a *dot*. *Black dots* represent sectors with normal latencies. *Gray dots* represent sectors with responses too small to accurately measure the latency. Colored sectors (*blue* in OD plot, *red* in OS plot) represent sectors with increased latencies significant at either the 5% (>1.96 SD, desaturated color) or 1% (>2.58 SD, saturated color) level compared to normal values. For example, the inferior hemifield OS has six sectors with increased latency, five of which are significant at the 5% level (desaturated, i.e., *pink*

color), and one of which is significant at the 1% level (saturated, i.e., *red* color). In this same hemifield, there are five *gray dots* (inadequate data) and 19 *black dots* (normal latencies). **b** mfVEP monocular amplitude plots. The superior hemifield OS (*red*) has seven sectors with decreased amplitude, five of which are significant at the 5% level, and two of which are significant at the 1% level. In this same hemifield, there are 23 *black boxes* (normal amplitudes)

Table 1Comparison of clinical data in eyes with and without β PPA

Variables	Eyes with β PPA (<i>n</i> = 223)	Eyes without β PPA (<i>n</i> = 171)	<i>P</i> value
Age (years)	59.7 $\pm$ 13.3	56.5 $\pm$ 14.4	<i>P</i> = 0.02
Spherical equivalent (diopters)	-4.0 $\pm$ 4.1	-1.3 $\pm$ 2.9	<i>P</i> < 0.01
Visual field mean deviation (dB)	-4.9 $\pm$ 5.9	-2.6 $\pm$ 4.3	<i>P</i> < 0.01
Visual field pattern standard deviation (dB)	4.4 $\pm$ 3.7	2.5 $\pm$ 2.0	<i>P</i> < 0.01
Mean latency (ms)	6.1 $\pm$ 5.3	4.0 $\pm$ 5.5	<i>P</i> < 0.01
Mean amplitude (log SNR)	0.49 $\pm$ 0.16	0.56 $\pm$ 0.15	<i>P</i> < 0.01

Values are shown as mean $\pm$ SD

Table 2

Generalized estimating equation (GEE) between multifocal visual evoked potentials mean latencies and different variables; A) multivariate analysis including all covariates in the final model, B) multivariate analysis including all covariates except for the spherical equivalent

	Outcome: mean latency		
	β	95% CI	P value
A)			
PPA (0/1)	0.96	-0.39, 2.31	0.16
MD (dB)	-0.05	-0.29, 0.18	0.67
PSD (dB)	-0.11	-0.46, 0.24	0.53
Spherical equivalent (diopters)	-0.27	-0.46, -0.09	0.004
Age (years)	0.15	0.10, 0.20	<0.001
B)			
PPA (0/1)	1.78	0.44, 3.11	0.009
MD (dB)	-0.07	-0.30, 0.17	0.58
PSD (dB)	-0.13	-0.48, 0.22	0.48
Age (years)	0.12	0.07, 0.18	<0.001

Table 3

Comparison between: A) hemidisc with greater β PPA and hemifield with greater mfVEP latency; B) hemidisc with greater β PPA and hemifield with smaller mfVEP amplitude

β PPA	Sectors with Increased mfVEP Latency		Total
	Superior hemifield	Inferior hemifield	
A) ^a			
Larger in inferior hemidisc	23	67	90
Larger in superior hemidisc	9	21	30
Total	32	88	120
B) ^b			
Larger in inferior hemidisc	43	29	72
Larger in superior hemidisc	11	16	27
Total	54	45	99

^a Kappa = -0.03; Agreement = 36.67%; Expected agreement = 38.33%; Standard error = 0.06; Z = -0.48; P value = 0.68

^b Kappa = 0.16; Agreement = 59.60%; Expected agreement = 52.07%; Standard error = 0.09; Z = 1.69; P value = 0.05

Association between β PPA clock hours (total area), visual field severity, and mfVEP latency and amplitude; A) simple model with β PPA as the only predictor of outcome; B) multivariable model adjusting for age and spherical equivalent

Table 4

PPA clock hours ^a						
4-5 clock hours (<i>n</i> = 76)			6-12 clock hours (<i>n</i> = 42)			
	β	95% CI	<i>P</i> value	β	95% CI	<i>P</i> value
A)						
MD (dB)	-2.33	-4.25, -0.41	0.02	-2.63	-5.31, 0.06	0.06
PSD (dB)	1.73	0.67, 2.79	0.001	1.76	0.23, 3.28	0.02
Mean latency	1.70	-0.44, 3.82	0.12	4.22	1.73, 6.71	0.001
Median latency	2.01	0.06, 3.96	0.43	4.32	1.82, 6.82	0.001
Monocular amplitude	-0.08	-0.15, -0.01	0.02	-0.11	-0.19, -0.04	0.004
B)						
MD (dB)	-2.67	-4.52, -0.81	0.005	-3.27	-5.97, -0.56	0.02
PSD (dB)	2.03	0.93, 3.13	<0.001	2.35	0.52, 4.17	0.01
Mean latency	0.96	-0.85, 2.76	0.30	2.90	0.87, 4.93	0.005
Median latency	1.32	-0.40, 3.05	0.13	3.10	0.72, 5.48	0.01
Monocular amplitude	-0.09	-0.16, -0.02	0.01	-0.13	-0.21, -0.04	0.003

^a 1–3 clock hours are reference category