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A method to detect progression of glaucoma using the multifocal visual evoked potential technique

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Abstract

Purpose—To describe a method for monitoring progression of glaucoma using the multifocal visual evoked potential (mfVEP) technique.

Methods—Eighty-seven patients diagnosed with open-angle glaucoma were divided into two groups. Group I, comprised 43 patients who had a repeat mfVEP test within 50 days (mean 0.9 ± 0.5 months), and group II, 44 patients who had a repeat test after at least 6 months (mean 20.7 ± 9.7 months). Monocular mfVEPs were obtained using a 60-sector pattern reversal dartboard display. Monocular and interocular analyses were performed. Data from the two visits were compared. The total number of abnormal test points with $P < 5\%$ within the visual field (total scores) and number of abnormal test points within a cluster (cluster size) were calculated. Data for group I provided a measure of test–retest variability independent of disease progression. Data for group II provided a possible measure of progression.

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Results—The difference in the total scores for group II between visit 1 and visit 2 for the interocular and monocular comparison was significant ($P < 0.05$) as was the difference in cluster size for the interocular comparison ($P < 0.05$). Group I did not show a significant change in either total score or cluster size.

Conclusion—The change in the total score and cluster size over time provides a possible method for assessing progression of glaucoma with the mfVEP technique.

Keywords

Multifocal visual evoked potentials; Visual field progression; Repeat reliability

Introduction

Determining progression remains one of the most important, but challenging aspects of glaucoma management. Documented progression of glaucomatous optic neuropathy not only results in re-evaluation of visual prognosis, but may also result in modification of treatment strategies. Progression can be assessed using both structural and functional tests. Examples of structural tests include imaging modalities that have been designed to detect morphologic glaucomatous abnormalities [e.g., confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), optical coherence tomography (OCT), and the retinal thickness analyzer (RTA)]. These techniques allow for quantitative measurements of optic disc and retinal nerve fiber layer and may help improve our ability to detect progression [1–7]. With regard to functional tests for assessing progression the current gold standard is standard automated perimetry (SAP). The drawback of SAP is that glaucomatous changes may only be detected after extensive optic disk damage has occurred [8–11]. Histological studies have demonstrated that retinal ganglion cell loss can be high (25–50%) prior to detection of visual field deficits [8]. In addition, because of high test–retest variability, particularly in areas of visual field loss it is very difficult to determine whether there is progression [12–14].

One of the newer tests of visual function that appears to be promising is the multifocal visual evoked potential (mfVEP) technique. It is an objective visual field test and therefore unlike SAP does not depend on the subject's response criterion. In addition, recent studies have shown that the inter-test variability is less than or equal to that of SAP [15–17]. Not only has its use in a clinical setting for detecting glaucomatous deficits been demonstrated [18–21], but studies have also reported that the mfVEP can detect visual field changes not seen with SAP [22–25]. However, there is little if any information, regarding its use for monitoring progression of glaucoma. As its use in the clinic is growing, it is important to design a method for monitoring progression of mfVEP deficits. The purpose of this study is to describe a method that can be used to distinguish between inter-test variability and progression.

Patients and methods

Subjects

The database for glaucoma patients recruited from the private clinical practice of two of the authors RR and JML over the last 4.5 years was searched. Eighty-seven patients, aged 25–80 years (mean 63 ± 12.1 years) with a diagnosis of open-angle glaucoma who met the inclusion criteria listed below were enrolled in the study. All subjects gave written informed consent before enrollment in the study. The protocol for this study was approved by the committee of the Institutional Board of Research Associates of Columbia University and procedures followed the tenets of Declaration of Helsinki.

The inclusion criteria were as follows: open-angle glaucoma with glaucomatous optic neuropathy in at least one eye, defined as a cup-disc ratio ≥ 0.6 , cup-disc asymmetry between eyes ≥ 0.2 , rim thinning, notching, excavation, and/or retinal nerve fiber layer defects; a corresponding repeatable, reliable visual field defect on SAP (defined as pattern standard deviation $< 5\%$ and/or glaucoma hemifield test outside normal limits); and an open anterior chamber angle by gonioscopy. In addition, the following were also required: best corrected visual acuity of at least 20/40, no significant opacities of the media, pupil diameter of ≥ 3 mm, refractive error not exceeding ± 6 diopters or two diopters cylinder and no history or evidence of other ocular/neurologic disease. If both eyes of patients were eligible for the study, the results of the mfVEP from one eye were randomly selected for statistical analysis. Patients were divided into two groups: group I, included patients who had a repeat mfVEP test less than 50 days after the initial test, and group II patients who had a repeat test more than 6 months after the initial test.

Multifocal visual evoked potential (mfVEP) technique

The mfVEPs were obtained from each eye using VERIS 4.3 software (Electro-Diagnostic Imaging, San Mateo, CA). The stimulus is shown in Fig. 1. The dartboard pattern consisted of 60 sectors, each with a checkerboard pattern of 16 checks, eight white (200 cd/m^2) and eight black (3 cd/m^2). The sectors were cortically scaled with eccentricity. The entire display subtended a diameter of 44.5° , and the central 12 sectors fell within a diameter of 5.2° of the foveal center. The stimulus array was displayed on a black- and-white monitor driven at a frame rate of 75 Hz. The 16-element checkerboard of each sector had a probability of 0.5 of reversing on any pair of frame changes, and the pattern of reversals for each sector followed a pseudorandom m-sequence. To ensure that any changes in mfVEP responses over time could not be attributed to changes in the luminance of the dartboard stimulus, the stimulus monitor was calibrated at monthly intervals.

Three channels of recording were obtained with gold cup electrodes. The electrodes for the midline channel were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). The same ground and reference were used for the other two channels, but the active electrode was placed 1 cm up and 4 cm lateral to the inion on either side. By subtracting different combinations of pairs of channels, three additional derived channels were obtained, resulting in effectively six channels of recording representing the six possible pairs of the four recording electrodes [21,26].

Electrical impedance of $\leq 5 \text{ K}$ was achieved for all subjects. The VEP records were amplified with the high and low frequency cutoffs set at 3 and 100 Hz (preamplifier P511J; Grass Instrument Co, Quincy, MA), and were sampled at 1,200 Hz (every 0.83 ms). The m-sequence was $2^{15}-1$ steps and approximately 7 min were required to complete the recording. Two 7-min recordings were obtained during monocular stimulation of each eye. Both eyes were tested twice in ABBA fashion. A refractor/camera (Electro-Diagnostic Imaging) was used to refract the subjects' eyes and monitor eye position and fixation stability. Subjects were asked to fixate on the center of a black "X" located in the center of the display. Segments contaminated by eye movements, loss of fixation, and/or noise were discarded and rerecorded.

Response analysis

After exporting mfVEP responses from VERIS for each channel, the two recordings from each eye were averaged and analyzed, using programs written in MATLAB (Mathworks Inc, MA). These analyses were done after the mfVEPs were low-pass filtered using a Fourier transform technique with a sharp cutoff at 35 Hz. Custom software produced monocular and interocular measures of amplitude. For the monocular measures, amplitude

measures were compared to monocular recordings from 100 normal control subjects [27]. For the interocular measures, the analyses compared the two eyes of a patient and related the resulting measures to a similar analysis of the control subjects. Briefly, root-mean-square (RMS) amplitudes were calculated for each mfVEP response over a 45–150 ms time interval. The signal-to-noise ratio (SNR) was also measured for each response. The SNR was obtained by dividing the RMS amplitude of the response, i.e., the signal, by the RMS of the noise. Noise was defined as the mean of all 60 RMS amplitudes over a 325–430 ms time interval for a given eye. [21,28] Analyses were performed on the “best” responses from the six channels. The arrays of “best” responses were derived as follows: for the interocular analysis at each of the 60 locations, the “best” response was the one with the largest SNR; it was selected from 12 possible responses (6 channels $\times$ 2 eyes). The response from the other eye at the same location and from the same channel contributed to the pair of responses. For the monocular analysis the “best” response was selected for each eye at each location; it was defined as the response with the largest SNR among the six channels. The 60 responses selected for each eye defined the “best” array for that eye. [21,26,28].

Interocular and monocular mfVEP probability plots

Probability plots, resembling the probability plots for the Humphrey visual field (HVF) test, were produced by coding whether the responses were significantly different from those of healthy controls [21,29]. Figure 2a, b show monocular mfVEP probability plots for the left and right eye of a patient. Figure 2c shows an interocular probability plot for another patient. The mfVEP responses for the right and left eye of this patient are shown in Fig. 2d. For the probability plots each symbol is in the center of a sector of the mfVEP display shown in Fig. 1. In the case of the monocular plots, a black square indicates that there is no significant difference between the patient’s response amplitudes and those of normal subjects and for the interocular plot a black square indicates that there is no significant difference between the two eyes of the patient. The colored squares indicate that there is a significant difference exceeding the 5% (desaturated) or 1% (saturated) level. The color denotes whether the right (blue) or left (red) eye had the smaller response. For the interocular plot, a gray square indicates that the responses from both eyes were too small to allow for a comparison.

Method for determining progression

From the 60 locations of the mfVEP probability plots (interocular and monocular plots), the total number of test points with significance exceeding the 5% level (total score) and the number of abnormal test points within a cluster (cluster size) were calculated for each visit. A cluster was defined as: (1) two contiguous points exceeding the 1% significance level or (2) three contiguous points exceeding 5% with one exceeding 1%, (3) the contiguous points were within a hemifield, and (4) a given cluster was within the same hemifield for visit 1 and visit 2. The total score and cluster size (calculated for both hemifields) between visit 1 and visit 2 were compared for both groups of patients. We assume that data for group I provide a measure of test–retest variability independent of disease progression. Data for group II provide a possible measure of progression when compared to data from group I.

Data analysis

To investigate test–retest variability and possible progression, scatter plots comparing total score and cluster size for visit 1 versus visit 2 and Bland–Altman plots of the difference between these measures versus the average value for visit 1 and visit 2 were created [30]. The differences in total score and cluster size between tests were evaluated by paired *t*-tests. The two-sample *t*-test was used to compare the mean differences between group I and group II for the total score and cluster size. The number of eyes that showed an increase, decrease, and no change in the total score and cluster size was also calculated.

Results

Eighty-seven patients with open-angle glaucoma were enrolled in this study. Group I had 43 patients and group II 44 patients. Baseline demographic data for both groups of patients are shown in Table 1. The mean interval between the mfVEP tests for group I was 1 month and for group II 20.7 months. There was no significant difference for age, HVF mean deviation, and pattern standard deviation between patients in group I and group II at baseline. However, there was a slightly greater number of males in group II.

Scatter plots comparing the total scores for visit 2 to those for visit 1 for interocular and monocular analyses are shown in Fig. 3a, b, respectively. The results for group I are represented by the filled circles (left hand panels) and for group II by filled triangles (right hand panels). Scatter plots comparing cluster size for visit 2 to those for visit 1 for interocular and monocular analyses are shown in Fig. 4a, b, respectively.

While the agreement between the results of the two tests was good for both groups, the correlations for the total scores for the interocular and monocular comparison for visit 1 versus visit 2 were higher for group I ($r = 0.94, 0.86$) than for group II ($r = 0.83, 0.83$). The correlations for cluster size were also higher for group I ($r = 0.93, 0.84$) than for group II ($r = 0.85, 0.81$). In addition, the relative coefficients of variation [$rCV = \text{abs}(\text{standard deviation}/\text{mean} \times 100)$] were calculated. With the exception of the rCV values for the total score for the interocular comparison ($rCV = 18\%$ for both group I and group II), the values were higher for group II than group I. For example, the rCV for total score for the monocular comparison for group II was 22% compared to 15% for group I, for cluster size it was 25% for the interocular comparison compared to 21% for group I, and 33% for the monocular comparison compared to 22% for group I. Presumably, the higher rCV values for group II were influenced by both repeat variability and progression. The Bland–Altman plots in Fig. 5, showing the relationship between the differences in total score for the two visits and the average total score, provide further indication of progression for group II. The results for group I are represented by the filled circles (left hand panels) and for group II by the filled triangles (right hand panels). The solid horizontal line represents the mean difference in the total score for the interocular analysis (Fig. 5a) and for the monocular analysis (Fig. 5b); the dashed horizontal lines represent ± 1.96 standard deviations. For group II the mean difference for the interocular analysis was 2.32 compared to -0.26 for group I, and for the monocular analysis it was 2.02 for group II compared to 0.19 for group I, i.e., the total score was increased for group II on visit 2. The Bland–Altman plots in Fig. 6, showing the relationship between the difference in cluster size for the two visits and the average cluster size, also suggest progression for group II. The mean difference for the interocular analysis for group II was 1.89 compared to -0.28 for group I (Fig. 6a), and the mean difference for the monocular analysis was 1.36 compared to 0.19 for group I (Fig. 6b).

To further test for progression, the changes in total score and cluster size were analyzed. Twenty-six out of 44 eyes in group II showed an increase in total score on the interocular comparison between tests as compared to only 19 out of 43 eyes in group I; for 10 eyes in group II, the increase exceeded the 95% confidence interval ($+1.96SDs$) for group I (see dashed horizontal line Fig. 5a). For the monocular comparison, the equivalent numbers were 27 out of 44 eyes (group II) and 24 out of 43 eyes (group I); for three eyes in group II, the increase exceeded the 95% confidence interval for group I (see Fig. 5b). The difference in the total score between visit 1 and visit 2 for the interocular and monocular comparison was statistically significant for group II ($P = 0.01, 0.03$, respectively), but not for group I (Table 2).

To evaluate cluster size as a possible measure of progression, we compared the change in cluster size between tests. Twenty-five out of 44 eyes in group II showed an increase in cluster size on the interocular comparison as compared to only 12 out of 43 eyes in group I; for seven eyes in group II the increase exceeded the 95% confidence interval for group I (see Fig. 6a). For the monocular comparison, the equivalent numbers were 21 out of 44 eyes (group II) and 22 out of 43 eyes (group I); for three eyes in group II, the increase exceeded the 95% confidence interval for group I (see Fig. 6b). The difference was statistically significant, but only for the interocular analysis of group II ($P = 0.04$). The number of eyes that showed an increase in cluster size for group II was greater than for group I for the interocular analysis. The mean differences between visit 1 and visit 2 for the total score and cluster size is also shown in Table 2. A comparison of these mean differences between group I and group II using the two-samples t -test showed they were significantly different for the interocular analysis ($P = 0.01$ and 0.04 , respectively).

Additional support for progression for group II eyes comes from a comparison of baseline HVF mean deviation and pattern standard deviation values to those obtained within ± 1 month of visit 2 for patients in group II. The mean deviation changed from -7.8 to minus 9.4 dB, and the pattern standard deviation from 8.4 to 8.8 dB. Paired t -tests showed that these changes were statistically significant ($P = 0.0001$, 0.05 , respectively).

Discussion

Determining progression is crucial for effective clinical management of patients with glaucoma. Delays in recognizing progression may result in significant visual loss. A number of approaches for identifying progression have been proposed for SAP, the current gold standard for monitoring changes in visual function. These include clinical judgment; classification and scoring systems for visual field defects such as the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Initial Glaucoma Treatment (CIGTS); trend analysis, i.e., the “Change analysis” option in the HVF that performs linear regression of the mean deviation (MD), and event analysis, i.e., the Glaucoma Change Probability (GCP) that examines changes on a point-by-point basis by calculating the difference in point-wise total deviation at each test location compared to baseline [31]. However, it is evident from the literature that no consensus exists regarding the best method for differentiating whether a visual field deficit is stable or progressing. The problem is the high variability of SAP, particularly in areas of visual field loss; the test–retest variability increases in areas with decreasing visual field sensitivity [32–35].

The mfVEP is a promising alternative technique for visual field testing in glaucoma [18–21]. It has a high sensitivity and specificity for detection of deficits [15,27,36–38]. However, there is little if any information regarding its use in monitoring progression. One of the requirements for reliable identification of progression is that the test shows good repeatability. The results we obtained on group I of patients demonstrate that the mfVEP has good repeat reliability. This is in agreement with previous studies that have compared the repeatability of the mfVEP to SAP. Two studies, one by Chen et al. [15] and the other by Fortune et al. [16], reported that repeatability of the mfVEP was slightly better than SAP. In the study by Chen et al. the repeat reliability of the mfVEP was evaluated within a day and across days (2–12 weeks) in normal and glaucomatous eyes and was found to be better than SAP [15]. Fortune et al. reported a similar finding in 50 normal controls who had repeat testing after 1 year [16]. The results of these studies imply that progression should be easier to detect with the mfVEP than with SAP as inter-test variability was slightly better.

In the current study, we assumed that group I data would provide a measure of test–retest variability, independent of disease progression, whereas the group II data would provide a

measure of progression. The methods we used to analyze the mfVEP results were similar to those used to assess visual field progression with SAP, i.e., inspection of total deviation and pattern deviation probability plots. In this study, we calculated the total number of test points with *P*-values exceeding 5% (total score), and the number of abnormal test points within a significant cluster (cluster size) on both the interocular and monocular probability plots. We analyzed both the interocular and monocular probability plots as a shortcoming of the interocular comparison is that it will miss damage located in corresponding field locations. In other words, defects in the same part of the field in both eyes (e.g., inferotemporal in one eye and inferonasal in the other eye) will not be detected. The two methods, total score and cluster size, showed good repeat reliability for the mfVEP. However, the agreement was better for group I than for group II eyes and with the exception of the rCV values for the total score for the interocular comparison the rCV values for group II were higher suggesting progression for the latter group. Our results for group I using the total score method resemble those obtained by Bjerre et al. [39]. They compared the number of defective mfVEP test locations within an interval of 1 month in 74 patients with varying degrees of visual field defects and reported that the inter-session repeatability was “good” [40].

With regard to the results of our method for monitoring progression, we found that the mean difference in both total score and cluster size was greater for group II than group I. This was true for interocular and monocular comparisons. These results suggest that we may be detecting progression of visual field deficits in group II eyes. Our findings are similar to an increase in mean deviation and pattern standard deviation in SAP in patients with glaucomatous visual field progression [40]. In fact when we compared baseline HVF mean deviation and pattern standard deviation values to those obtained within a month of visit 2 for group II eyes, we found significant changes in both values indicating progression of visual field deficits.

Of the two methods for determining progression, the total score has one drawback; it does not take the spatial contiguity of abnormal points into account. An increase in the number of abnormal points may not necessarily reflect progression of a visual field deficit in every patient. Fortune et al. demonstrated that abnormal points and clusters of points could occur repeatedly even in some normal eyes, but they were unlikely to occur in the same locations [16]. Therefore our second method, the calculation of cluster size, may be a more specific indicator of progression. An increase in cluster size from visit 1 to visit 2 means that the visual field defect has expanded and/or a new visual field defect has occurred. Although theoretically an increase in cluster size seems to be more specific for detecting visual field progression than the total score approach, our results showed a similar trend for both methods and both appear to provide information regarding glaucomatous visual field progression.

A possible limitation of the mfVEP technique for detecting glaucomatous visual field progression is that there is evidence that progression is more likely to occur as a deepening or expansion of an existing defect than the development of a new defect [41]. The detection of progression in the form of a deepening of a defect is a problem for the mfVEP technique. The mfVEP has a relatively narrow dynamic range [21,42] that may limit the detection of a deepening of a visual field defect especially in the later or advanced stages of glaucoma. However, the finding of good repeatability of the mfVEP and our finding of a difference in cluster size and total score between group I and group II suggest that the mfVEP will be a useful tool for monitoring progression, at least in the earlier stages of the disease process. It should be noted that a drawback of this study is that the decision to place patients in group I versus group II was based simply on the duration between mfVEP tests and not on any clinical evidence of progression. Ideally we would have obtained additional repeat data on

the group I and II patients, at <50 days for the group I patients and within a month of visit 2 for the group II patients. We would also have added a “gold standard”, for example, a structural measure, against which we could assess whether progression had occurred. Despite these limitations we were able to detect a difference between the two groups, and this suggests that our method for detecting progression would be more powerful in eyes that are progressing by standard clinical criteria. This has implications not only for patient care, but for neuro-protection research as well. Of course, it is necessary to confirm that we are indeed detecting progression by continuing to follow the group I and II patients, repeating the mfVEP and comparing the results to SAP and structural tests.

In summary, we have presented a method that may be useful in monitoring the progression of functional deficits in glaucoma using the mfVEP. It has the advantage that both total score and cluster size are easily calculated based on probability plots of the mfVEP and they can be directly compared to global indices of SAP. Thus, clinicians can use the data from the probability plots for additional information for assessing glaucoma progression.

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Fig. 1.

The multifocal visual evoked potential (mfVEP) stimulus display: the dartboard pattern consists of 60 sectors, each with a checkerboard pattern of 16 checks, eight white (200 cd/m²) and eight black (3 cd/m²). The sectors are cortically scaled with eccentricity, and the entire display has a diameter of 44.5°

Fig. 2.

a Monocular multifocal visual evoked potential (mfVEP) probability plot for the left eye of a patient with open-angle glaucoma. The red squares indicate locations where the responses for the left eye are smaller than normal values for the left eye **b**. A mfVEP probability plot for the right eye of the same patient. The blue squares indicate locations where the responses for the right eye are smaller than normal values **c**. An example of an interocular probability plot for another patient. For the interocular plot the blue squares indicate locations where the response for the right eye was significantly decreased compared to the left eye at either the 5% (light blue) or 1% (dark blue) level **d**. The mfVEP responses obtained from the left (red) and right (blue) eyes of the patient. The responses within the ellipse are significantly smaller in the right eye

Fig. 3.

A comparison of the total score for visit 2 versus visit 1 for group I and group II. The results for the interocular comparisons are shown in panel **A** and for the monocular comparisons in panel **B**

Fig. 4.

A comparison of cluster size for visit 2 versus visit 1 for group I and group II. The results for the interocular comparisons are shown in panel **A** and for the monocular comparisons in panel **B**

Fig. 5. Bland–Altman plots of the differences in total scores for visit 1 and visit 2 versus the average of the total scores for both visits for group I and group II. The results for the interocular comparisons are shown in panel **A** and for the monocular comparisons in panel **B**

Fig. 6. Bland–Altman plots of the differences in cluster size for visit 1 and visit 2 versus the average of the cluster size for both visits for group I and group II. The results for the interocular comparisons are shown in panel **A** and for the monocular comparisons in panel **B**

Table 1

Baseline demographic data

	Group I <i>n</i> = 43	Group II <i>n</i> = 44	<i>P</i> -values ^a
Mean age, years (SD)	63 (12.97)	63 (11.34)	0.71
Gender			
Male	15	20	
Female	28	24	
Interval between mfVEP tests (months)			
Mean (SD)	0.9 (0.5)	20.7 (9.7)	< 0.0001
Range	0.1–1.7	6.2–44.9	
Baseline HVF 24-2 SITA standard			
Mean MD (SD)	−7.88 (5.26)	−7.80 (6.39)	0.95
Mean PSD (SD)	8.63 (3.68)	8.40 (4.21)	0.79

^aTwo-sample *t*-test

Table 2

Mean differences between the two groups for total score and cluster size

Criteria	N (eyes)	Mean Δ (V2 – V1) ^a	95% CI	SD	P-values ^b
<i>Total score (points)</i>					
Interocular comparison					
Group I	43	-0.26	(-7.17, 6.66)	3.53	0.64
Group II	44	2.32	(-9.09, 13.73)	5.82	0.01
Monocular comparison					
Group I	43	0.19	(-10.76, 11.13)	5.59	0.83
Group II	44	2.02	(-10.02, 14.06)	6.14	0.03
<i>Cluster size (points)</i>					
Interocular comparison					
Group I	43	-0.28	(-8.01, 7.45)	3.94	0.64
Group II	44	1.89	(-9.51, 13.29)	5.82	0.04
Monocular comparison					
Group I	43	0.19	(-12.00, 12.37)	6.22	0.85
Group II	44	1.36	(-11.97, 14.70)	6.80	0.19

^aMean difference of total score and cluster size between visit 1 and visit 2, (V1, visit 1; V2, visit 2). 95% CI, confidence interval; SD, standard deviation^bPaired t-test