The Effects of Optic Disc Drusen on the Latency of the Pattern-Reversal Checkerboard and Multifocal Visual Evoked Potentials

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PURPOSE. To determine the effect of optic disc drusen on the latency of the pattern-reversal checkerboard visual evoked potentials (VEPs) and multifocal (mf)VEPs and to better understand the pathophysiology of the condition.

METHODS. Eighteen eyes with optic disc drusen (10 patients) and 38 control eyes (19 subjects) underwent VEP, mfVEP, and visual field testing. Only one eye of each individual, the one with the more affected visual field, was used in the analyses. The VEPs were recorded with a 15′ and 60′ reversing checkerboard pattern, and the mfVEPs were elicited by a 60-sector dartboard display.

RESULTS. Unlike the VEP results, the mfVEP revealed a significant increase in the average monocular latency of the optic disc drusen group compared with that of the control group. The average mfVEP relative latency for the optic disc drusen group (4.1 ms) was greater than that (0.8 ms) in the control group. For monocular and interocular analyses, the average percentage of points delayed in the drusen group was significantly greater than that in the control group.

CONCLUSIONS. Optic disc drusen produced significant latency delays on the mfVEP test but not on the VEP test, presumably due to the mfVEP's ability to detect the effects of local changes. The results are consistent with the hypothesis that local mechanical compression by optic disc drusen leads to abnormal retinal ganglion cell activity. (*Invest Ophthalmol Vis Sci.* 2009; 50:4199–4204) DOI:10.1167/iovs.08-2887

The pathophysiology of visual field loss related to optic disc drusen, a condition believed to develop early in life, is not clearly understood. Some evidence suggests that patients experience field loss during the period when optic disc drusen become more superficial, prominent, and visible.[1,2] Visible superficial drusen, in contrast to buried drusen, are associated with a greater prevalence of field loss.[2] These findings support the hypothesis that enlarging optic disc drusen may damage nerve fibers by direct mechanical compression and/or by compressing surrounding vessels, producing acute or chronic ischemia.[1] It has also been suggested that development of optic disc drusen results from a congenitally smaller scleral canal, which compresses the axons and produces metabolic abnormalities.[2-5] This compression may lead to mitochondrial calcium deposition, axonal disruption, and eventual extrusion of calcified mitochondria into the extracellular space, which develop into drusen.[5] With either scenario, mechanical compression has been suggested to play a major role in optic disc drusen pathophysiology.

Compression of nerve fibers markedly increases the latency of evoked responses. Recently, Semela et al.[6] showed local latency delays with the multifocal visual evoked potential (mfVEP) test in patients with external compression of the optic nerve. In cases of massive compression, latency delays are easily recognized using the pattern-reversal checkerboard visual evoked potential (VEP).[7,8] However when the compression is more subtle and localized, as may be the case in optic disc drusen, the delays may be obscured by the response from the surrounding healthy axons when local responses are summed, as with the VEP, especially considering the wide range of latencies in individuals with normal vision.[9] These factors decrease the sensitivity of the VEP test in detecting localized latency delays and may play a role in the discrepancy among previous studies attempting to assess latency delays with the VEP in patients with optic disc drusen.[9-11]

The mfVEP allows the measurement of the latency of local VEP responses from 60 sectors within the central 24° visual field.[12-14] In a condition like optic disc drusen, for which a compressive effect may be local, the mfVEP may help detect latency delays masked in the VEP test. In the present study, we used the mfVEP to analyze the presence of local latency delays in patients with optic disc drusen. A group of individuals with healthy vision was used as the control, and a comparison of VEP to mfVEP responses was performed in the same groups of subjects.

METHODS

Subjects

Eighteen eyes of 10 patients with optic disc drusen and 38 eyes of 19 control subjects with no eye disease were studied. To avoid statistical confusion due to possible correlation between eyes of a given subject, when both eyes of an individual were eligible, only data from the more affected eye were included in the primary analyses. All individuals underwent a full ophthalmic examination including visual acuity, slit lamp biomicroscopy, achromatic automated perimetry, stereoscopic optic nerve head photography, VEP, and mfVEP testing.

Eight patients (15 eyes) had optic disc drusen visible on clinical examination and two patients (3 eyes) had optic disc drusen detectable

only by B-scan ultrasonography. Of the 15 eyes with visible drusen, 13 also underwent B-scan ultrasonography, which showed drusen in all but 1 eye. Of the 10 eyes with optic disc drusen selected for the primary analysis, 8 showed visible optic disc drusen on fundoscopy, and the remaining 2 had optic disc drusen detected only with B-scan ultrasonography.

Standard, full-threshold, or SITA-standard 24-2 automated perimetry was performed (Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA). All subjects had reliable visual fields with fewer than 33% fixation losses, false positives, and false negatives.

To be considered abnormal, the fields had to meet one of the following minimal criteria for abnormality: glaucoma hemifield test results outside normal limits, corrected pattern SD with a probability <5%, or a cluster of three or more points in the pattern deviation plot in a single hemifield (superior or inferior) with a probability <5%, one of which must have a probability level <1%. A significant asymmetry of visual field abnormalities was defined as the presence of an abnormal 24-2 Humphrey visual field (HVF) in only one eye or in cases of bilateral field loss an MD asymmetry of at least 2 dB between fellow eyes as previously described in the literature.[15] The worse eye for both groups was defined as the eye with the worse (more negative) mean deviation (MD) on the HVF. Of the 10 eyes selected from the group of patients with drusen, 6 had an abnormal HVF, and 4 of those met the criteria for asymmetric visual field abnormalities. None of the control subjects presented an abnormal visual field, and none of them had an MD difference greater than 2 dB between fellow eyes.

The patients had no known abnormalities of the visual system besides the one studied. Eyes were excluded that had best corrected visual acuity worse than 20/30, pupil diameter <2 mm, or refractive error exceeding ±6 D.

Optic Disc Drusen. The optic disc drusen group ranged in age from 47 to 78 years (mean, 60.6 ± 10.0 years). The average mean deviation (MD) of the 24-2 HVF for the worse eye of each subject was −6.5 ± 7.9 dB (range, −19.84–1.54 dB). Recorded maximum intraocular pressure (IOP) ranged from 11 to 21 mm Hg (mean, 17 ± 5.1 mm Hg). The only exceptions were one eye in which, during a 17-year history, a single reading was 26 mm Hg and two readings were 22 mm Hg with a central corneal thickness (CCT) of 649 μm, and another eye with a maximum intraocular pressure of 22 mm Hg and a CCT of 633 μm.

Controls. Thirty-eight eyes of 19 healthy subjects with normal ophthalmic examination results, normal HVF, and a maximum recorded IOP of ≤20 mm Hg were included. Subjects ranged in age from 38 to 69 years (mean, 52.9 ± 9.6 years). For the worse eye of each subject, the average MD of the 24-2 HVF was −0.7 ± 1.0 dB (range, −3.09–0.55 dB). The recorded maximum IOP ranged from 8 to 19 mm Hg (mean, 14.1 ± 3.6 mm Hg).

Informed consent was obtained from all subjects before participation. Procedures adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by the Institutional Review Boards of Columbia University and of The New York Eye and Ear Infirmary.

Stimuli and Recording

The mfVEP. Figure 1A is a schematic of the stimulus array produced by the software (VERIS Dart Board 60 with Pattern; Electro-diagnostic Imaging, Inc. [EDI], San Mateo, CA). The stimulus display, viewed on a CRT through natural pupils with the appropriate refractive correction, consisted of 60 sectors, each with 16 checks: 8 white (200 cd/m^2) and 8 black (<1 cd/m^2). The sectors were scaled for
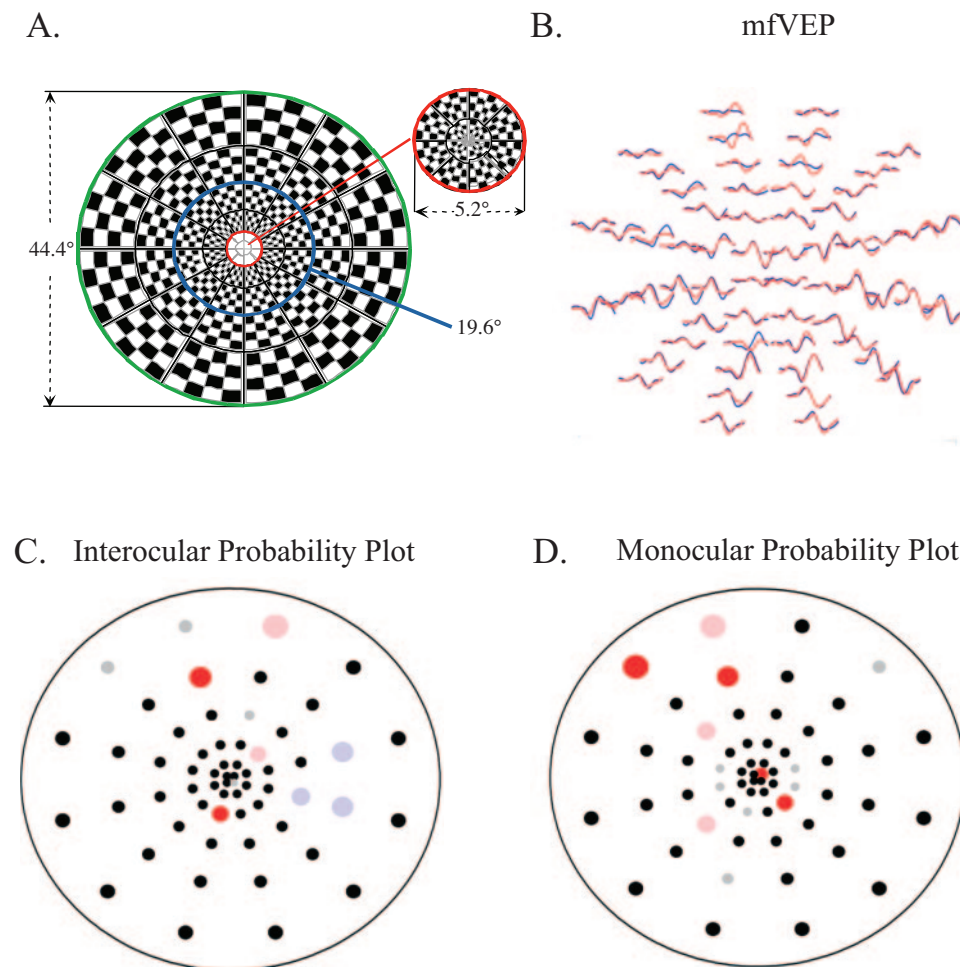
FIGURE 1. (A) Dartboard pattern display used for mfVEP stimulus. (B) Sample mfVEP response identifying 60 sectors. *Blue*: right eye response; *red*: left eye response. (C) Probability plot showing the locations (in color) with significantly delayed responses based on an interocular comparison. *Black*: no delay; *gray*: insignificant point due to low SNR; *blue*: right eye delay; *pink/red*: left eye delay. (D) Same as (C) for a monocular analysis.

cortical magnification with the central 12 sectors falling within the central 5.2° (diameter). The entire dartboard display subtended 44.4° in diameter at the viewing distance. The stimulus array was displayed on a black-and-white monitor driven at a frame rate of 75 Hz. On each frame change, each of the 16-element sectors had a 0.5 probability of reversing in contrast or staying the same. The mean luminance was 100 cd/m^2 with a contrast close to 100%. Stimulation was monocular after occlusion of the other eye. See Baseler et al.[12] and Hood and Greenstein[13] for a detail description of the mfVEP technique.

The recording procedures are described in detail elsewhere.[13,14] Briefly, three channels of continuous VEP (EEG) recordings were obtained with gold cup electrodes. For the midline channel, the electrodes were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). For the other two channels, the same ground and reference electrodes were used, but the active electrodes were placed 1 cm above and 4 cm lateral to the inion on either side. By taking the difference between pairs of channels, three additional "derived" channels were obtained, resulting in effectively six channels of recording. The records were amplified with the high- and low-frequency cutoffs set at 3 and 100 Hz, respectively (half amplitude preamplifier P511J; Grass Instruments, Rockland, MA), and sampled at 1200 Hz (every 0.83 ms). The impedance was <5 K for all subjects. In a single session, two 7-minute recordings were obtained from monocular stimulation of each eye (ABBA order). Second-order response components were then extracted (VERIS 4.3 software; EDI).

The VEP. The VEP test was run after completion of the mfVEP. The conditions of stimulation and recording adhered to ISCEV guidelines.[16] The display, a reversing checkerboard, was 48° in diameter and had a mean luminance of 70 cd/m^2 and a contrast close to 100%. Checkerboard stimuli with check sizes of 15 minutes and 60 minutes of arc were used, reversed at two reversals per second. Subjects were refracted for the viewing distance and wore the appropriate refractive correction. The stimuli were viewed through natural pupils. Recordings were obtained for each eye separately; the nontested eye was occluded. A small red dot was placed at the center of the stimulus to aid in fixation. The VEP responses were recorded (Espion System Software ver. 4.0.12; Diagnosys, Boston, MA) with cutoff frequencies of 3 and 100 Hz. A reference electrode, Fz was added and placed one third the distance from the nasion to the inion. Impedance was kept below 5 K. For each eye and each check size, two recordings were obtained between the inion+4 cm electrode and Fz, with a forehead electrode serving as the ground.

Analysis of Latency

VEP. As explained in detail previously,[17] to obtain the latency of the peak near 100 ms (P100), we exported the 15- and 60-minute check size responses to a graphics program for analysis. The two responses for each condition were averaged after visual inspection to assure that they were reasonably similar. The latency of the averaged response for each eye was measured using the following technique: In most cases, a single peak was present at approximately 100 ms, and its latency was easily measured. In cases where the peak of P100 was not easily localizable, two lines were drawn, each line representing an estimated best fit to the rising or declining phases of the wave. The point of intersection of these lines provided the latency measure.

mfVEP. The mfVEP responses from each channel were exported from the VEP system (VERIS; EDI), and two recordings from each eye were averaged. This averaging, as well as all other analyses, was computed with programs written in commercial software (MatLab; Mathworks Inc., Natick, MA). Analyses were performed on the best responses (i.e., those with the largest signal-to-noise ratio [SNR]), from the six channels, as described elsewhere.[13,18] Monocular latencies were also measured and analyzed according to a published method.[19] Briefly, to obtain a measure of the monocular latency of responses, a cross-correlation was calculated between the patient's response and a template. A template was created for each location, eye, and channel, and derived from averaging the responses of 100 normal subjects.[19,20]

The relative mfVEP latency is the shift in time (milliseconds) that maximizes the cross-correlation with the template, with amplitude scaling of the template as is typically done. Records with small SNRs (<0.23 log unit) or with cross-correlation values of less than 0 were excluded as previously described.[19] The difference in interocular latencies at each location was determined by shifting the right eye response along the time axis for best cross correlation with the left eye. The amount of shift was the interocular latency difference, with a positive value signifying that the response of the more affected eye was slower than that of the less affected eye.

RESULTS

As stated in the Methods section, to avoid statistical confusion due to possible correlation between eyes of a given subject, the primary analyses used data only from the more affected eye of each individual. The designation of the more affected eye was determined by the mean deviation (MD) of the visual field. However, an analysis of all eyes produced equivalent results.

VEP Latency Analysis

Figure 2 shows the VEP results for a check size of 60 minutes. Each circle represents the latency of P100 for an individual eye. There was considerable overlap between the optic disc drusen and the control groups, and overall the difference in latency was not statistically significantly. Eight of the optic disc drusen (ODD) eyes fell above the mean, and two exceeded the 95% CI of the control (dashed line in Fig. 2). For the 15-minute check size (Table 1), only four fell above the mean and one fell above the 95% CI of the control group.

mfVEP Latency Analysis

Unlike the VEP results, the mfVEP revealed a significant increase in the average monocular latency values of the optic disc drusen group compared with the control (Wilcoxon rank-sum test $P < 0.05$). These data are represented graphically in Figure 3. The mean mfVEP relative latency for the optic disc drusen group (4.1 ms) was greater than the value (0.8 ms) for the control group (t-test for independent samples: $P < 0.05$).
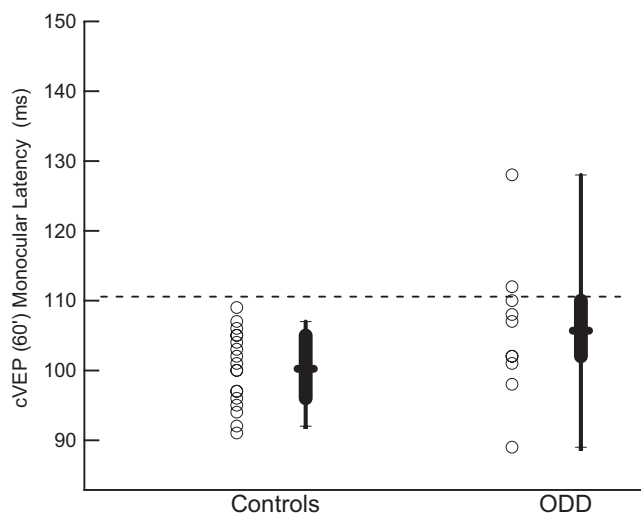

FIGURE 2. VEP 60′ latencies. Each *circle* represents the 60′ P100 VEP latency in each eye in both the optic disc drusen (ODD) and the control groups. The associated box plots represent the 25th and 75th percentiles; the *horizontal lines* near the ends of the box-and-whisker plots represent the 5th and 95th percentiles. *Bold horizontal line*: the average. *Dashed line*: the upper boundary of the 95% CI for the control group.

TABLE 1. Summary of Results for Latencies, the Percentage of Eyes above the 95% CI and the Level of Significance

Test	Control Mean (±SD)	Optic Disc Drusen Mean (±SD)	P (Optic Disc Drusen vs. Control)	% Optic Disc Drusen Eyes Greater Than Control Mean	95% CI of Control	% Optic Disc Drusen Eyes Greater Than 95% CI of Control
VEP 15′	112.5 (9.3)	115.1 (11.4)	NS	40	130.8	10
VEP 60′	100.2 (5.3)	105.7 (10.3)	NS	80	110.6	20
mfVEP latency						
Monocular	0.8 (2.3)	4.1 (4.3)	<0.05	70	5.3	40
Interocular	−0.5 (1.0)	1.0 (2.2)	<0.05	70	1.4	30
mfVEP % delayed						
Monocular	4.9 (5.0)	14.6 (11.2)	<0.05	80	14.7	40
Interocular	4.4 (4.4)	13.9 (11.4)	<0.05	70	13.1	60

Four of the optic disc drusen eyes showed a latency greater than the 95% CI (dashed line) of the control group, and in seven eyes, the latency fell above the mean. Interocular and monocular comparisons revealed a significant difference between the optic disc drusen group and the control group as shown in Table 1 (Wilcoxon rank-sum test $P < 0.05$).

Individual Response Analysis

The mfVEP has the ability to localize responses to 60 sectors within a visual field. The latency probability plot summarizes the significance of local latencies. (A sample latency probability plot is shown in Fig. 1C and described in the Methods section). The percentage of significantly delayed responses in each eye was determined by dividing the number of significant (colored) locations in the probability plot by the total number of responses that met the criteria (i.e., 60 minus the number of gray locations in Figs. 1C, 1D). The percentage of locations excluded for the optic disc drusen group ranged between 15% and 58% (mean, 33.9% ± 15.6%) and 0% to 38.1% (mean, 13.9% ± 11.39%) for the monocular and the interocular analysis, respectively. For the control group the percentage of locations excluded ranged between 6.7 and 45 (mean, 23.3 ± 11.09) and 0 to 55 (mean, 17.9 ± 15.9) for the monocular and interocular locations, respectively. Figures 4 and 5 show the percentage of delayed responses for the monocular (more affected eye) and interocular analyses. Each circle represents the individual's percentage of responses delayed, and the box plots are as

described in Figure 2. For monocular and interocular analyses, the average percentage of points delayed for the drusen group was significantly greater than that in the control group (Wilcoxon rank-sum test $P < 0.05$). Four of the 10 optic disc drusen eyes fell outside the 95% CI for the control eyes and 8 of the 10 eyes fell above the mean. The mfVEP interocular sector analysis (Fig. 5) revealed a greater difference, as 6 of 10 optic disc drusen eyes fell above the 95% CI of the control. Table 1 summarizes these results.

DISCUSSION

Compression of the optic nerve as seen in cases of intracranial and/or intraorbital masses, can produce significant and readily evident latency delays both on VEP and mfVEP.[6–8] One proposed mechanism of injury in optic disc drusen is compression of the optic nerve by drusen. If compression were involved, one might expect to see delays in VEP latencies. However, if compression by drusen is a factor in producing visual field loss, one might expect to see a smaller delay in latency than is the case in massive compression by tumors, as compression by drusen should be focal in nature. Spencer[4] suggested that optic disc drusen develop slowly and progress from buried to superficial drusen as they increase in size; the generally larger, superficial drusen have been strongly associated with a higher prevalence of visual field loss.[21] As the drusen grow, increasing mechanical compression on the surrounding tissue may lead to
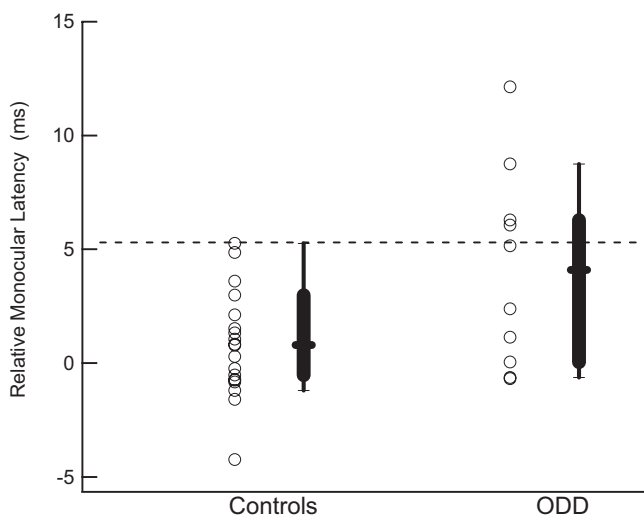

FIGURE 3. Each *circle* represents the relative monocular mfVEP latency value for each eye of both groups. Box-and-whisker plots are as described in Figure 2.
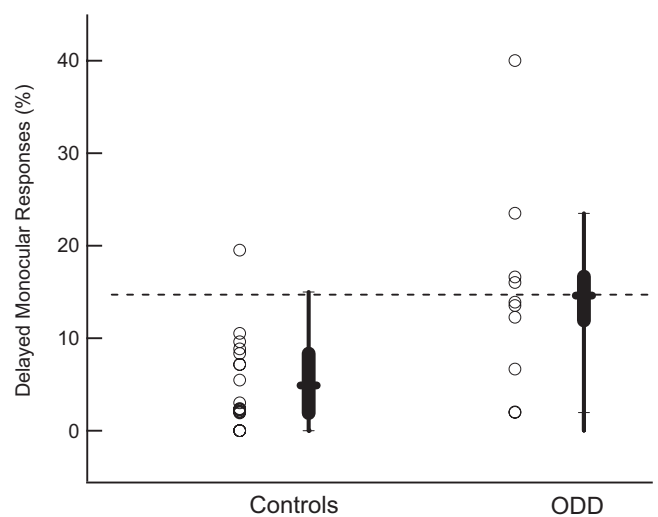

FIGURE 4. Each *circle* represents the percentage of monocular mfVEP responses delayed for each eye of both groups. Box-and-whisker plots are as described in Figure 2.
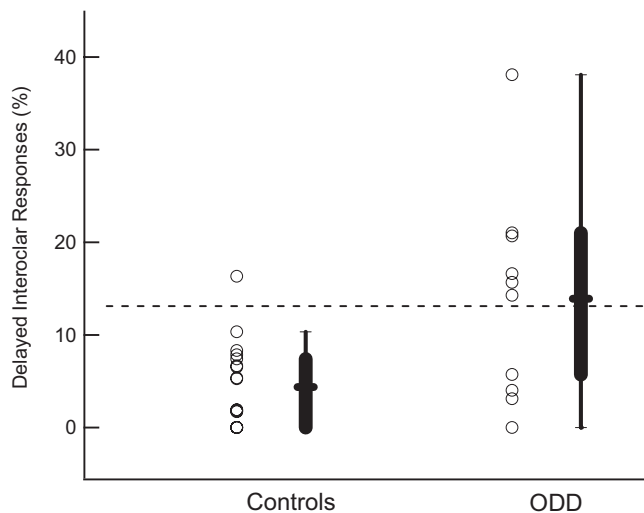
FIGURE 5. Each *circle* represents the percentage of interocular mfVEP responses delayed for each individual of both groups. Box-and-whisker plots are as described in Figure 2.

local damage, delayed responses, and ultimately death of retinal ganglion cells.

Unlike reports of VEP latency delays due to massive compression, there are conflicting data in the literature on the effect of optic disc drusen on such latencies. Brudet-Wickel et al.[10] reported no delays, whereas Scholl et al.[11] observed delayed VEP responses in 41% of patients with optic disc drusen. Of note, different techniques and inclusion–exclusion criteria were used in these studies, which makes detailed comparison difficult. For example, Mustonen et al.[9] included patients with concomitant eye disorders, and Scholl et al.[11] included eyes with suboptimal visual acuity and classified responses as abnormal if there was a delay in any one of the presented checkerboard patterns used for the study. The present study was motivated by these contradictory findings and by the availability of the recently developed mfVEP technique. To isolate the etiology of any observed VEP delays, we included only eyes without other diseases. For example, we excluded several patients with concomitant ocular hypertension given that we could not rule out that ocular hypertension itself may have caused the increase in latency. Indeed, in a prior publication, we found that eyes with both ocular hypertension and optic disc drusen show a higher frequency of visual field loss compared with optic disc drusen eyes with normal tension.[22]

Using an ISCEV standardized VEP technique,[16] we did not find significant delay in VEP latency with either the 15- or the 60-minute checkerboard displays, although one and two patients, respectively, had VEP latencies that were greater than the 95% CI of the control group. These results fall in the range previously reported for the VEP.[9–11]

Because optic disc drusen probably affect localized regions of nerve fibers in the optic nerve head, we hypothesized that the reported low incidence of latency delays on the VEP may, in part, be explained by the fact that the VEP represents the weighted sum of many local responses where abnormal responses from damaged retinal ganglion cells may be obscured by the surrounding healthy axons. We speculated that the mfVEP technique, with its capacity to measure local VEP responses from 60 sectors within a 24° visual field, may allow us to better detect delayed latencies in this group of patients. In fact, contrary to the VEP findings, the optic disc drusen group had significantly longer latencies than did the control group; and second, more eyes had abnormal average latencies on the mfVEP (four eyes for the monocular analysis and three eyes for

the interocular analysis) compared to the VEP (one to two eyes). Finally, the mfVEP detected a significant increase in the percentage of localized delays within optic disc drusen eyes (four eyes for the monocular analysis and six eyes for the interocular analysis).

In summary, optic disc drusen can produce latency delays in both the VEP and the mfVEP. Our VEP findings are consistent with those in earlier studies that failed to demonstrate a significant latency delay between eyes with optic disc drusen and healthy eyes. Contrary to the VEP, the local mfVEP showed a significant difference between the groups. The localizing ability of the mfVEP may more accurately detect these delays, as in our sample the mfVEP outperformed the VEP by detecting abnormal latencies in up to 60% of patients. As Brudet-Wickel et al.[10] pointed out, the absence of latency delays may rule out, or at least significantly decrease, the chance that mechanical compression is a cause of retinal ganglion cell damage; however, the presence of delays, although possibly related to other causes, supports the possibility of compression being the etiologic factor of retinal ganglion cell damage. In light of our results, mechanical compression due to enlarging drusen is a viable explanation for retinal ganglion cell damage in patients with optic disc drusen and the mfVEP may be a useful technique for the evaluation of nerve damage in optic disc drusen.

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