Pattern reversal visual evoked potentials in eyes with macular holes and their fellow eyes

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ABSTRACT.

Purpose: To investigate whether the pattern reversal visual evoked potential can be useful in the diagnosis and management of macular hole patients.

Methods: The pattern reversal visual evoked potential was measured in 66 patients with a macular hole and in 43 healthy control subjects. Check sizes of 34', 17' and 10' were applied.

Results: Results showed that, for the check sizes of 34', 17' and 10', eyes with a macular hole had significantly prolonged N80 and P100 latencies and a significantly reduced P100 amplitude as compared to their fellow eyes. Furthermore, for the 10' check size, the fellow eyes appeared to have a significantly reduced P100 amplitude as compared to their fellow eyes. Nonetheless, the latencies of the fellow eyes of the macular hole patients were not prolonged.

Conclusion: Significant pattern reversal visual evoked potential alterations were shown in eyes with macular holes and fellow eyes for small check sizes.

Key words: amplitude - fellow eye - latency - macular hole - pattern reversal visual evoked potential - VEP.


The pattern reversal visual evoked potentials (PRVEP) recorded from the occipital midline arise predominantly from stimulation of the macula (Kato et al. 1991; Regan 1972). Few reports on the outcome of PRVEP stimulation in patients with a macular hole were published, and the authors reported controversial results. All reports agreed that in eyes with macular holes PRVEP amplitudes are significantly reduced (Kato et al. 1991; Johnson et al. 1987; Bass et al. 1985; Smith et al. 1990; Wu et al. 1992). There was no agreement however, on the PRVEP (P100) latency in macular holes. Whereas some authors reported a statistically significant prolongation of (P100) latency in macular holes (Johnson et al. 1987; Bass et al. 1985; Wu et al. 1992), others did not confirm this finding (Kato et al. 1991; Smith et al. 1990). Results in previous reports were obtained from relatively small groups of patients; varying from 7 to 32 (Johnson et al. 1987; Smith et al. 1990). The check sizes used in former reports varied from 12' to 75' (Kato et al. 1991; Johnson et al. 1987). In this study we present the outcome of the PRVEP in a larger group of patients with unilateral or bilateral macular hole (N = 66). The data of the macular hole eyes were compared to the data of the fellow eyes and with a separate group of control subjects (N = 43). Goal is to investigate whether PRVEP can be useful in the diagnosis and management of macular hole patients.

Material and Methods

Patient selection

The PRVEP registration was part of a preoperative protocol for patients with unilateral or bilateral macular hole, and was measured one day prior to surgical intervention. Apart from PRVEP, the patients were submitted to routine ophthalmologic examination, 3 mirror contact lens ophthalmoscopy, and a slit beam test.

For comparison of the data we distinguished three groups of eyes: 1) eyes with a macular hole, 2) contralateral eyes of patients with unilateral macular hole (fellow eyes), and 3) control subjects (separate group).

In patients with unilateral macular hole we only included the data of the eye that was indicated to undergo surgery. The eyes with macular holes that underwent surgery almost all showed stage three macular holes, according to the Gass criteria for macular holes (Gass 1995). Selection of contralateral eyes and control eyes for analysis was based on the following criteria: 1) visual acuity (VA) > 0.8, 2) no known ophthalmological disease in the examined eye and 3) reliable PRVEP response.

To eliminate possible confounding caused by age differences (Bemelmans et al. 1995) between the macular hole patients and the control subjects, we restricted the comparison to the age range of 55-65 years.

PRVEP registration, analysis and labeling of PRVEP components

The active electrode was placed at position O2, 2.5 cm above the inion, the referring electrode at T3, the mastoid process. The grounding was done with an electrode on the earlobe (A1). Impedance, measured at 2 Hz, was kept below five kilo Ohms. The ambient illumination of the room was not standardized, though kept at mesopic level.

Every eye was optimally refracted for the viewing distance. PRVEPs were recorded monocularly, using a reversing checkerboard pattern generated by a galvanometer-mirror system (Medilog VPS-20). The stimulus consisted of patterns of 34', 17', and 10' (minutes of arc), reversal
rate was 2 Hz. Field size was 18 degrees for the check size of 34' and 9 degrees for the 17' and 10' pattern. The contrast of the checks was 80%, mean luminance of stimulus was 40 cd/m². After a 100 dB amplification, analog bandpass filtering (4th order linear phase filter, bandpass: 0.16-70 Hz), the evoked response signals were digitized (Keithley DAS-16 ADC, sampling rate 1000 Hz), 64 successful sweeps of 500 ms duration were averaged and stored in a computer (Tulip 386 SX MSDOS). In addition, a digital low pass filter (zero phase) with a cut-off frequency of 40 Hz was applied to the averaged evoked response.

The N80 latency of the PRVEP complex was measured as the time difference between the stimulus reversal and the first negative peak (N80) of the response (see also Figs. 1 and 2a,b for representative traces and component labelling). The P100 latency of the PRVEP complex was measured as the time difference between stimulus reversal and the appearance of the first (major) positive peak (P100). The amplitude of the PRVEP was calculated as the difference (in µV) between the N80 trough and the P100 peak. This amplitude is labelled as the ‘P100 amplitude’.

Statistical comparison of PRVEP parameters among the groups

Statistical analysis was performed with the SAS statistical analysis software package (SAS Institute Inc., Cary, NC, USA). Exploring the distribution of the data in the three groups (macular holes, fellow eyes, and control subjects) we found that in the macular hole eyes the P100 amplitudes, the N80 and the P100 latencies were not distributed in a Gaussian manner (Shapiro-Wilk test; p<0.01). For this reason the hypothesis test was done with non-parametric methods: a Wilcoxon-signed-ranks test (paired design) for comparison of the data from the macular hole eyes and their fellow eyes, and a Wilcoxon rank-sum test for comparison with the (independent) control group (Dawson & Trapp 1994; Rossner 1982; Ederer 1973).

Results

The macular hole group consisted of 66 patients, 23 male and 43 female. Nine patients, 3 male and 6 female, had bilateral macular holes. Group 2 contained 39 fellow eyes of patients with macular holes, according to the inclusion criteria, 14 male and 25 female. Group 3 included 43 control eyes, 9 male and 34 female. In group 1 (macular holes), 5 patients had a cataract operation in the affected eye in their history, 5 patients underwent a vitrectomy before the development of the macular hole in the same eye, one patient had retinal detachment surgery performed earlier, one patient had an endophthalmitis in the eye with the macular hole in his history, one patient had a retinal defect prior to the macular hole, one patient had the combination of a macular hole and an epiretinal membrane, and the remaining 52 patients (52 eyes) idiopathically developed a macular hole.

Mean VA in the macular hole eyes (group 1) was 0.2 (SD = 0.4), mean VA in the fellow eyes (group 2) was 0.9 (SD = 0.1), and 1.0 (SD = 0.1) in the control eyes (group 3). Mean age of the macular hole patients was 66 years, ranging from 46 to 85 years of age, in the control group (3) mean age was 58 years, ranging from 46 to 82 years of age.

At first, we compared the differences within a subject between the macular hole eye and the fellow eye. Compared to their fellow eyes, eyes with macular hole showed significantly (p<0.01) prolonged N80 and P100 latencies and a reduced P100 amplitude for all three check sizes (Tables 1 and 2). When the group of eyes with macular hole was compared with a separate group of control eyes, both a significantly (p<0.01) prolonged N80 and P100 latency and a reduced P100 amplitude were found. This was confirmed by statistical analysis on a restricted age-interval (between 55-65 years) in both groups, the comparison between eyes with macular hole and control eyes showing more pronounced results.

Secondly, for subjects within the age range of 55-65 years, we compared the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Check size</th>
<th>Mean (SD)</th>
<th>N</th>
<th>Mean (SD)</th>
<th>N</th>
<th>Mean (SD)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>N80 latency (ms)</td>
<td>34'</td>
<td>83.0 (11.5)</td>
<td>58</td>
<td>78.6 (8.2)</td>
<td>38</td>
<td>*</td>
<td>*</td>
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<tr>
<td></td>
<td>17'</td>
<td>87.9 (9.2)</td>
<td>53</td>
<td>82.1 (4.0)</td>
<td>35</td>
<td>82.5 (3.4)</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>10'</td>
<td>96.1 (11.9)</td>
<td>49</td>
<td>85.7 (5.0)</td>
<td>36</td>
<td>85.2 (3.7)</td>
<td>43</td>
</tr>
<tr>
<td>P100 latency (ms)</td>
<td>34'</td>
<td>109.4 (8.6)</td>
<td>58</td>
<td>106.4 (7.9)</td>
<td>38</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>17'</td>
<td>115.6 (12.9)</td>
<td>53</td>
<td>107.0 (6.9)</td>
<td>35</td>
<td>106.3 (4.6)</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>10'</td>
<td>124.5 (16.0)</td>
<td>49</td>
<td>111.8 (8.5)</td>
<td>36</td>
<td>110.6 (5.2)</td>
<td>43</td>
</tr>
<tr>
<td>P100 amplitude (µV)</td>
<td>34'</td>
<td>5.6 (3.6)</td>
<td>58</td>
<td>8.0 (4.5)</td>
<td>38</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>17'</td>
<td>5.6 (3.4)</td>
<td>53</td>
<td>7.6 (4.1)</td>
<td>35</td>
<td>9.4 (4.3)</td>
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<tr>
<td></td>
<td>10'</td>
<td>5.3 (3.9)</td>
<td>49</td>
<td>7.7 (4.8)</td>
<td>36</td>
<td>10.2 (4.0)</td>
<td>43</td>
</tr>
</tbody>
</table>

SD: standard deviation; N: total number; * not examined.

**Table 1. Means and standard deviations of N80 and P100 latencies and P100 amplitude for the overall groups.**

**Table 2. Outcome of the hypothesis testing. p < 0.05 was considered significant. Comparison of groups 1 vs. 3, and groups 2 vs. 3 was done within the age range of 55-65 years. Table contains probabilities of Wilcoxon-signed-ranks-test of eyes in group 1 and 2 (n = 33), and probabilities of age-matched two-sample comparisons (Wilcoxon rank-sum test) of macular hole eyes (n = 22) and fellow eyes (n = 16) to the separate group of control eyes (n = 14).**

<table>
<thead>
<tr>
<th>PRVEP parameter</th>
<th>Check size</th>
<th>Group 1 vs. 3</th>
<th>Group 1 vs. 2</th>
<th>Group 2 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N80 latency (ms)</td>
<td>34'</td>
<td>*</td>
<td>0.0011</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>17'</td>
<td>0.0036</td>
<td>0.0001</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>10'</td>
<td>0.0014</td>
<td>0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>P100 latency (ms)</td>
<td>34'</td>
<td>*</td>
<td>0.0015</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>17'</td>
<td>0.0006</td>
<td>0.0001</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>10'</td>
<td>0.0002</td>
<td>0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>P100 amplitude (µV)</td>
<td>34'</td>
<td>*</td>
<td>0.0001</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>17'</td>
<td>0.0009</td>
<td>0.0001</td>
<td>0.0396</td>
</tr>
<tr>
<td></td>
<td>10'</td>
<td>0.0007</td>
<td>0.0001</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns: not significant; * not examined.
Discussion
In earlier publications some seemingly controversial findings can be found. Authors agreed on the finding that PRVEP amplitude is significantly reduced in patients with macular hole (Kato et al. 1991; Johnson et al. 1987; Bass et al. 1985), whereas other authors did not find significant differences between eyes with a macular hole and controls (Smith et al. 1990). Kato et al. (1991), found no difference in P100 latency between affected eye and fellow eye, evoking a steady-state PRVEP with check sizes of 50' and 12'. We did find, measuring a transient response, significantly prolonged N80 and P100 latencies between macular holes and the fellow eyes (Table 2), in conformity with Wu et al. (1992), who also found a prolonged P100 latency in the affected group compared to the fellow eyes.

The difference in results between the reports may be due to the pattern sizes applied. Small check sizes (up to and about 15 min of arc) would be expected to enhance contributions from the central 3' of vision, whereas larger check sizes would progressively emphasize parafoveal contributions (Regan 1989). Most earlier reports concluded that the smaller check sizes are more likely to detect abnormalities produced by small lesions such as a macular hole (Kato et al. 1991; Johnson et al. 1987; Bass et al. 1985; Smith et al. 1990). Their best results were obtained with check sizes that vary from 12' to 36'. In our study the differences for both amplitude and latencies were also best expressed for the 10' and the 17' check size. For the larger check size (34') the differences were less significant (Table 2). Furthermore, the numbers of patients studied in other reports were smaller, resulting in less reliable outcome.

Several authors described that in fellow eyes of eyes with macular holes a similar pathogenic process can be found which may even result in a contralateral macular hole. Percentages vary on the incidence of a macular hole in the fellow eye (Trempe et al. 1986; Akiba et al. 1990, 1992; Aaberg et al. 1970; James & Feman 1980; Bronstein et al. 1981; Morgan & Schatz 1985, 1986, McDonnel et al. 1982). Comparing the fellow eyes with the control eyes, we found a significantly reduced amplitude for the 17' check size in the fellow eyes (Table 2). No significant difference in latency was seen between fellow eyes and control eyes. Our results suggest that in the process of macular hole formation the fellow eye is also involved. The fact that the amplitude is significantly reduced in the fellow eyes suggests that in the process of macular hole development the amplitude is the first parameter to alter. As no significant correlation can be found between the VA and the P100 amplitude, the VA cannot be seen as a causal factor for the amplitude reduction in the fellow eyes. What is exactly the cause of this amplitude reduction in these fellow eyes, cannot be concluded from our data. Alteration of the N80 and P100 latencies is less pronounced in this preclinical stage and may occur later. However, it is not implicated that a macular hole in the fellow eye will develop.

It is important to realize that prolonged latencies and a reduced PRVEP amplitude are not specific for maculo-
pathy or subclinical alterations of the posterior pole of the eye (Johnson et al. 1987; Lennerstrand 1982), but that usually PRVEP examination is indicated for pathology of the more central parts of the optical visual pathway (Bemelmans et al. 1995). Two investigations providing additional information about maculopathy in this context are the focal cone ERG and the pattern reversal ERG. The focal cone ERG has been described to show a reduced amplitude in eyes with full-thickness macular holes, as well as in fellow eyes that are at risk to develop a macular hole in the near future (Birch et al. 1988). This investigation provides, however, little information about the detailed retinal layers. The pattern reversal ERG, most likely providing information on the ganglion cell layer, adds more specified information to the long pathway the PRVEP investigation is obtained from (Hull & Thompson 1989).

A prospective and longitudinal study will be required to investigate whether or not the PRVEP has a predictive value in the development of macular holes, and furthermore whether the PRVEP amplitude or latencies are useful predictors for postoperative recovery of VA. If the outcome would be positive, methods for macular hole prevention could be developed or evaluated.

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References


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