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RESEARCH REPORT

VEP ANALYSIS OF PARAFOVEAL VISUAL LOSS IN MULTIPLE SCLEROSIS

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Summary—A patient with optic neuritis had transient loss of visual acuity and a prolonged and profound afferent pupillary defect. The afferent pupillary defect was substantially greater than that predicted from standard perimetry. Visual evoked potentials elicited from the affected eye by gratings presented with the fovea masked revealed parafoveal visual loss not readily appreciated by perimetry.

Key words—Afferent pupillary defect; multiple sclerosis; visual evoked potential; visual fields.

INTRODUCTION

It is well-known that visual acuity and afferent pupillary defect may be dissociated in diseases of the retina and optic nerve (Cox *et al.*, 1982; Thompson *et al.*, 1982). In a series of patients with dense visual field losses, Thompson *et al.* (1982) showed that the magnitude of the afferent pupillary defect depended on both the extent and severity of the field loss, while acuity depended only on the integrity of the central retina. They derived a means for calculating the "volume" of visual field loss, an index which incorporates both extent and severity of field loss, from standard perimetric data. The volume of field loss was directly proportional to a quantitative measure (Thompson *et al.*, 1981) of the size of the afferent pupillary defect.

We studied a patient with unilateral optic neuritis who had a profound afferent pupillary defect but preserved visual acuity. The volume of visual field loss as calculated from formal perimetry accounted for only a small fraction of the observed afferent pupillary defect (Thompson *et al.*, 1982). Visual evoked potentials (VEP) to reversing gratings with and without central masking were measured to define central visual function in further detail. These studies readily demonstrated dysfunction at eccentricities between 0.5 and 2.0 deg. The additional field loss, not evident from perimetry, probably accounts for the large afferent pupillary defect. This evoked-response procedure is a practical method for the monitoring of near-foveal function, and provides information not readily revealed by standard perimetry.

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MATERIALS AND METHODS

Case report

A 34-year-old woman with clinically definite multiple sclerosis (Poser *et al.*, 1983) experienced unilateral visual blurring OS, which progressed to complete visual loss over 12 hours. There was no clinical change with prednisone 80 mg/day for 10 days. Four days after pulse treatment with intravenous methylprednisolone sodium succinate 1000 mg/day, visual acuity had returned to 20/30 (OS), but color discrimination was absent on all of 10 Ishihara plates and a marked afferent pupillary defect remained.

Four weeks after the onset of visual loss, the patient was able to read fine print but reported difficulty with low-contrast targets (such as faded print) and color discriminations. Prednisone dosage was 30 mg/day. Examination of the left (affected) eye revealed visual acuity of 20/20, a normal visual field except for a central 1-deg relative desaturation to red as tested by

confrontation with a red match, and correct identification of 14 of 25 Ishihara plates. The afferent pupillary defect was measured by determining the amount of light attenuation in the right eye that is required to neutralize the unequal response to alternate illumination of the two eyes (Thompson *et al.*, 1981). Measured in this fashion, the afferent pupillary defect was 1.7–2.0 log units. There were no abnormalities OD, and stereopsis was present with a disparity of 40 arcsec (normal). The remainder of the neurological examination was normal.

Eight weeks after the onset of visual loss, on a prednisone dosage of 10 mg/day, visual fields as tested by confrontation were entirely normal and 21 of 25 Ishihara plates were correctly identified. Visual acuity and afferent pupillary defect were unchanged; the left optic disc was now pale. Forty-eight weeks after the onset of visual loss, on no medications, the examination was unchanged.

VEP studies

Flash, checkerboard, and sine grating VEP studies were performed 2, 4, 8 and 48 weeks after the onset of visual symptoms. Visual stimuli were generated by a computer-controlled Tektronix 608 display oscilloscope with a fast (P31) phosphor (Milkman *et al.*, 1980). The display subtended an 8.8 × 8.8 deg region at the viewing distance of 57 cm. Flash stimuli were delivered at a rate of 1.056/s, with an intensity of 300 cd/m^2 and a duration of 3.7 ms. Pattern-reversal stimuli had a mean luminance of 154 cd/m^2, a contrast ratio $[(I_{max} - I_{min})/(I_{max} + I_{min})]$ of 0.3, and a reversal rate of 2.112/s. The checkerboard consisted of a 64 × 64 square lattice, with each square 8.25 min on a side. The spatial frequencies of the sine grating stimuli were 1.5 c/deg and 8.0 c/deg. In the masking experiments, a circular region around the fixation point was kept unpatterned (i.e. uniform and at the mean luminance). The VEP was recorded using bipolar cup electrodes at the usual midline locations C_z and O_z, using mastoid as ground. After amplification and bandpass filtering (0.03–100 Hz), the computer averaged the scalp signal over each 0.947 s stimulus cycle of a 60 s episode. The first major occiput-positive component was identified in the averaged waveforms. The latency of the peak and the peak-to-trough amplitude of this wave were measured. (In instances in which the waveform was W-shaped, the first component of the wave was selected.) The run-to-run reproducibility of amplitudes measured in this fashion was approximately 1 μV. For waveforms in which no clear peak was present, the latency is reported as indeterminate. These waveforms had excursions of less than two microvolts from baseline.

Table 1. Summary of transient evoked-response data obtained from a patient with optic neuritis OS, characterized by a profound afferent pupillary defect but normal acuity. Latencies in ms; amplitudes (peak to trough) in μV

	Time since first symptoms (weeks)	2		4		8		48	
	Eye stimulated	OS	OD	OS	OD	OS	OD	OS	OD
Stimulus									
Flash	lat:	133	120	131	114	131	113	152	111
	amp:	18.5	18.1	18.9	18.5	12.3	16.2	13.6	15.5
Checkerboard	lat:	140	129	176	129	159	127	144	128
	amp:	3.5	7.8	3.3	8.7	2.2	7.6	7.6	13.2
1.5 c/deg grating full-field	lat:	Ind	131	155	137	146	138	133	133
	amp:	<2.0	6.3	5.3	5.9	8.1	8.3	10.4	11.5
1 deg mask	lat:	ND		163	138	157	131	152	137
	amp:	ND		4.4	6.0	3.3	7.0	6.8	11.2
4 deg mask	lat:	ND		146	141	133	105	120	113
	amp:	ND		2.6	5.4	4.1	4.6	2.7	6.4
8.0 c/deg grating full-field	lat:	Ind	130	Ind	144	150	133	139	120
	amp:	<2.0	7.4	<2.0	6.5	3.7	5.7	3.6	11.9
1 deg mask	lat:	ND		Ind	142	Ind	120	Ind	122
	amp:	ND		<2.0	6.7	<2.0	5.0	<2.0	9.1
4 deg mask	lat:	ND		Ind	Ind	Ind	Ind	Ind	146
	amp:	ND		<2.0	<2.0	<2.0	<2.0	<2.0	6.6

ND: not done; Ind: indeterminate (response amplitude <2 μV).

RESULTS

The results of evoked-response testing are shown in Table 1. VEPs elicited by full-field flash were of approximately equal amplitude in the two eyes, but prolonged by an average of 22 ms OS. Responses to the fine checkerboard were attenuated by approximately 50% and the latency was increased by an average of 26 ms OS. The abnormalities in responses to the full-field grating of low spatial frequency (1.5 c/deg) were similar to abnormalities in the flash responses, except that no response was elicitable OS in the first session. There was no response OS to the grating of high spatial frequency (8.0 c/deg) except in the third session, when the response was both attenuated and of increased latency. All responses OD were within the normal range for our laboratory.

In the last three testing sessions, we measured grating responses with the central portion of the gratings masked (Fig. 1). Of note, the amplitudes of the responses to the full-field grating of low spatial frequency (1.5 c/deg) were equal in both eyes. In the unaffected eye (OD), the 1-deg mask produced little or no attenuation of the response (average attenuation, 6%). Two normal eyes also showed no significant attenuation with this mask. However, in the affected eye (OS), this mask resulted in a marked attenuation of response amplitude on all three occasions (average attenuation, 37%). The larger (4-deg) produced some attenuation of the response from the unaffected eye (average attenuation, 32%). This is comparable to the 40% average attenuation seen in responses from two normal eyes. However, on all three occasions, the 4-deg mask produced a more pronounced attenuation in the response from the affected eye (average attenuation, 58%). There was a trend toward decreasing latency with increasing central masking in both eyes in the last two sessions.

Responses OS to the 8.0 c/deg grating were only detectable in the last two testing sessions, and were smaller in amplitude than the responses OD. In both sessions, this smaller response was entirely obliterated by foveal masking; responses from the unaffected eye were attenuated but not obliterated by foveal masking. The latency of the response to the 8 c/deg grating OD was increased at 4 weeks, and shortened progressively at 8 and 48 weeks. This

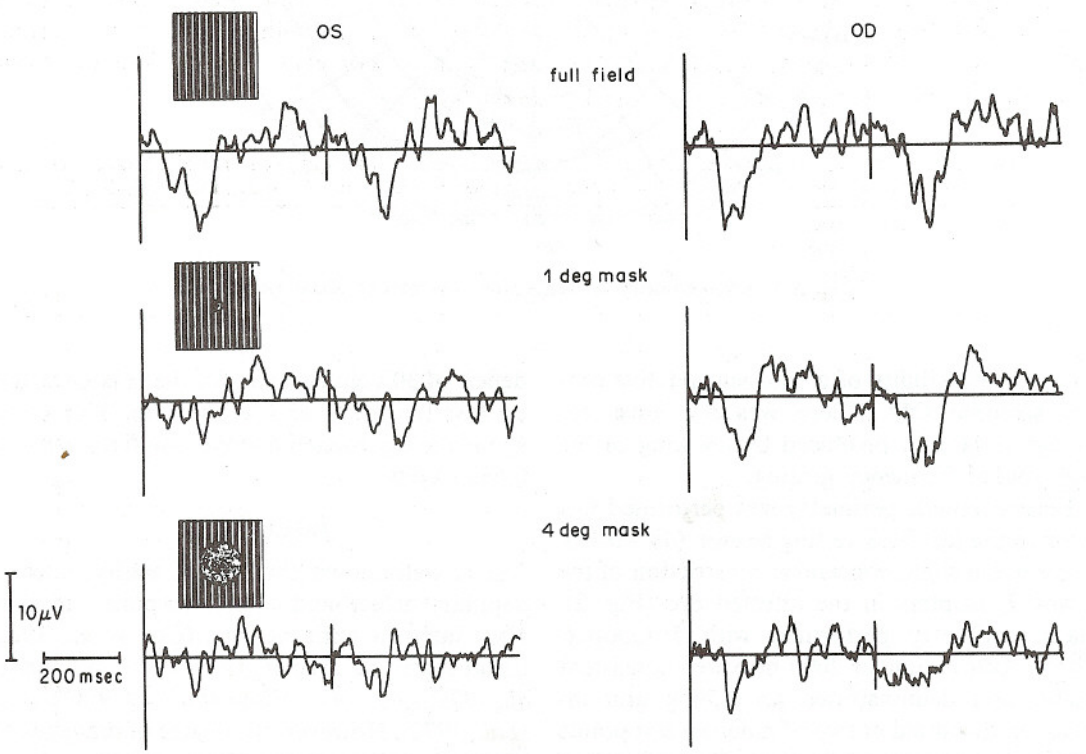

Fig. 1. Transient evoked responses obtained eight weeks after the onset of visual symptoms. VEPs were elicited by a 1.5 c/deg sine grating with and without foveal masking by a uniform circle. One stimulus cycle (consisting of two reversals) is shown. The inset over each pair of responses shows the relative sizes of the stimulus components.

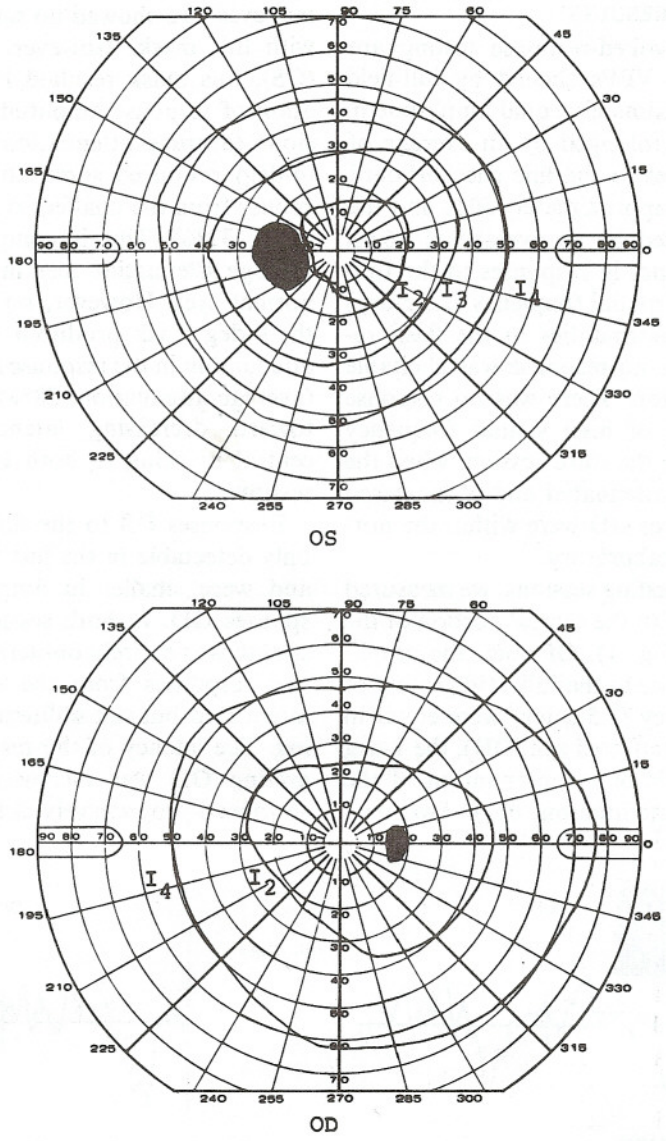

Fig. 2. Kinetic perimetry 48 weeks after the onset of visual symptoms.

raises the possibility of a transient relative central scotoma OD. There was no consistent change in latency produced by masking of the high spatial frequency grating.

Formal kinetic perimetry was performed just prior to the last VEP testing session (48 weeks). There was a slight concentric constriction of the I_2 and I_4 isopters in the affected eye (Fig. 2). Static perimetry performed with a Cooper-Vision AutoPerimeter 2000 provided consistent results and demonstrated an 0.5-log unit increase in threshold at two of nineteen test points within five degrees of fixation. The volume of relative visual loss was calculated from the kinetic perimetry as described by Thompson and coworkers (1982). There was a relative deficit of 30 volume units for the I_2 isopter, and no loss for the I_4 and V_4 isopters. This corresponds to a predicted afferent pupillary defect of 0.5 log units.

DISCUSSION

It is well-known that visual acuity, afferent pupillary defect, and evoked responses may be dissociated in optic neuritis (Cox *et al.*, 1982; Ellenberger and Ziegler, 1977; Bodis-Wollner *et al.*, 1979; Ellis, 1979; Fison *et al.*, 1979; Halliday *et al.*, 1972). However, the degree of dissociation of visual acuity and the afferent pupillary defect seen in this patient is unusual: in one series (Cox *et al.*, 1982) of 23 patients with optic neuritis and visual acuity of 20/25 or better, the typical

afferent pupillary defect was 0.6–0.9, and the maximum afferent pupillary defect was 1.5; this patient had a visual acuity of 20/20 and an afferent pupillary defect of 1.7–2.0.

Demyelinating lesions differ from other kinds of lesions in that the signs and symptoms have a greater tendency to fluctuate (Regan *et al.*, 1977). However, fluctuations *per se* cannot be the basis of the dissociation of visual acuity and the afferent pupillary defect observed consistently over a 10-month period. In visual disturbances due to lesions which cause fixed, dense field losses, Thompson *et al.* (1982) have clearly demonstrated the basis of this dissociation: visual acuity depends only on foveal function, but the afferent response depends on input from the entire retina and thus the afferent pupillary defect is proportional to the extent of field loss. Patients with optic neuritis were excluded from Thompson's study because their field loss was "shallow, variable, and uncertain" (1982). Probably the same basic pathophysiology is at work in patients with optic neuritis and a dissociation of visual acuity and afferent pupillary defect. In particular, this patient had diffuse pallor of the optic disc and therefore a generalized optic nerve dysfunction. However, the extrafoveal visual loss was not dense enough to be manifest in a scotoma, and was underestimated by perimetry.

Assessment of subtle defects in the function of the extrafoveal retina may be very difficult in the presence of relatively normal foveal function. Testing of peripheral retinal function by visual fields is limited in that the detection of a high-contrast and well-defined target is measured; deficits in suprathreshold vision and contrast sensitivity may not be detected. This is one cause for the disparity between visual field defects and VEP abnormalities (Ellenberger and Ziegler, 1977). Contrast-sensitivity measurements over a wide range of spatial frequencies (Bodis-Wollner *et al.*, 1979) may not detect peripheral retinal abnormalities, since the fovea has the lowest threshold at all spatial frequencies (Robson and Graham, 1981). For this reason we resorted to a VEP technique to test extrafoveal retinal function. Because pattern VEP signals are small beyond about 5–10 deg from the fovea, such techniques are limited to the analysis of parafoveal function. On the other hand, because of the large cortical representation of the central retina, a VEP approach is particularly suited to the objective measurement of visual function in this region.

As retinal eccentricity increases, the check size which yields the optimal response increases (Harter, 1970). Nevertheless, to test extrafoveal function with the VEP, it is not sufficient to use a full-field coarse pattern because even for low spatial frequencies, the foveal contribution to the VEP dominates. A low spatial-frequency pattern in conjunction with a foveal mask provides a VEP stimulus which tests parafoveal function above threshold (Cannon, 1983).

In the patient reported here, the greater sensitivity of the affected eye's VEP to the foveal mask demonstrates dysfunction of the extrafoveal retina. The additional visual loss, not readily measured by routine examination or formal perimetry, is the likely source of the profound afferent pupillar defect.

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