The effects of glaucoma on the latency of the multifocal visual evoked potential.

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Aims: To determine the effect of glaucomatous damage on the latency of the multifocal visual evoked potential (mfVEP).

Methods: The subjects consisted of: 1) an early glaucoma group of 50 patients defined by a glaucomatous disc and an abnormal result on static automated achromatic perimetry (SAP) with a mean deviation better than -8 dB and 2) a normal control group of 47 subjects. Based on intraocular pressures, 25 patients were characterized as normal tension glaucoma (NTG), and 25 as high-tension glaucoma (HTG). Monocular mfVEPs were obtained for both eyes using a pattern-reversal dartboard display with 60 locations. Monocular analysis of the more affected eye (based upon SAP results) and an interocular comparison of the two eyes were obtained using custom software and expressed relative to a normative group. The mfVEP latencies were analyzed in two ways: 1. average relative latency of all points and 2. percent of points with a significant delay.

Results: On interocular analysis, both the HTG and NTG group showed a statistically significant increase in mean mfVEP latency with average relative latencies and percent of points with significant delays of 1.7 ms & 10.3% (HTG) and 1.3 ms & 8.2% (NTG) compared to –0.3 ms & 2.7% (controls). On monocular analysis, only the HTG group showed a significant increase in latency with measures of 5.7 ms & 14.6% (HTG) as compared to 3.2 ms & 10.6% (NTG) and 2.1 ms & 9.6 % (controls). Using the 95 percentile of a normative group as the cutoff criterion, the sensitivity ranged from 20 to 38% and the specificity from 87 to 100% with the interocular analysis providing the best discrimination,

Conclusion: Although up to 40% of patients showed delays in the mfVEP latency, these delays were modest, on average a few milliseconds. These results differ markedly from those of a recent conventional VEP study, which reported 100% sensitivity, 100% specificity and an average delay that exceeded 25 ms.
Glaucoma, a widely prevalent eye disease, is characterized by an optic neuropathy, often associated with elevated intraocular pressure, leading to characteristic visual field defects and optic nerve head damage. The diagnosis is typically based on optic nerve head appearance and static automated achromatic perimetry (SAP). The mainstay of glaucoma treatment is pressure lowering eye drops in an attempt to halt the progression of ganglion cell death. Although current treatment is very effective at stopping visual loss, the initial visual defects as measured on SAP are irreversible. Therefore, early detection, before substantial damage has taken place, is an important aspect of glaucoma management. Furthermore, some studies suggest that substantial ganglion cell damage can take place prior to detectable defects on SAP.\textsuperscript{1,2} There has been much interest, therefore, in ways of detecting visual changes before irreversible damage occurs.

To this end, electrophysiological testing has been considered as a possible means of early detection. The multifocal visual evoked potential (mfVEP) is one such promising test. With this technique, multiple responses correlating to specific localized regions of the visual field can be tested simultaneously.\textsuperscript{3} Multiple studies have shown the relatively high sensitivity of the mfVEP in detecting glaucomatous damage.\textsuperscript{e.g.,4-13} However, nearly all of this work has been based on amplitude measures of the mfVEP. Relatively little has been reported about the latency of mfVEP responses in glaucoma patients.\textsuperscript{14}

There have been a number of studies with conventional visual evoked potentials (cVEP) showing large latency delays, on the order of 20 ms, in glaucoma patients.\textsuperscript{15-19} A recent study\textsuperscript{19} reported that the cVEP latency had a 100% sensitivity and specificity in distinguishing normal controls from patients with open-angle glaucoma. Further, the cVEP latency has been used as a marker of reversible ganglion cell damage in trials of neuroprotective agents for the treatment of glaucoma.\textsuperscript{20} The implication is that latency can be used as a measure of early glaucomatous damage prior to retinal ganglion cell death.

A potential problem with the cVEP is that it represents the weighted sum of many local responses. Thus, the technique may obscure delays in local responses. These delays in latency should be seen more easily with the mfVEP. However, a report, in abstract form, suggested rather small latency changes with glaucomatous damage.\textsuperscript{14} Considering the importance of early detection, and the implications for neuroprotection, a greater understanding of mfVEP latency in patients with glaucoma is important. Here we investigate the effect of glaucoma on the latency of
the mfVEP responses. A preliminary version of this work was presented at the meeting of ARVO in May, 2005.

**METHODS**

**Subjects**

High Tension Glaucoma (HTG)

This group consisted of 25 patients with intraocular pressures > 21 mm Hg. The inclusion criteria were: 1) cup-to-disk ratio > 0.6, 2) abnormal GHT on 24-2 Humphrey visual field (HVF), 4) open angles, 5) a mean deviation (MD) on HVF of better than –8 dB in both eyes. The patients’ age ranged from 30 to 77 years with a mean age of 58 (SD +/- 12) years. The average MD was -4.2 (SD +/- 1.7) dB.

Normal Tension Glaucoma (NTG)

This group consisted of 25 patients with IOP < 21 mm Hg but otherwise satisfying the same criteria as the HTG group. The patients’ age ranged from 34 to 75 years with a mean age of 59.6 (SD +/- 12) years. The average MD was –3.6 (SD +/- 2.2) dB.

**Controls**

This group consisted of 47 individuals with normal vision who ranged in age from 31 years to 81 years with a mean age of 50 (SD +/- 10) years. These individuals had a visual acuity ≥ 20/20, a normal fundus exam and a normal HVF (i.e. normal GHT and MD). The average MD was –0.8 (SD +/- 1.1) dB.

Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the Committee of the Institutional Board of Research of Columbia University.

**mfVEP stimulus**

The mfVEP stimulus was a dartboard display of 60 cortically scaled sectors produced using the VERIS software from EDI (Electro-Diagnostic Imaging, San Mateo, CA). The stimulus display (Fig. 1A), viewed 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$^2$). Each of the 60 sectors followed an independent pseudorandom sequence of pattern reversals in which there was
a 50% probability of reversing at each frame shift. For more details about the mfVEP see Baseler et al.\textsuperscript{3} and Hood & Greenstein\textsuperscript{10}.

**mfVEP recording**
Three signal channels were recorded simultaneously with gold cup electrodes. The ground and reference electrodes were placed on the forehead and inion, respectively. The three active electrodes were placed 4 cm above the inion (midline channel), and 4 cm on either side of and 1 cm above the inion (lateral channels). All three channels were filtered with a low and high frequency cutoff of 3 Hz and 100 Hz (Grass Instruments preamplifier P511J, Quincy, Mass.). The resistance was less than 5k for all subjects. Four monocular, 7 minute recordings were obtained, two for each eye (ABBA order). The mfVEP responses were exported from the VERIS 4.3 software from EDI (San Mateo, CA). See Hood et al.\textsuperscript{21} and Hood and Greenstein\textsuperscript{10} for more details.

**mfVEP analysis**
The exported mfVEP records were processed using custom software written in MATLAB (Mathworks Inc., Natick, MA) and an array of best channel responses derived as previously described.\textsuperscript{10,21,22} The mfVEP best channel responses for a NTG patient are shown as the records in color in Fig. 1B.

Relative monocular latency and the interocular difference in latency were determined at each of the 60 locations and compared with a normative set using computerized techniques previously described.\textsuperscript{23,24} Briefly, relative monocular latencies were determined by shifting the subject’s best channel response along the time axis to give the maximal overlap (cross-correlation) with a template trace determined from a normative group. The normative group consisted of 100 individuals whose characteristics have been previously described.\textsuperscript{25} The amount of shift was the relative monocular latency, as compared to the norms, in milliseconds. Only the more affected eye, based on 24-2 Humphrey visual field (HVF) mean deviation, was included in the monocular latency analysis. The difference in interocular latencies at each location was determined by shifting the right eye response along the time axis to overlap maximally (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
Probability plots were created by comparing the relative latency values to those of the normative set. Interocular and monocular latency probability plots for a typical NTG patient are shown in Figs 1C and 1D. The points on the plot are located at the centers of the 60 sectors in the mfVEP display. Blue (right eye) and red (left eye) circles represent locations that are delayed at either the 5% (desaturated) or 1% (saturated) level. Gray circles represent responses that are either too small (SNR < 1.7) or with waveforms deviating too much from normal templates (cross correlation < 0) to give reliable latency values. See refs. 23 and 24 for details.

RESULTS

Examples of mfVEP responses and latency probability plots for a typical NTG patient are shown in Fig. 1. Figure 1B shows the mfVEP responses from both eyes (red: OS; blue: OD). As indicated by the colored circles in Figs. 1C and D, 14 and 10 locations were significantly delayed on the interocular and monocular probability plots, respectively. However, these delays were relatively small. As will be seen below, the results for this patient were typical.

Average Latency

The monocular analysis provides the most direct comparison to previous cVEP data. Each symbol in Figs. 2A is the average relative monocular latency for an individual. An individual’s relative monocular latency is the average relative monocular latency of all traces meeting reliability criteria for the more affected eye (poorer MD on HVF). It is clear from Fig. 2A that there is considerable overlap among the groups. This is easier to see in the box plots. In this presentation, the 25 and 75% range and the 5 and 95% range are shown by the box and lines, respectively, with the bold horizontal bar indicating the mean. Table 1 contains the means for the different groups where, for example, a value of 3 ms indicates that, on average, this group’s mfVEPs were delayed by 3 ms relative to the normative group. Only the HTG group showed a significant difference from controls with a mean value of 5.7 ms (Mann Whitney rank sum test; p < 0.001) compared to 3.2 ms for NTG and 2.1 ms for controls. Only one patient (1 NTG) fell above the range of control values, while 30% (15 patients: 10 HTG and 5 NTG) fell above the 95 percentile for the norms. Using the 95 percentile of the norms as a criterion, the sensitivity and specificity were 30% and 87%, respectively (Table 2).
Table 1: Mean (median) latency and percent of points delayed for both monocular and interocular tests.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Relative Monocular Latency (ms)</th>
<th>Mean Interocular Latency Difference (ms)</th>
<th>% Monocular Points Delayed</th>
<th>% Interocular Points Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normative</td>
<td>0.4</td>
<td>0.1</td>
<td>5.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Control</td>
<td>2.1</td>
<td>–0.3</td>
<td>9.6</td>
<td>2.7%</td>
</tr>
<tr>
<td>HTG</td>
<td>5.7**</td>
<td>1.7**</td>
<td>14.6*</td>
<td>10.3%**</td>
</tr>
<tr>
<td>NTG</td>
<td>3.2</td>
<td>1.3**</td>
<td>10.6</td>
<td>8.2%**</td>
</tr>
</tbody>
</table>

* P<.02 when compared to the Control group
** P<.001 when compared to the Control group

Table 2: Specificity and sensitivity for monocular and interocular latency and percent of points criteria.

<table>
<thead>
<tr>
<th>Group</th>
<th>Specificity (controls)</th>
<th>Sensitivity (NTG+HTG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Relative Monocular Latency (ms)</td>
<td>Mean Interocular Latency Difference (ms)</td>
</tr>
<tr>
<td>Specificity (controls)</td>
<td>87%</td>
<td>100%</td>
</tr>
<tr>
<td>Sensitivity (NTG+HTG)</td>
<td>30%</td>
<td>36%</td>
</tr>
</tbody>
</table>

The interocular analysis does a slightly better job of distinguishing among the patients and the controls. Each symbol in Fig. 2B is the average interocular latency. An individual’s average interocular latency difference was calculated as the mean of the interocular latency differences for all locations meeting reliability criteria. Positive values signify the eye with the poorer MD was delayed relative to the eye with the better MD. The box plots are described above. Although there is overlap among individual values and the interocular differences were relatively small, both the HTG and NTG groups showed significantly higher mean interocular latency values of 1.7 and 1.3 ms (Mann Whitney rank sum test; p < 0.001), respectively, compared to –0.3 ms for controls. Fifty percent (25 patients: 13 HTG and 12 NTG) of the patients fell above the range of control values and 36% (20 patients: 10 HTG and 8 NTG) fell above the 95 percentile for the norms. The sensitivity and specificity were 36% and 100%, respectively.

The latency data from Fig. 2 for the three groups of subjects are shown as a function of MD in Fig. 3. For the monocular data (Fig. 3A) the latency and MD values are for the more affected eye, while for the interocular data (Fig. 3B) the latency is plotted against the difference between the MDs of the more (poorer MD) and less affected eyes. There was no relationship between either the monocular (panel A) or interocular latency (panel B) and MD.
Percent Delayed Traces

To take advantage of the localizing ability of the mfVEP, the latency probability plots (Fig. 1C,D) were analyzed. For each subject the percentage of significantly delayed responses was determined by dividing the number of significant (colored) locations in Fig. 1C,D by the total number of responses that met criteria for measurement (i.e. 60 minus the number of gray locations). Table 1 shows the mean results. For the interocular analysis, both the HTG and NTG groups differed significantly from controls with a mean of 10.3% and 8.2% significantly delayed responses compared to 2.7% for controls ($p < 0.001$). Only the HTG group was significantly different on monocular analysis with 14.6% delayed ($p = 0.013$) compared to 10.6% for NTG and 9.5% for controls.

The symbols in Fig. 4 are each individual’s percent of locations delayed and the box plots are as described above. For the monocular analysis (Fig. 4A), there is considerable overlap of the groups. Only 2% (1 NTG) of the patients fell above the range of control values, while 20% (10 patients: 5 NTG and 5 HTG) fell above the 95 percentile for the norms. Using the 95 percentile as a criterion, the sensitivity and specificity were 20% and 91%, respectively (Table 2). For the interocular analysis, 32% (16 patients: 9 HTG and 7 NTG) fell above the range of control values and 38% (19 patients: 11 HTG and 8 NTG) fell above the 95 percentile for the norms. The sensitivity and specificity were 38% and 98%, respectively.

DISCUSSION

The identification of glaucoma patients with abnormal latencies could open the possibility of neuroprotection of unhealthy retinal ganglion cells. In this regard, reports of substantial delays in the conventional VEP (cVEP) encouraged us to assess delays with the locally more sensitive mfVEP technique. The delays in the glaucoma group were modest, on average less than 4 ms, when compared to the control group, and involved fewer than 40% of the patients.

Our results provide a marked contrast to those recently reported by Parisi et al. In that study, all 84 patients with OAG had cVEP latencies that were longer than the longest latency found among the 80 normal control subjects. Further, the mean latency of the OAG group was 27.8 ms longer than that of the control group. The monocular mean latency analysis of our HTG group provides the most direct comparison to their study. Our HTG group had, on average, an increase in latency of only 5.3 ms as compared to the normative group and only 3.6 ms compared...
to the control group. Further, there was considerable overlap with the control and normative groups with only one patient’s value falling above the control group range. Using the 95 percentile of the normative data as a definition of abnormal latency resulted in a sensitivity and specificity of 30 and 87%, respectively, values far from the 100% sensitivity and specificity reported for the cVEP by Parisi et al.\textsuperscript{19}

For our patients, the interocular test for mean latency does a little better. Using the 95 percentile of the norms, the sensitivity and specificity were 36 and 100%, respectively. Using the percent of points in the field with abnormal latencies yielded similar results with again the interocular comparison providing better discrimination than the monocular comparison.

The reasons for these discrepancies with the Parisi et al study are not entirely clear. While the OAG patients in their study had, on average, more severe field losses than our HTG group, their results were substantially the same for their patients with MDs in the same range (better than -8 dB) as ours. In addition, other patient characteristics (e.g. age) cannot explain the difference in results. On the other hand, the mfVEP and cVEP techniques differ in both the stimulus used and the analysis employed. Further, the evidence suggests that the mfVEP has less of a post V1 contribution, than does the cVEP. Theoretically it is possible the delays are introduced beyond V1. However, before invoking such speculative explanations, recordings of both cVEP and mfVEP from the same group of patients need to be made. We are completing such a study.

In summary, in a group of patients with glaucoma and mild to moderate visual field loss, the delays in the mfVEP were modest. On average the delays were a few milliseconds and they rarely exceeded 10 ms. On the other hand, up to 40% of these patients may have abnormal latencies and these are best detected with an interocular analysis. Before a decision is made to use either the mfVEP or cVEP in neuroprotection trials the discrepancy between the mfVEP and cVEP needs to be understood.

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REFERENCES


FIGURE CAPTIONS

Figure 1. (A) The mfVEP stimulus display of 60 cortically scaled sectors. Each of the 60 sectors of the display is an independent pattern-reversing checkerboard. (B) Sample responses for a patient with glaucoma for monocular stimulation of the left (red) and right (blue) eyes. (C) Latency probability plots for the interocular analysis of the responses in B. (D) Latency probability plots for the monocular analysis of the responses from the left eye in B.

Figure 2. (A) Average monocular latency of the more affected eye (poorer MD) relative to a normative group is shown for individual eyes (symbols) of the normative (n=100), control (n=47), NTG (n=25), and HTG (n=25) groups. The box plot shows the 25/75% range (box), the 5/95% range (vertical line) and the mean of the group (horizontal bar). (B) As in panel A for the average interocular latency difference for each individual.

Figure 3. (A) Average relative monocular latency of the more affected eye (poorer MD) as a function of the mean deviation of that eye is shown for individual eyes (symbols) of the control (+), NTG (open square), and HTG (filled square) groups. The box plot shows the 25/75% range (box), the 5/95% range (vertical line) and the mean of the normative group (horizontal bar). Its placement along the x-axis is arbitrary. (B) As in panel A for the average interocular latency difference.

Figure 4. (A) The percent of points in the more affected eye (poorer MD) with significant delays (see Fig. 1B) is shown for individual eyes (symbols) of the normative (n=100), control (n=47), NTG (n=25), and HTG (n=25) groups. The box plot shows the 25/75% range (box), the 5/95% range (vertical line) and the mean of the group (horizontal bar). (B) As in panel A for the percentage of points in the interocular probability plot.
Figure 1

A. Interocular Probability Plot

B. Interocular Responses

C. Interocular Probability Plot

D. Monocular Probability Plot (OS)
Figure 2

A. Relative Monocular Latency (ms)

B. Interocular Latency Difference (ms)
Figure 3

A.

B.
Figure 4

A. Percent Delayed Monocular (%)

B. Percent Delayed Interocular (%)

Categories: Norms, Controls, HTG, NTG