

Visual Evoked Potentials in Macular Disease

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Although a delayed visual evoked potential is considered to be the hallmark of optic nerve disease, relatively little has been published about VEP delays in macular disease. In this study, 20 patients with either acquired unilateral maculopathy or bilateral maculopathy in which one eye was more affected than the other were evaluated. VEP amplitudes and peak latencies were compared between eyes when recordable. Nine patients (45%) exhibited significant interocular delays in the affected or more affected eye while only four patients (20%) exhibited significant interocular attenuations in amplitude. In the nine patients exhibiting delays, three patients had a visual acuity of 20/30 or better in the affected eye or more affected eye. In the patients exhibiting amplitude attenuations, no patient had a visual acuity better than 20/50 in the affected or more affected eye. Although the mechanism of VEP delays in maculopathy is not clear, a VEP delay, in isolation of other tests, should not be used in the differential diagnosis of macular vs optic nerve disease. The clinician should specifically rule out macular disease in any patient with a delayed VEP before presuming the presence of a visual pathway dysfunction. *Invest Ophthalmol Vis Sci* 26:1071-1074, 1985

A delayed visual evoked potential (VEP) is widely used to support the diagnosis of optic neuropathy and multiple sclerosis.¹ VEP delays have also been reported in other diseases, not necessarily causing demyelination or affecting the optic nerve, such as spinocerebellar degeneration,² Friedreich's ataxia,³ Parkinson's Disease,⁴ Vitamin B12 deficiency,⁵⁻⁷ nonproliferative diabetic retinopathy,⁸ use of select drugs,^{9,10} as well as in conditions which may result in degradation of retinal images, such as cataracts and pupillary miosis. Nevertheless, a delayed VEP is still considered to be the hallmark of optic nerve disease.

The current study was undertaken to investigate the VEP in macular disease and to thereby assess the specificity of a delayed VEP for the diagnosis of optic nerve disease. Although previous studies conducted in patients with macular disease have demonstrated VEP amplitude changes,^{11,12} there is a relative paucity of data concerning VEP peak latency changes. Some investigators have reported VEP phase shifts in macular disease,¹³ and recently we^{14,15} and others^{16,17} have reported VEP peak latency changes in patients with central serous choroidopathy. Lennerstrand¹⁸ has also reported abnormal VEP peak latencies in a majority of patients having macular lesions.

In this current study, 20 patients with either acquired unilateral maculopathy or bilateral maculopathy in which one eye was more affected than the other were evaluated. VEP amplitudes and peak latencies were compared from each eye when recordable. Patients with good visual acuities were of special interest because they provided a basis for determining whether or not a relationship exists between the subjective visual acuity and the objective visual evoked potential in macular disease.

As an additional aspect of the study, the effect of pattern element size was investigated in all of the patients to determine which stimuli would be most informative for studying the VEP in macular disease.

Materials and Methods

Twenty patients (13 males and 7 females) with a diagnosis of macular disease were examined. The males ranged from 28 to 72 yr of age with a mean age of 49.9 yr. The females ranged from 12 to 68 yr of age with a mean age of 51.4 yr.

No patient had anisocoria and there was no prior history of amblyopia in any patient. All patients had normal looking optic discs, and other than the maculopathy, there was no other ocular pathology.

Five patients had macular holes in one eye, two patients had lamellar holes, four patients had resolved central serous choroidopathy (one was examined during the active stage), three patients had dry, atrophic senile macular degeneration, two patients had traumatic maculopathy, one patient had inactive exudative macular degeneration, one patient had Best's disease, one patient had a macular cyst, and one patient had

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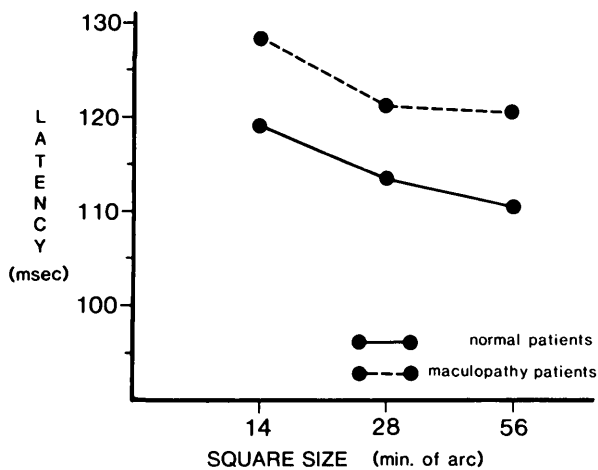


Fig. 1. Mean values for latency in normal and maculopathy patients.

mottling of the retinal pigment epithelium at the macula.

Visual acuity measurements ranged from 20/20 to finger counting in the affected eye. The best corrected visual acuity measurement in 11 patients ranged from 20/20 to 20/40 or better in the affected eye. Three patients had visual acuities ranging from 20/50 to 20/70, three patients had acuities ranging from 20/100 to 20/200, and three patients had visual acuities worse than 20/200.

Pattern-reversal VEPs were recorded from each eye separately, using a clinical averager (Nicolet CA-1000, Nicolet Biomedical; Madison, WI) and a visual stimulator (Nicolet 1005). A gold cup electrode (Grass), attached to the scalp 2 cm above the inion, was used to record the VEP. Two ear clip electrodes were used, one for the reference and the other for the common ground. Electrode impedance was maintained below 6000K ohms. An artifact rejection was utilized to reject any signal greater than about 50 μ V which might be created by blinks or large eye movements. Patient consent was received from all patients involved in the study.

Pattern elements consisted of squares of 14, 28, and 56 min of arc presented in a checkerboard pattern. The pattern was reversed at 7.5 reversals/sec. The stimulus distance was 1 m. The overall field size at 1 m was 12 deg vertical by 15 deg horizontal. Mean luminance was maintained at 25 cd/m² and contrast $(L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$ at 76%.

All patients were optically corrected for the stimulus distance and mydriatics and cycloplegics were not utilized. The analysis time was set at 200 msec and between 100 and 200 responses were averaged for each trial.

VEPs were also obtained from each eye of 16 normal controls who were age-matched (same decade) to our study sample. The criteria for a normal control

was a best corrected visual acuity of 20/20 or better in each eye and no biomicroscopic or ophthalmoscopic evidence of any abnormalities. Pupil size was equal between eyes and was no smaller than 3 mm. All normals were asymptomatic and there was no history of any ocular pathology. There were nine males ranging in age from 24 to 75 yr (mean age was 45.5 yr) and seven females ranging in age from 18 to 62 yr (mean age was 43.8 yr). Although the mean age of the study sample exceeded that of the normal controls by approximately 5 yr for the males and 7 yr for the females, our main focus was to evaluate interocular differences. At this point in time, there is no evidence of a significant age effect on interocular difference in VEP peak latency or amplitude in normals.¹⁹

VEP amplitudes on all patients in this study were determined by measuring the difference between the major positive and major negative peaks. Peak times (to be referred to as "peak latency") were taken from the stimulus trigger to the main positive peak.

Peak latency and amplitude measurements for each eye as well as differences between eyes were measured for both the study sample and the normal controls. Mean values and standard deviations for all three square sizes were determined for both samples. Peak latency and amplitude differences between eyes of the study population were arbitrarily considered to be significantly abnormal if these differences were greater than 2.5 standard deviations from the mean difference of the normal controls. Since we compared the good eye with the fellow eye in all the patients, eventual age-related changes in monocular peak latency¹⁹ will not be discussed in the context of this article.

Results

The mean peak latency and mean amplitude values for 14, 28, and 56 min of arc squares were determined for the 32 normal eyes and 40 study eyes. These values are depicted in Figures 1 and 2. The mean difference in peak latency and mean difference in amplitude between eyes for all three square sizes is evident from these two figures.

In the analysis for the significance of the overall mean peak latency and amplitude values of the normal sample compared with the study sample, we found a statistically significant difference between the two samples for all three square sizes for peak latency ($P < 0.01$) and amplitude ($P < 0.05$) using a two-factor mixed design analysis of variance. The VEP peak latencies of the entire study sample were significantly greater and amplitudes were significantly more attenuated than those of the normal sample. This difference was significant even though the study sample included ten patients with presumed monocular

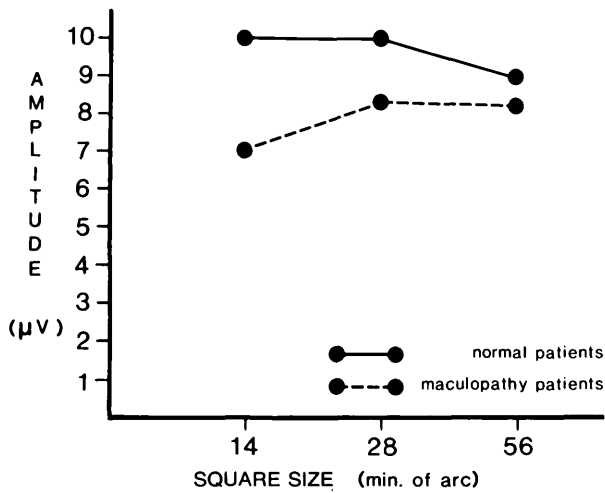


Fig. 2. Mean values for amplitude in normal and maculopathy patients.

pathology, and thus ten "normal"* fellow eyes of these maculopathy patients. Since there was a small mean difference in age between the study group and the normal controls, we cannot conclude unequivocally that these results are related to maculopathy and not to age. However, by extrapolating the curve for age vs VEP peak latencies in Sokol's study¹⁹ for the mean age difference between our two groups, peak latency roughly increases by only 2 msec.

Nine patients (45% of the total study sample) exhibited significant interocular delays in the affected or more affected eye to one or more square sizes. Only two of these nine patients (22%) demonstrated significant interocular differences in amplitude.

All nine of the affected or more affected eyes exhibited significant delays to 28 min or arc squares, while only six affected eyes exhibited delays to 56 min squares; and four, to 14 min squares (Fig. 3).

The macular disease conditions in these patients included: (1) Four cases of macular hole (VA = 10/100, 10/200, 10/300, and 10/400). The VEPs from patient 1 with 10/100 vision in the right eye are depicted in Figure 4. (2) Three cases of atrophic senile macular degeneration (VA = 20/30, 20/50, 20/100). (3) One case of active central serous choroidopathy (VA = 20/20). (4) One case of Best's disease (VA = 20/30).

Two of the nine patients had monocular acquired maculopathy with a presumably normal fellow eye. The other seven patients had bilateral acquired maculopathy in which one eye was more affected than the other.

Eleven patients (55% of the total sample) demonstrated either no interocular VEP delays in the affected

* An eye having good visual acuity although there may have been evidence of minimal fundus changes, eg, macular RPE pigment mottling.

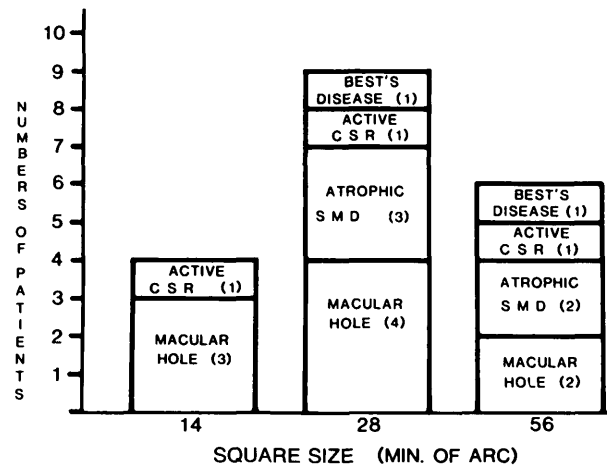


Fig. 3. Numbers of patients with specific disease entities exhibiting significant interocular delays to various square sizes. CSR: central serous choroidopathy; SMD: senile macular degeneration.

or more affected eye or insignificant interocular VEP delays. Of these eleven, only two (18%) demonstrated significant interocular attenuations in amplitude in the affected or more affected eye. All 11 patients had monocular acquired maculopathy with a presumably normal fellow eye.

In the entire study sample, only two out of the 10 patients (20%) having monocular acquired maculopathy had significant interocular delays in the affected eye. However, seven out of the 10 patients (70%) with bilateral acquired maculopathy had significant interocular delays in the more affected eye.

Almost one-half (44%) of the patients having significant VEP delays in the affected eye had a visual acuity of 20/50 or better. One had a visual acuity of 20/20 (active central serous choroidopathy), two had

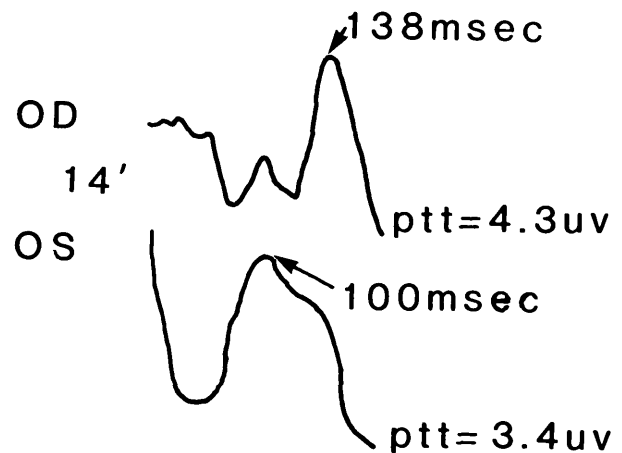


Fig. 4. VEPs recorded from the right and left eye of patient 1 with a macular hole in the right eye. VA: OD, 10/100 and OS, 20/25. The peak latency from the right eye is delayed by 38 msec compared with the left eye. There is no significant difference in amplitude. Square size: 14 min of arc; reversal rate: 7.5 rev/sec; analysis time: 200 msec; averages per trial: 100. Responses are peak to trough and positive is up.

a visual acuity of 20/30 (SMD and Best's disease) and one had 20/50 (SMD). The other patients having significant VEP delays had visual acuities as follows: one had 20/100 (SMD) and four had acuities ranging from 20/200 to finger counting (all with macular holes).

A total of four patients out of 20 (20%) demonstrated significant attenuations in amplitude in the affected eye. Visual acuities ranged from 20/50 to 20/200. Three patients had senile macular degeneration (SMD) and one had a macular hole.

Discussion

The results of the present study demonstrate that VEP delays may occur in some patients with maculopathy without evidence of optic neuropathy. VEP delays, as recorded and analyzed in this study, are therefore not specific in the differentiation of optic nerve disease from maculopathy. A VEP method for distinguishing patients with multiple sclerosis from maculopathy has been suggested²⁰ based upon varying orientation of sine-wave gratings, but further studies are needed. For the moment, however, since VEP delays may occur in maculopathy, a thorough ophthalmoscopic evaluation and other routine clinical testing is recommended in each patient having an abnormal VEP.

It has been postulated that VEP amplitude changes are due to axonal pathology without demyelination and that a pure delay without amplitude reduction is characteristic of a demyelinating optic neuropathy. The results of our study demonstrate that there is no apparent relationship between VEP peak latency increase and concomitant amplitude attenuation in eyes with maculopathy and one can occur independently of the other. This suggests that the physiological mechanisms responsible for VEP delays in maculopathy do not necessarily represent secondary retrobulbar demyelination. Our findings thus raise questions concerning the pathophysiological explanation of VEP delays in general.

Additionally, we have found that VEP delays and an attenuation in VEP amplitude may occur despite normal or near normal visual acuity in some maculopathy patients. These observations suggest that VEP peak latency and amplitude measurements may provide information in addition to visual acuity in some maculopathy patients.

Our findings also indicate that for patients having significant interocular VEP delays and attenuations in amplitude in the affected eye, there does not appear to be a statistically significant difference between square sizes in demonstrating interocular VEP delays or amplitude attenuations. Although we found that more patients demonstrated VEP delays to 28 min

squares than to 14 or 56 min squares, this is not considered to be significant given the small number of patients. However, this issue warrants further investigation and our current study will continue to address it.

Key words: visual evoked potential, macular disease, optic nerve disease, VEP delays

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