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VISUAL LOSS IN MULTIPLE SCLEROSIS AND ITS RELATION TO PREVIOUS OPTIC NEURITIS, DISEASE DURATION AND CLINICAL CLASSIFICATION

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SUMMARY

Visual function was investigated in a group of 58 clinically classified cases of multiple sclerosis (MS). Psychophysical measures of luminance and chromatic threshold sensitivity and temporal contrast sensitivity were undertaken, together with visual evoked potentials and Bjerrum screen perimetry. The patient group was divided on the basis of optic neuritis (ON), clinical disease duration and clinical classification. A comparison of the results of all visual measures suggested a nonuniform loss of function in the patient group without ON and a more consistent loss of function in the group with ON. The various measures were equally efficient in detecting abnormal function, albeit from different areas of the central visual field. Clinical disease duration was not a significant independent factor in predicting visual dysfunction. In contrast, a comparison of clinical classification categories revealed significantly fewer abnormalities of visual function in the suspected MS category (31%) than in the ON, early probable and clinically definite categories (75–100%), a result which indicated the importance of clinical classification as a predictor of visual dysfunction.

INTRODUCTION

The anterior visual pathways are affected in almost all cases of clinically definite multiple sclerosis (MS) examined at postmortem (Lumsden, 1970; Ulrich and Groebke-Lorenz, 1983). During life, abnormalities of the visual pathway have been detected in a high proportion of clinically definite MS and optic neuritis (ON) patients by means of a variety of experimental techniques, including visual evoked potentials (VEPs) (Halliday *et al.*, 1973; Wright *et al.*, 1987), psychophysical measures (Heron *et al.*, 1974; Regan *et al.*, 1977; Hess and Plant, 1983) and visual fields (Patterson and Heron, 1980; Meienberg *et al.*, 1982). In cases of suspected MS, with a single clinical episode of neurological dysfunction, abnormalities of visual function have been found in a much smaller

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Blumhardt *et al.* (1982) studied undiagnosed progressive spinal cord disease and found that the VEP abnormality rate increased from 10% to 36% between subacute and chronic cases with a symptom duration of more than 3 yrs. However, Patterson and Heron (1980), in their visual field study, detected a field defect in 81% of cases with possible MS with a mean duration of 2 yrs. The role of psychophysical measures in determining the extent of visual loss in suspected MS has not been investigated systematically because the McAlpine (1972) category of possible MS used previously excludes isolated clinical episodes, except for progressive paraplegia.

In the present study, visual function was assessed by psychophysical measures made at the fovea, including sensitivity to stimuli selective for luminance and chromatic function and sensitivity to temporal contrast (the de Lange attenuation characteristic; de Lange, 1958), together with VEPs and Bjerrum screen visual fields. Two groups of MS patients were examined: a 'first attack' group, investigated as soon as possible after the clinical onset of the disease, and a group of MS cases of longer duration. The study had two aims: first to assess the pattern of visual loss in cases with and without ON and, secondly, to examine abnormalities of visual function in relation to clinical disease duration and clinical classification. Preliminary reports on some aspects of this study have appeared in abstract form (Honan *et al.*, 1987; Edgar *et al.*, 1988).

METHODS

Luminance and chromatic threshold

Psychophysical measures were performed with a modified visual perimeter, with the stimulus located centrally in the field. The system, which was controlled by a laboratory microcomputer, was similar to that described previously (Foster *et al.*, 1985). The subject was seated in a chair with a firm headrest, 1.2 m from the perimeter screen. An artificial pupil was not used. The test was performed monocularly; the other eye was occluded by a patch. Patients were examined for refractive errors and either wore their own spectacles or a suitable lens was inserted into an eyepiece in front of the eye. The circular stimulus flash, of angle subtense 0.25°, duration 200 ms, selected spectral content (either white, correlated colour temperature 3250 K, or red, cut-on wavelength 622 nm) and variable luminance, appeared superimposed on a steady, concentric, uniform white (correlated colour temperature 3250 K) auxiliary field, of luminance 1.85 log $cd \cdot m^{-2}$ and variable subtense (either 0.25° or 1.25°); an additional, steady, concentric, uniform white conditioning field, luminance 1.42 log $cd \cdot m^{-2}$ and subtense 20°, was introduced to maintain a constant state of retinal adaptation. The stimulus and conditioning fields were both derived from a tungsten-halogen light source. The subject controlled initiation of the stimulus using a push-button box connected to a laboratory microcomputer.

To assess luminance and chromatic sensitivity, four separate stimulus conditions were employed in which a red or white flash was presented on either the large or small (spatially coincident) auxiliary field. Previous studies (Foster, 1981; Foster and Snelgar, 1983; Foster *et al.*, 1985) had shown that the white flash on the large auxiliary field ('white large' experimental condition) yielded a luminance threshold and the red flash on the small auxiliary field ('red small' experimental condition) yielded a chromatic threshold. (The other conditions provided control data, which are not reported here as they were similar to those of previous reports, e.g., Foster *et al.*, 1985.)

The subject was given practice trials before each of the four separate experimental conditions and was instructed to respond (forced choice) 'yes' or 'no' according to whether the stimulus was seen or not. The threshold for each experimental condition was based on 45 stimulus trials, including 5 randomly placed 'empty' trials, containing no stimulus light. The empty trials were inserted to assess subject bias. The

luminance level of the stimulus was adjusted by the microcomputer during each trial sequence using a hybrid adaptive technique (Taylor and Creelman, 1967; Hall, 1981). The time taken to complete the trial sequence for each experimental condition was 5 – 10 min. Response scores as a function of stimulus luminance were analysed using a computer-based method which fitted a cumulative gaussian frequency-of-seeing curve to each set of data (Foster and Bischof, 1987). The stimulus threshold was defined as the level at which the stimulus was seen on 50% of trials.

de Lange attenuation characteristic

Temporal contrast sensitivity was determined using an arrangement of stimulus and background fields in which the 0.25° stimulus had a sinusoidal temporal profile and appeared within a fixed, contiguous surround field (inner diameter 0.25°, outer diameter 1.25°), of luminance 2.0 log cd·m^{-2}. The stimulus and surround fields were produced by yellow light-emitting diodes (peak emission wavelength 584 nm, half-height bandwidth 26 nm), driven by a digital electronic system under the control of the microcomputer. The large conditioning field was identical to that used in the luminance and chromatic thresholds measurements. The luminance L(t) of the stimulus varied as a function of time, t, according to the relationship $L(t) = a + b \cdot \cos(2\ ft)$, where a was the mean (d.c.) light level, b was the modulation depth, normally expressed as a percentage of the mean a, and f was the temporal frequency. The total duration of the stimulus was 2 s.

The subject was again given preliminary practice trials. The temporal frequency was held constant at 8 Hz, the modulation depth of the stimulus was varied, and the subject was instructed to say 'yes' or 'no' according to whether the stimulus appeared to be flickering or steady. The temporal frequency was then set to 2 Hz, the first of the range of values to be tested. A temporal contrast threshold was obtained by varying the modulation depth over 30 stimulus trials according to the adaptive technique described earlier. Five 'empty' trials, in which the stimulus had the constant luminance value b, were again inserted to assess subject bias. This whole sequence of trials lasted about 5 min. Temporal contrast thresholds were determined at temporal frequencies increasing in 3 Hz increments, up to 29 Hz or until a threshold could no longer be recorded because the stimulus appeared not to flicker even at maximum modulation depth. At the end of this series of measurements, the temporal contrast threshold at 2 Hz was redetermined to test for possible fatigue or practice effects. The data were analysed using the same computer-based method described above (Foster and Bischof, 1987).

Visual evoked potentials

Pattern reversal VEPs were measured by a conventional technique. The checkerboard stimulus was generated by a Medelec Sensor ST10, displayed on a Hitachi television screen and the time-locked responses were recorded with a Medelec Sensor ER94a averager. The pattern was reversed at 2 Hz. The test was performed monocularly, the other eye being lightly occluded with an eyepatch. The subject was seated 1.7 m from the screen. The stimulus field subtended 12° horizontal by 9° vertical at the subject's eye; the check size was 48 min arc. The luminance of the dark squares was 1.29 log cd·m^{-2} and of the white squares 2.86 log cd·m^{-2}.

Visual fields

A Bjerrum screen was used to plot visual fields, after the method of Patterson and Heron (1980), where the criteria for detection are defined. The average screen luminance was 0.53 log cd·m^{-2} and the luminance of the white targets was 2.25 log cd·m^{-2}.

Patients

Fifty-eight patients were entered into the study and were divided in two ways, yielding groups according to clinical disease duration and visual history. Additional details concerning Snellen acuity and pallor of the optic disc are given in the Results section.

Classification by disease duration. Group A, the 'first attack' group, consisted of 37 cases investigated as soon as possible after the clinical onset of the disease; the mean duration ± SD was 7.1 ± 4.8, range 0.25 − 14 months. Group B consisted of 21 MS cases of longer duration with a mean of 95 ± 64, range 19 − 228 months. The large variation in disease duration in group B was introduced deliberately to assess the effect of this variable. The patients were classified using the clinical criteria of McDonald and Halliday (1977), although isolated ON was also accepted as a separate diagnostic category. The number of cases in each category is shown in Table 1. Group A contained 11 males and 26 females; mean age was 33.3 ± 8.5, range 20 − 50 yrs. Group B contained 4 males and 17 females; mean age was 34.8 ± 5.4, range 22 − 46 yrs.

Classification by visual history. Patients were reclassified as follows. Group 1 consisted of 29 patients without ON, and group 2 of 29 patients with ON. For cases in group A, the mean duration from the last episode of ON was 5.3 ± 4.5, range 0.25 − 12 months; for cases in group B, mean duration from the last episode of ON was 56.8 ± 55.4, range 6 − 168 months. Therefore both groups consisted mainly of cases which had passed the acute phase (first 6 wks) and were, with respect to duration, comparable with previous follow-up ON studies (Nikoskelainen, 1975).

TABLE 1. CLINICAL CLASSIFICATION*

*Group A***		*Group B***	
MS category		MS category	
Suspected	15	Early probable	6
Optic neuritis	7	Clinically definite	15
Progressive possible	1		
Progressive probable	2		
Early probable	12		
Total	37		21

* Based on the McDonald and Halliday (1977) criteria. ** Group A = first-attack cases; group B = longer-duration MS cases. The number of cases in each category is shown.

A control group of 33 healthy volunteers participated in the psychophysical measures. There was no significant difference between control and patient groups for age ($t = 1.187$, $df = 89$, n.s.) or sex ($\chi^2 = 1.112$, $df = 1$, n.s.). For VEP measurements, a separate control group of 22 healthy volunteers was used which was also well matched to the patient group for age and sex.

Patients were tested in three separate sessions, each lasting 1 − 1.5 h. The first contained the clinical assessment and measurement of visual fields and VEPs. Luminance and chromatic thresholds were measured in the second session and the de Lange attenuation characteristic in the third. The three sessions were usually spread over 2 successive days, to reduce subject fatigue. The sessions were not always performed in the same order. Because of the time-consuming nature of the experimental protocol, visual function was assessed in one eye only. A few patients, because of personal or professional commitments, were unable to attend all sessions.

Statistical analysis

The majority of the statistical analyses involved comparisons of mean threshold levels or VEP latencies, and independent t tests, with pooled estimates of variance, were used. Two-tailed tests were applied, with P values classified as not significant (n.s.) for $P > 0.05$. Where appropriate, mean values and 95% confidence intervals (CIs) were computed. The Mann-Whitney U test was used for data on ordinal scales, and for comparison of clinical disease durations, which were positively skewed. The χ^2 test was used for data on nominal scales. The Pearson correlation coefficient was used to quantify the relationship between duration and measures of visual function.

RESULTS

Effect of optic neuritis

Clinical details. Snellen acuity was impaired, relative to the control group, in both group 1, without ON, median acuity 6/6, range 6/4−6/9 ($U = 296$, $n_1 = 29$ $n_2 = 33$, $P < 0.01$) and in group 2, with ON, median acuity 6/9, range 6/5 to greater than 6/60 ($U = 141$, $n_1 = 29$ $n_2 = 33$, $P < 0.001$). Snellen acuity was also significantly more impaired in group 2 than group 1 ($U = 214$, $n_1 = n_2 = 29$, $P < 0.001$). An afferent pupillary defect occurred in 6/27 cases in group 1 and 13/27 cases in group 2. Pallor of the optic disc was present in 6/28 cases in group 1 and 15/28 cases in group 2. Visual field defects occurred in 9/24 cases in group 1; 5 cases with arcuate scotomata, 2 cases with focal constriction and 2 cases with general peripheral constriction. In group 2, visual field defects occurred in 16/27 cases; 8 cases with central or paracentral scotomata, 5 cases with arcuate scotomata and 1 case each of sector defect, focal constriction and general peripheral constriction respectively.

Psychophysical measures. The luminance and chromatic threshold results are shown graphically in fig. 1A. The mean and 95% CI for control and patient groups are shown. In group 1, without ON, the mean increase in threshold, compared with the control group, for the white large (luminance) condition was 0.22 log $cd \cdot m^{-2}$ ($t = 1.954$, $df = 48$, n.s.) and for the red small (chromatic) condition was 0.18 log $cd \cdot m^{-2}$ ($t = 2.761$, $df = 48$, $P < 0.01$). In group 2, with ON, the mean increase in threshold for the white large condition was 0.62 log $cd \cdot m^{-2}$ ($t = 4.161$, $df = 53$, $P < 0.001$) and for the red small condition was 0.71 log $cd \cdot m^{-2}$ ($t = 3.908$, $df = 52$, $P < 0.001$). Therefore, relative to the control group, each patient group showed approximately equal mean losses of luminance and chromatic sensitivity and the losses were highly significant in the group with ON. This result confirms and extends the findings previously reported from this laboratory on a smaller group of ON cases (Foster *et al.*, 1985). In addition, losses in group 2 were significantly greater than in group 1, both for the white large condition ($t = 2.186$, $df = 51$, $P < 0.05$) and the red small condition ($t = 2.733$, $df = 50$, $P < 0.01$).

The de Lange attenuation characteristic results are shown graphically in fig. 1B. Mean threshold modulation depths and 95% CI for control and patient groups are shown at each temporal frequency. The mean differences (d) between the 2 Hz thresholds obtained at the beginning and end of the sessions for the various groups were as follows: control group $d = 0.02$ log percent ($t = 0.478$, $df = 26$, n.s.); group 1 $d = 0.03$ log percent ($t = 0.939$, $df = 24$, n.s.); group 2 $d = 0.04$ log percent ($t = 0.302$, $df = 26$, n.s.). The differences were very small, confirming that no significant practice or fatigue effects occurred.

In group 1, without ON, there were small, relatively uniform, mean reductions in temporal contrast sensitivity of 0.05−0.12 log percent relative to the control group; these small losses of function were not statistically significant. In group 2, with ON, there were statistically significant mean reductions, relative to the control group, in temporal contrast sensitivity of 0.29−0.37 log percent ($t \geq 4.026$, $df = 55$, $P < 0.001$)

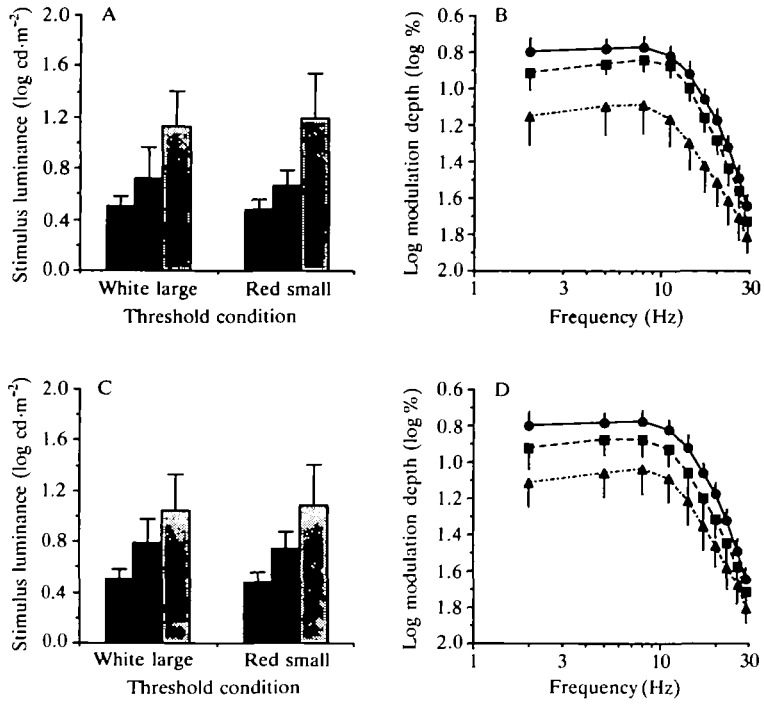

FIG. 1. Mean threshold values and 95% confidence intervals for control and patient groups. The results for patients with and without ON are shown in (A) for luminance and chromatic thresholds, and in (B) for the de Lange attenuation characteristics. The results for patients in group A (first-attack) and group B (longer-duration MS) are shown in (C) for luminance and chromatic thresholds, and in (D) for the de Lange attenuation characteristics. In A, C, filled columns = controls; hatched columns = patients without ON; dotted columns = patients with ON. In B, D, filled circle = controls, filled square = patients without ON; filled triangle = patients with ON.

at all temporal frequencies from 2 to 23 Hz; at 26 and 29 Hz, the mean differences decreased slightly but remained significant ($t \geq 3.103$, $df = 54$, $P < 0.01$) (compare Hess and Plant, 1983; Wright *et al.*, 1987). This pattern of loss was similar to that reported by Edgar *et al.* (1990) in the fovea of patients with ON, although there were differences in the level of statistical significance.

Visual evoked potentials. In group 1, without ON, the mean increase in latency relative to the control group was 7.0 ms ($t = 2.102$, $df = 48$, $P < 0.05$). In group 2, with ON, the mean increase in latency relative to the control group was 27 ms ($t = 5.085$, $df = 47$, $P < 0.001$). The increase in latency of 20 ms for group 2 relative to group 1 was also significant ($t = 3.865$, $df = 53$, $P < 0.001$).

Comparison of individual values. As expected, the psychophysical, VEP and Bjerrum screen visual measures revealed abnormalities of function in the patient groups, both with and without ON. To assess these measures from the standpoint of diagnostic efficiency, a comparison of abnormal results for individual cases was made. It should be noted, however, that the measures assessed different aspects of visual function over

different, but overlapping, regions of the central visual field: psychophysical measures from the central 0.25° diameter region, VEPs from the central 12°×9° region, and Bjerrum screen fields from the central 50° diameter region. For both psychophysical and VEP measures, the normal range was defined as the mean ± 2 SD of the control group. The number of abnormal cases for each individual visual measure is shown in Table 2.

TABLE 2. COMPARISON OF INDIVIDUAL ABNORMALITIES FOR THE DIFFERENT VISUAL MEASURES IN CASES WITH AND WITHOUT OPTIC NEURITIS*

	Group 1 (without ON, n = 19)	*Group 2 (with ON, n = 26)*
Visual measure		
Visual field	6	16
Luminance and chromatic thresholds	7	19
de Lange attenuation characteristic	5	15
Visual evoked potentials	4	20
Cases with at least one abnormal measure	14	24

* Only cases in which all measures were performed are included. The number of abnormal cases in each category is shown.

In group 1, without ON, 14/19 cases had at least one abnormal value. Results for each individual measure, however, showed a much lower proportion of abnormal cases, with no single measure being more sensitive than the others ($\chi^2 = 1.23$, df = 3, n.s.). This variation in proportions of abnormal results can probably be attributed to the patchy character of the demyelination. Psychophysical and VEP measures were recorded from overlapping areas, and in principle may have involved the same affected fibres but, in all 5 cases in which an isolated visual field abnormality occurred, it was an arcuate scotoma located at more than 10° eccentricity from the fovea and thus outside the test region of the other measures. Insofar as comparisons can be made over different measures and different areas of the visual field, the findings were broadly consistent with Regan *et al.* (1976), who also reported a patchy abnormality of visual function, particularly in cases of spinal MS.

In group 2, with ON, 24/26 cases had at least one abnormal visual measure. Again, no single visual measure was more sensitive than the others ($\chi^2 = 2.97$, df = 3, n.s.). The proportion of abnormal cases was much greater than in group 1 and the distribution of abnormal values was more uniform. There were no cases with isolated arcuate scotomata, suggesting a more consistent loss of function in the central visual field. There remained a small variation in relative sensitivity of the two psychophysical measures, although both measures were taken from the same area of the central fovea. Functional differences within the central field have been reported previously for relative perceptual latency and two-flash resolution (Galvin *et al.*, 1976; *see also* Snelgar *et al.*, 1985).

Effect of disease duration

The effect of clinical disease duration was assessed by comparing the results of the psychophysical and VEP measures for the first attack group, group A, and the longer-duration MS group, group B (*see* Table 1 for clinical classification).

Psychophysical measures. Mean luminance and chromatic thresholds and 95% CI for the control and patient groups are shown graphically in fig. 1C. Both patient groups had significantly elevated thresholds relative to the control group. There was a trend for a more severe loss of function in group A, the first-attack group, than in group B, the longer-duration MS group. However, the mean threshold differences (d) did not reach significance either for the white-large (luminance) condition, d = 0.25 log $cd \cdot m^{-2}$ (t = 1.304, df = 51, n.s.) or for the red-small (chromatic) condition, d = 0.34 log $cd \cdot m^{-2}$ (t = 1.668, df = 50, n.s.).

For the de Lange attenuation characteristic, mean threshold modulation depths and 95% CI for the control and patient groups are shown graphically in fig. 1D. There was a well defined reduction of temporal contrast sensitivity in group A, relative to the control group (over 2−23 Hz, mean difference (d) = 0.26−0.31 log percent, $t \geq 3.572$, df = 60, $P < 0.001$). In group B, the loss of temporal contrast sensitivity was smaller (over 2−23 Hz, d = 0.09−0.14 log percent, $t \geq 1.820$, df = 47, n.s.). As in the luminance and chromatic threshold measurements, there was a trend towards a greater loss of function in group A than in group B. Mean differences in threshold modulation depth between groups A and B from 8 to 23 Hz were between 0.14 and 0.16 log percent; these differences were not significant. At 2 Hz the mean difference was 0.19 log percent (t = 2.035, df = 51, $P < 0.05$) which, although statistically significant, probably had no physiological significance. At high frequencies the mean difference between groups A and B also decreased.

Visual evoked potentials. In group A, the mean P100 latency was 120.6 ms, 95% CI 112.9−128.3 ms; the mean increase in latency relative to the control group was 18.1 ms (t = 3.626, df = 56, $P < 0.001$). In group B, the mean P100 latency was 116.9 ms, 95% CI 107.3−126.5 ms; the mean increase in latency relative to the control group was 14.4 ms (t = 3.172, df = 39, $P < 0.01$). Again, there was a small nonsignificant trend towards a greater abnormality of function in group A, the mean difference in latency between groups A and B being 3.7 ms (t = 0.608, df = 53, n.s.).

Correlation of disease duration and visual function. The correlation analysis was undertaken on the combined patient groups. For individual patients, values for each visual measure were compared with the clinical disease duration. There was no evidence of a linear correlation between any aspect of visual function and disease duration or duration from the most recent clinical relapse. This finding cannot be explained by any difference between the groups with and without ON in respect of either disease duration (z = 0.016, $n_1 = n_2 = 29$, n.s.) or duration from the most recent relapse (z = 0.770, $n_1 = n_2 = 29$, n.s.). Thus there was no evidence that disease duration, as an independent variable, was a contributory factor in determining abnormal visual function. However, the time from the most recent episode of ON was significantly shorter in

TABLE 3. EFFECT OF CLINICAL CLASSIFICATION ON ABNORMALITIES OF VISUAL FUNCTION IN INDIVIDUAL CASES*

	Luminance and chromatic threshold (n = 53)	*de Lange attenuation characteristic (n = 53)*	*Visual evoked potentials (n = 56)*	*Total (n = 56)*
Classification				
Suspected	3 (14)	3 (13)	2 (16)	5 (16)
Optic neuritis	6 (7)	5 (7)	6 (7)	7 (7)
Early probable	9 (17)	7 (18)	13 (20)	15 (20)
Clinically definite	9 (15)	5 (15)	7 (13)	10 (13)

* The number of abnormal cases is shown together (in parentheses) with the number of cases measured in each category. The Total column represents the number of cases with at least one abnormal measure.

group A than in group B ($z = 4.229$, $n_1 = 12$ $n_2 = 17$, $P < 0.001$). The trend towards greater losses of visual function in group A can probably be explained by relative recovery in the cases of old ON in group B.

Effect of clinical classification

The effect of clinical classification was assessed by comparing the proportion of individual visual abnormalities in each diagnostic category. There was only 1 case of progressive possible MS, so this was included in the suspected MS category. Similarly, the 2 cases of progressive probable MS were included in the early probable MS category. The number of abnormal cases in the suspected MS group was 5/16, which represented the proportion of cases in which the laboratory visual measures modified the diagnosis (Poser *et al.*, 1983). The number of abnormal cases in the suspected MS category was significantly less than in the other three categories ($\chi^2 = 13.64$, df = 3, $P < 0.01$), whereas no significant difference occurred in the number of abnormal cases in the ON, early probable and clinically definite MS categories ($\chi^2 = 2.14$, df = 2, n.s.).

DISCUSSION

Classification and duration

This study supports the conclusion that clinical classification (McDonald and Halliday, 1977) is an important variable in predicting the occurrence of abnormal visual function. The suspected MS group contained 31% abnormal cases, compared with 75–100% abnormal cases in the early probable, clinically definite and ON groups. Previous VEP reports had found 5–30% abnormal suspected MS cases (Matthews *et al.*, 1977; Ormerod *et al.*, 1987); although these findings are broadly similar to the present ones, they are not directly comparable as all our measurements were obtained from one eye only in each patient. Two previous psychophysical studies (Regan *et al.*, 1976; Galvin *et al.*, 1977) reported 2/4 and 4/5 abnormal cases, respectively, in the possible MS category (McAlpine, 1972): the higher proportion of abnormal cases detected in their series may be related to the different diagnostic criteria and the very small number of cases studied.

The finding that clinical disease duration was not an important independent factor in determining abnormal visual function is at variance with some previous work. For example, Blumhardt *et al.* (1982) reported that the frequency of abnormal VEPs in cases of undiagnosed progressive spinal cord disease increased with disease duration. Ormerod *et al.* (1987) did not observe an increased frequency of VEP abnormality with duration in cases of clinically isolated spinal cord syndromes, although the phenomenon did occur with clinically isolated brainstem lesions. Two combined psychophysical and evoked potential studies are of interest in this context. Salmi (1985) compared critical flicker frequency with VEPs: the proportion of abnormalities in cases of MS or ON with a short clinical disease duration was roughly equivalent, whereas in chronic MS VEPs were more often abnormal than critical flicker frequency. Similar findings, in respect of disease duration, were reported by Lorance *et al.* (1987) in their study comparing spatial contrast sensitivity with VEPs. These psychophysical studies provide supportive evidence that perceptual aspects of visual dysfunction are not necessarily directly related to disease duration.

Some of the differences among these reports may represent a confounding effect of classification on duration. About 90% of cases of clinically definite MS have measurably abnormal visual function (Halliday *et al.*, 1973; Regan *et al.*, 1976); it is likely that with increasing disease duration, more MS cases would fall into this category. The discriminative effect of clinical classification on the probability of detecting abnormal visual function was clearly demonstrated in our series of measurements.

Distribution of lesions

It has been estimated that between a quarter and a third of fibres within the optic nerve subserve vision within 10° eccentricity of the fovea (Polyak, 1957; Potts *et al.*, 1972; Perry and Cowey, 1985). The proportion of cases with central scotomata in the ON group in this study was 8/27 (30%), similar to the 27% and 33% of cases with central scotomata detected in two large follow-up studies of ON (Nikoskelainen, 1975; Perkin and Rose, 1979). Patterson and Heron (1980) detected a high frequency of arcuate scotomata in their study of MS cases in remission. The series was later extended to 100 cases when 359 arcuate scotomata were detected, of which 56% were in the temporal field (V. H. Patterson and J. R. Heron, unpublished observations). Perry *et al.* (1984) in a study of the primate retina, indicated that the nasal retina contained 60% of the retinal ganglion cells, implying that 60% of optic nerve fibres subserved the temporal half-field.

Regan *et al.* (1976) used the term 'islands of demyelination' to describe scattered defects in visual function, particularly in spinal MS cases. A combination of scattered lesions and natural variation in nerve fibre density within the optic nerve may explain the patchy individual visual losses in the group without ON and the more uniform visual losses in the group with ON, where demyelination is likely to affect a larger proportion of the optic nerve. Ulrich and Groebke-Lorenz's (1983) postmortem study of chronic MS cases has provided some support for this view. In all cases in which a clinical episode of ON had occurred, the schematic drawings indicated that the full thickness of the

nerve was affected at some point along its course. However, in the remaining optic nerves the schematic drawings showed that although some nerves showed full-thickness demyelination others were affected in patches and that no part of the optic nerve was selectively damaged.

The clinical importance of this phenomenon is highlighted by the investigation of MS cases without ON, in which a single visual measurement may not reveal abnormal function; this was apparent in our series and that of Hammond and Yiannikas (1986), who compared the usefulness of foveal and full-field VEPs and found the greatest diagnostic benefit in suspected MS.

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REFERENCES

BLUMHARDT LD, BARRETT G, HALLIDAY AM (1982) The pattern visual evoked potential in the clinical assessment of undiagnosed spinal cord disease. *Advances in Neurology*, **32**, 463–471.

EDGAR GK, FOSTER DH, HONAN WP, HERON JR (1988) Changing temporal response characteristics of the visual pathway during the course of demyelinating disease. *Ophthalmic and Physiological Optics*, **8**, 104.

EDGAR GK, FOSTER DH, HONAN WP, HERON JR, SNELGAR RS (1990) Optic neuritis: variations in temporal modulation sensitivity with retinal eccentricity. *Brain*, **113**, 487–496.

FOSTER DH (1981) Changes in field spectral sensitivities of red-, green- and blue-sensitive colour mechanisms obtained on small background fields. *Vision Research*, **21**, 1433–1455.

FOSTER DH, SNELGAR RS (1983) Test and field spectral sensitivities of colour mechanisms obtained on small white backgrounds: action of unitary opponent-colour processes? *Vision Research*, **23**, 787–797.

FOSTER DH, SNELGAR RS, HERON JR (1985) Nonselective losses in foveal chromatic and luminance sensitivity in multiple sclerosis. *Investigative Ophthalmology and Visual Science*, **26**, 1431–1441.

FOSTER DH, BISCHOF WF (1987) Bootstrap variance estimators for the parameters of small-sample sensory-performance functions. *Biological Cybernetics*, **57**, 341–347.

GALVIN RJ, REGAN D, HERON JR (1976) Impaired temporal resolution of vision after acute retrobulbar neuritis. *Brain*, **99**, 255–268.

GALVIN RJ, HERON JR, REGAN D (1977) Subclinical optic neuropathy in multiple sclerosis. *Archives of Neurology, Chicago*, **34**, 666–670.

HALL JL (1981) Hybrid adaptive procedure for estimation of psychometric functions. *Journal of the Acoustical Society of America*, **69**, 1763–1769.

HALLIDAY AM, MCDONALD WI, MUSHIN J (1973) Visual evoked response in diagnosis of multiple sclerosis. *British Medical Journal*, **4**, 661–664.

HAMMOND SR, YIANNIKAS C (1986) Contribution of pattern reversal foveal and half-field stimulation to analysis of VEP abnormalities in multiple sclerosis. *Electroencephalography and Clinical Neurophysiology*, **64**, 101–118.

HERON JR, REGAN D, MILNER BA (1974) Delay in visual perception in unilateral optic atrophy after retrobulbar neuritis. *Brain*, **97**, 69–78.

HESS RF, PLANT GT (1983) The effect of temporal frequency variation on threshold contrast sensitivity deficits in optic neuritis. *Journal of Neurology, Neurosurgery and Psychiatry*, **46**, 322–330.

HONAN WP, HERON JR, FOSTER DH, SCASE MO, EDGAR GK (1987) Visual function and cerebrospinal fluid immunoglobulins in early multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 1718.

LANGE H DE (1958) Research into the dynamic nature of the human fovea–cortex systems with intermittent and modulated light. 1. Attenuation characteristics with white and colored light. *Journal of the Optical Society of America*, **48**, 777–784.

LORANCE RW, KAUFMAN D, WRAY SH, MAO C (1987) Contrast visual testing in neurovisual diagnosis. *Neurology, Minneapolis*, **37**, 923–929.

LUMSDEN CE (1970) The neuropathology of multiple sclerosis. In: *Handbook of Clinical Neurology*, Volume 9. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, pp. 217–309.

MCALPINE D (1972) Clinical studies. In: *Multiple Sclerosis: A Reappraisal*. Second edition. Edited by D. McAlpine, C. E. Lumsden and E. D. Acheson. Edinburgh: Churchill Livingstone, pp. 83–307.

MCDONALD WI, HALLIDAY AM (1977) Diagnosis and classification of multiple sclerosis. *British Medical Bulletin*, **33**, 4–9.

MATTHEWS WB, SMALL DG, SMALL M, POUNTNEY E (1977) Pattern reversal evoked visual potential in the diagnosis of multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 1009–1014.

MEIENBERG O, FLAMMER J, LUDIN H-P (1982) Subclinical visual field defects in multiple sclerosis: demonstration and quantification with automated perimetry, and comparison with visually evoked potentials. *Journal of Neurology*, **227**, 125–133.

NIKOSKELAINEN E (1975) Later course and prognosis of optic neuritis. *Acta Ophthalmologica, Copenhagen*, **53**, 273–291.

ORMEROD IEC, MILLER DH, MCDONALD WI, DU BOULAY EPGH, RUDGE P, KENDALL BE, MOSELEY IF, JOHNSON G, TOFTS PS, HALLIDAY AM, BRONSTEIN AM, SCARAVILLI F, HARDING AE, BARNES D, ZILKHA KJ (1987) The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. *Brain*, **110**, 1579–1616.

PATTERSON VH, HERON JR (1980) Visual field abnormalities in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **43**, 205–209.

PERKIN GD, ROSE FC (1979) *Optic Neuritis and its Differential Diagnosis*. Oxford: Oxford University Press.

PERRY VH, OEHLER R, COWEY A (1984) Retinal ganglion cells that project to the dorsal lateral geniculate nucleus in the macaque monkey. *Neuroscience*, **12**, 1101–1123.

PERRY VH, COWEY A (1985) The ganglion cell and cone distributions in the monkey's retina: implications for central magnification factors. *Vision Research*, **25**, 1795–1810.

POLYAK SL (1957) *The Vertebrate Visual System*. Chicago: University of Chicago Press.

POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FA, EBERS GC, JOHNSON KP, SIBLEY WA, SILBERBERG DH, TOURTELLOTTE WW (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.

POTTS AM, HODGES D, SHELMAN CB, FRITZ KJ, LEVY NS, MANGNALL Y (1972) Morphology of the primate optic nerve. III. Fiber characteristics of the foveal outflow. *Investigative Ophthalmology*, **11**, 1004–1016.

REGAN D, MILNER BA, HERON JR (1976) Delayed visual perception and delayed visual evoked potentials in the spinal form of multiple sclerosis and in retrobulbar neuritis. *Brain*, **99**, 43–66.

REGAN D, SILVER R, MURRAY TJ (1977) Visual acuity and contrast sensitivity in multiple sclerosis–hidden visual loss: an auxiliary diagnostic test. *Brain*, **100**, 563–579.

SALMI T (1985) Critical flicker frequencies in MS patients with normal or abnormal pattern VEP. *Acta Neurologica Scandinavica*, **71**, 354–358.

SNELGAR RS, FOSTER DH, HERON JR, JONES RE, MASON RJ (1985) Multiple sclerosis: abnormalities in luminance, chromatic, and temporal function at multiple retinal sites. *Documenta Ophthalmologica*, **60**, 79–92.

TAYLOR MM, CREELMAN CD (1967) PEST: efficient estimates on probability functions. *Journal of the Acoustical Society of America*, **41**, 782–787.

ULRICH J, GROEBKE-LORENZ W (1983) The optic nerve in multiple sclerosis: a morphological study with retrospective clinico-pathological correlations. *Neuro-ophthalmology, Amsterdam*, **3**, 149–159.

WRIGHT CE, DRASDO N, HARDING GFA (1987) Pathology of the optic nerve and visual association areas: information given by the flash and pattern visual evoked potential, and the temporal and spatial contrast sensitivity function. *Brain*, **110**, 107–120.

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