The rapid assessment of visual dysfunction in multiple sclerosis

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SUMMARY A consecutive series of patients with normal activity and a diagnosis of multiple sclerosis (10 male and 31 female) underwent extensive ophthalmological examination including visual evoked potentials (VEPs) and a new test of contrast sensitivity, which is described in detail. Seventy three per cent of patients had abnormal contrast sensitivity and 83% had abnormal VEPs. There was no association between abnormalities of the two types, but patients who had impaired contrast sensitivity and normal VEPs were younger than those whose contrast sensitivity was normal but whose VEPs were not. The test of contrast sensitivity (which took less than 5 minutes to administer) was the only examination to reveal visual abnormalities in all nine patients with a history of optic neuritis, and would be a useful supplementary test in the examination of patients with suspected multiple sclerosis.

A substantial proportion of patients with multiple sclerosis appear to have no visual involvement when examined by conventional clinical tests. They may complain of imperfect vision despite 6/6 visual acuity on the Snellen test. The purpose of this paper is to present a new technique suitable for routine clinical use that is sensitive to the visual deficits of which the patients complain.

The contrast at which the human observer is just able to perceive a pattern of striped lines (a grating) has been shown to provide a measure of visual function that is sensitive to the impairments associated with a wide range of disorders,¹ including multiple sclerosis.²⁻⁹ Impairments in contrast sensitivity obtain in 60-80% of patients with multiple sclerosis, some of whom have normal Snellen acuity.⁶ Delayed visual evoked potentials (VEPs) are found in about 60-90% of patients, some with normal Snellen acuity, and some who have never had visual symptoms.^{6, 10-18} There is uncertainty as to the strength of the relationship between abnormalities in the VEP and the visual impairments measured by tests of contrast sensitivity,^{4, 18, 19} some authors reporting a stronger association than others, although it is

generally recognised that patients may have one impairment without the other.^{4, 6, 20}

The sensitivity to gratings varies with the angle at the eye subtended by the stripes. When one cycle of the pattern (one pair of stripes) subtends about 15 minutes of arc (that is when the pattern has a spatial frequency of 4 cycles/degree) the human observer is able to detect gratings with a Michelson contrast lower than 0.5%. In other words the difference in the luminance of neighbouring stripes is only 0.0025 times their mean luminance. It is difficult to measure the contrast of gratings when the contrast is so low, and it is usual to generate gratings with a higher, and therefore measurable, contrast using a method that enables lower contrasts to be estimated. For these purposes the most convenient method is to generate the gratings on the surface of an oscilloscope screen using linear amplifiers.^{21, 22} Despite its sensitivity, this method has certain disadvantages from the clinical point of view: it is not suitable as a screening test which requires cheapness, speed, simplicity and portability.

Arden has developed a set of printed gratings for use as a simple clinical test.²³ Each plate contains a sinusoidal grating with a different spatial frequency. The contrast of the stripes varies continuously in a direction parallel to the long axis of the grating bars. In the second edition of this test, the individual plates are withdrawn upwards from behind a stationary mask, slowly exposing portions of the plates with

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progressively increasing contrast. Unfortunately this method has the following disadvantages: (1) an observers' willingness to report weak sensations (his criterion) cannot be separated from his ability to detect them (his sensitivity), and the elderly, for example, may have different criteria from the young;²⁴⁻²⁸ (2) the rate at which the plates are exposed is critical, and a patient's slowness to respond may be confused with a lack of sensitivity; (3) attention has continuously to be maintained and momentary inattention can increase the variability of scores; (4) scores vary considerably from one examiner to another: 95% confidence limits associated with inter-clinician variance cover approximately one quarter of the total dynamic range of the test (Reeves and Hill, in preparation). In addition to these difficulties, the scoring criteria used in many early studies with the Arden gratings were based on norms that failed to take into account the decrease in contrast sensitivity with age.^{24, 29, 30} As a result, high rates of detection of abnormalities were accompanied by high false positive rates.^{28, 29, 31, 32}

Vaegan and Halliday used a revision of the Arden plates that had the advantage of incorporating a criterion-free measure of sensitivity: the observer was forced to choose a grating with a particular orientation from among four low-contrast plates, each with a different orientation. The technique was demonstrably superior in the detection of visual deficits.²⁷

Ginsberg³³ recently developed a similar technique that measures contrast sensitivity over a wider range of spatial frequencies. The observer is shown a series of gratings that descend in contrast arranged in rows on a single chart. The gratings are oriented vertically, obliquely to the left or obliquely to the right, and the observer is instructed to say whether a grating is present, and if so, to give its orientation. Although there are as yet no published data from the test, its discriminability is likely to be poor. This is because there are rather large steps of contrast between grating samples at each spatial frequency. Each test series contains no blanks, other than those gratings that the observer cannot see. The observer is told that there are four alternatives (vertical, oblique left, oblique right, and blank), but it is only if he takes these instructions at face value that the test can be regarded as four-alternative forced choice. The thresholds may be affected by orientation after-effects if observers stare at one of the gratings for too long.³⁴ The arrangement of the test gratings is such that the observer can learn the sequence of grating orientations if the test is administered repeatedly.

The present paper describes a simple test (the Cambridge Low Contrast Gratings³⁵ that, without any loss of reliability, sensitivity or discriminability, cir-

cumvents some of the problems and difficulties posed by the earlier tests. The technique uses very inexpensive printing methods, and measures contrast threshold near the peak of the contrast sensitivity function using a simple two-alternative forced choice method. Any desired orientation can be examined. The following study demonstrates the utility of the test in the examination of patients with multiple sclerosis, and compares the test findings with the results of more conventional examinations, including the visual evoked potential.

Methods

Contrast sensitivity test

The Cambridge Low Contrast Gratings were generated by computer as described by Della Sala *et al.*³⁵ A graph plotter was used to rule parallel lines. Series of lines with a separation of 2 mm alternated with those in which the separation was a few fractions of a millimetre greater. From distances at which the parallel lines could not be resolved only the variations in separation were visible as fluctuations in line density. These fluctuations comprised a grating with square-wave luminance profile. At a viewing distance of 5 m the gratings subtended $1.5^\circ \times 1.5^\circ$ and had a spatial frequency of 4 cycles/degree.

The plates were mounted with a horizontal orientation of the bars on the pages of a spiral bound book, and the book fixed on a stand. The book was illuminated by a filament lamp (60 watts at a distance of 1.5 m) so that the mean luminance was about 50 cd/m². The position of the observers' eyes as well as that of the lamp and plates remained constant from one test to the next. A series of eight pairs of plates (one plate in each pair containing the grating and the other blank) was presented in random order, a total of three times for each eye. The order of testing of the eyes was also randomised. The observer was forced to choose whether the top or the bottom plate contained the grating, guessing if necessary. The errors on each of the three presentations of the test were added giving a total range of 0-24 errors.

VEP examination

VEPs were recorded with MK7 Amplaid equipment. Pattern reversal stimulation used a television display of a phase-reversing checkerboard subtending 11° . The check sizes were 11 mm and 5.2 mm subtending respectively angles of $30'$ and $15'$ at the eye. The rate of reversal was 1.6 Hz and the contrast constant at about 70%. The electrodes (silver-silver chloride discs 7 mm diameter) were positioned at Oz (active), Cz (reference) and Fpz (ground). Bandwidth was 1-100 Hz. The subject was seated in a comfortable armchair and required to stare at a central fixation square for the duration of stimulation. Fixation was monitored. Stimulation was monocular, beginning with the right eye and alternating from eye to eye. Responses (100) were averaged for a period of 250 ms following the change in phase. Two averaged responses were recorded for each check size. The peak latencies of N75, P100 and N140 were measured together with the peak-to-peak amplitude of N75-P100. The criteria for the assessment of abnormalities were based on a difference of

more than two standard deviations from the mean of the worst eye for normal controls as follows: (1) a P100 latency of more than 115.5 for 30' checks; (2) a P100 latency of more than 122.9 for 15' checks; an interocular P100 latency difference of more than 8 ms; (3) an amplitude difference between the two eyes of more than 50%; (4) an N75-P100 interpeak latency difference greater than 90 ms.

Subjects

Ten male and 31 female subjects aged 18–57 years with normal or corrected-to-normal (5/5) Snellen acuity and a diagnosis of multiple sclerosis were selected consecutively from among patients attending the neurology clinic of the University of Milan. Patients were classified according to Rose's³⁶ criteria as definite (19 patients), probable (13 patients) and possible (9 patients). Twenty-six patients reported visual involvement (blurred or washed out vision) in one or both eyes in spite of clinically normal visual acuity. Normative data for contrast sensitivity were derived from 44 male and 30 female age-matched subjects with normal Snellen acuity who were selected from students and patients with non-neurological disease. A further 21 male and 29 female volunteers (aged 10–57) were separately selected to provide normative data for the VEP according to the same criteria as for acuity. All subjects, patients and normal volunteers, underwent a routine ophthalmological examination which included Snellen acuity, slit-lamp examination, tonometry and ophthalmoscopy. In addition, patients had a visual field evaluation by means of a Goldmann perimeter (three tar-

gets: V-4, I-4, I-2). In one patient and two normal subjects one eye was not examined for contrast sensitivity because of incipient lens opacity, and in one patient because of chorioretinitis. None of the patients or the controls was observed to have any other alteration known to affect contrast sensitivity, such as glaucoma, corneal or macular disease etc. Furthermore, all the eyes considered had a Snellen acuity of 5/5 or more, after optical correction when necessary.

Nine patients had a well-documented history of retrobulbar neuritis in one or both eyes, with complete recovery of visual acuity. As far as patients were concerned, particular care was given to the detection of visual disturbances such as blurring by the use of a short questionnaire. Visual fields were considered abnormal if an enlargement of the blind spot or a central-paracentral scotoma could be detected. The minimum requirement for an abnormal fundus was evidence of pallor of the optic disc, even if confined to the temporal area.

Results

The scores from control subjects on the Cambridge Low Contrast Gratings Test were divided into age groups by decade: 20–29 (N = 30); 30–39 (N = 15); 40–49 (N = 16); 50–59 (N = 13) in order to estimate the normal limits (2 SD from the mean of each group). The mean test scores for the worse eye were as

Fig Percentage of total errors made by the worse eye on each pair of plates shown separately for patients and control subjects.

follows: 23.4 (SD 1.0); 21.5 (SD 3.0); 22.1 (SD 2.1); 19.2 (SD 4.9). A post hoc Sheffé analysis based on the ranked data³⁷ revealed a significant difference between all pairwise comparisons of the four groups except that between the third and fourth decades. Page's trend test showed a significant reduction in contrast sensitivity with age ($L = 95511$; $Z = 22.9$, $p < 0.001$). The Pearson product moment correlations between the scores on the three presentations of the test were greater than 0.78.

An analysis of the effects of age similar to the above was performed for the VEP latencies from the worse eye and there was no significant trend as a function of age. For this reason the data for all control subjects were combined and the normal limits expressed as 2 SD from the overall mean for the worse eye. The

figure shows, for both patients and controls, the percent of total errors made by the worst eye on each pair of plates. The table summarises the results of most of the clinical and laboratory investigations. The results of the tonometry are not shown because in every case the intraocular pressure was normal. The patients with normal VEP latencies are shown before those with prolonged VEPs and these two groups are subdivided into those with normal and abnormal contrast sensitivity. The four resulting groups are ordered on the basis of the diagnosis as "possible", "probable" and "definite". There were no significant differences between these groups with respect to the incidence of abnormalities in any of the variables considered.

Seventy-three per cent of the patients had abnor-

Table Details of patients and results of investigations

Sex	Age	Diag	Dn	ON	Sm	VEP				CS	VF	Fs
						30'		15'				
F	57	PROB	4	---	---	---	§	---	§	---	---	---
M	33	PROB	1	---	L---	---	---	---	---	---	---	---
F	35	POSS	3	---	---	---	---	---	---	LR	L---	L---
M	27	POSS	1	---	---	---	---	---	---	LR	---	---
M	24	PROB	0.5	---	---	---	---	---	---	LR	---	---
F	24	PROB	2	---	LR	---	---	---	---	LR	---	---
F	20	DEF	4	---	LR	---	---	---	---	LR	---	---
M	57	POSS	6	---	LR	L%	R%	L%	R%	---	---	LR
F	54	POSS	17	---	---	L%	R%*	L%	R%*	---	---	---
M	35	PROB	3	---	---	L%	R%	L%	R%	---	---	---
F	51	PROB	5	---	---	L%*	---	L%*	---	---	---	---
F	36	DEF	6	---	LR	L%	R%	L%	R%	---	---	---
F	37	DEF	12	---	---	L%*	R%*	L%*	R%*	---	---	---
F	45	DEF	14	---	LR	L%*	---	L%*	R%	---	---	---
F	45	DEF	9	---	L---	L%	---	L%	---	---	LR	---
F	50	DEF	4	---	LR	L%	R%	L%	R%	---	---	LR
M	51	POSS	20	---	L---	---	---	L†%	---	LR	LR	LR
F	30	POSS	2	---	LR	L†	---	---	---	LR	L---	L---
F	38	POSS	0.1	---	LR	---	---	L†	---	LR	---	---
F	18	POSS	3	---	---	L%	R%	L%	R%	LR	LR	---
F	35	POSS	2.5	---	L---	---	R%	---	R%	LR	---	---
M	23	PROB	0.5	---	LR	L%*	R%*	L%*	R%*	LR	---	LR
M	26	PROB	1.5	---	LR	L%	R%	L%*	R%*	LR	LR	LR
M	37	PROB	13	LR	LR	L%	R%	L%	R%	LR	LR	---
F	40	PROB	5	---	---	L%	R%	L%	R%	LR	---	---
F	44	PROB	?	---	---	¶	R%	¶	R%	¶R	---	---
F	44	PROB	?	---	---	L%	R%	L%	R%	LR	---	---
F	48	PROB	3	---	LR	L%	R%	L%	R%	LR	---	LR
F	20	DEF	3	---	LR	L†	---	L†	---	LR	---	---
M	24	DEF	3	L---	L---	---	---	L%	---	LR	---	L---
F	30	DEF	6	L---	L---	L†	---	L†	---	L---	LR	---
M	48	DEF	15	L---	L---	L%	---	L%	---	L---	---	---
F	25	DEF	2.5	L---	L---	L%	---	L%	---	L---	LR	---
F	49	DEF	2	---	L---	L%	R%	L%	---	L---	---	---
F	21	DEF	5	LR	LR	L%	R%	L%	R%	LR	---	---
F	22	DEF	2	---	---	L%	R%	L%	R%	LR	---	---
F	23	DEF	1	---	---	L%	R%	---	---	LR	---	---
F	31	DEF	1	---	---	L%	R%	L%	R%	LR	---	---
F	41	DEF	10	---	LR	L%*	R%*	L%*	R%*	---	LR	---
F	41	DEF	2	---	---	---	---	---	R%	LR	LR	---
F	48	DEF	5	---	---	---	---	---	R%†	LR	---	---

¶ increased P100 latency; * increased N75-N140 interpeak latency; † reduction of P100 amplitude; ‡ increased interocular P100 latency; § chorioretinitis; ¶ lens opacity.

The data are shown in four groups: those with impairments in neither contrast sensitivity (CS) nor visual evoked potential (VEP) in response to 30' or 15' checks, those with deficits on one or other of these tests, and those with deficits on both. Within each group the patients are ordered in terms of their diagnostic criteria (36) as possible (POSS), probable (PROB) or definite (DEF). The duration (Dn) of the illness is shown (in years), and the incidence of optic neuritis (ON), and ocular symptoms (Sm), are shown separately for the left (L) and right (R) eyes, together with abnormalities in the visual field (VF) and Fundus (Fs).

mal contrast sensitivity in one or both eyes. The abnormality was unequivocally monocular in only five (17%) of these patients. Thirty-four patients (83%) had one or more of the VEP abnormalities summarised in the table. Latencies for the 30' checks were abnormal in 73% and those for the 15' checks abnormal in 80%. The correspondence between abnormalities on the two VEP tests was significant (Kendall's contingency coefficient = 0.48). With 15' checks, an increase in absolute P100 latency was observed in 29 of the 33 patients; seven of these also had increased N75-N140 interpeak latency. Two of the four patients without increased latencies showed a significant reduction of P100 amplitude when the left eye was stimulated. Two patients had an interocular P100 latency greater than 8 ms.

All patients but two (95%) had an abnormality in one or both eyes on contrast sensitivity or on the visual evoked response to 15' checks. Five had normal VEP latencies but abnormal contrast sensitivity and nine had the reverse. The association between abnormalities on the two examinations does not approach statistical significance ($P = 0.62$ Fisher's exact test). The patients who had impaired contrast sensitivity but normal VEPs were significantly younger than those whose contrast sensitivity was normal and whose VEPs were not ($Z = 3.011$, $p < 0.0001$).³⁷

The association between abnormal contrast sensitivity and the presence of visual symptoms such as blurred vision did not approach significance, but this was partly due to the large number of asymptomatic patients with impaired contrast sensitivity. Only six of the 41 patients (15%) complained of blurred vision but had normal contrast sensitivity. The association between visual symptoms and delayed VEP also failed to approach significance for similar reasons, and a similar proportion (3/41) complained of blurred vision but had normal latencies. Only one patient complaining of blurred vision had both normal contrast sensitivity and normal VEPs. There was a significant association between the occurrence in either eye of visual field abnormalities and of impaired contrast sensitivity ($p = 0.045$, Fisher exact test): only one patient had impaired visual fields and normal contrast sensitivity, although two others showed this combination in one eye. The association between visual field abnormalities and VEP changes did not approach significance. Abnormalities in the fundus were not associated with impaired contrast sensitivity or with abnormal VEPs.

The nine patients with a well documented history of optic neuritis all had abnormalities in contrast sensitivity and eight of the nine had delayed VEPs. Three of the patients with a history of optic neuritis in the left eye had impaired contrast sensitivity only in that eye. The remainder had impairments in both eyes.

All the five patients with uniocular VEP abnormalities had a history of optic neuritis confined to the abnormal eye. These associations between the history of optic neuritis and uniocular impairments, while suggestive, do not reach statistical significance.

Discussion

All the patients had a Snellen acuity of 5/5 or better, corrected if necessary. Nevertheless 73% of patients had impaired contrast sensitivity in one or both eyes when compared with the sensitivity of the weakest eye in control subjects. The performance of the latter demonstrated the high test-retest reliability and showed the expected decline in sensitivity with age. Patients' scores were considered abnormal when more than 2 standard deviations below the mean of age-matched controls so that a false positive rate in normal subjects of about 2.5% is to be anticipated. Eighty-three per cent of the patients had some abnormality in the VEP examination, but there was no significant association between the incidence of these abnormalities and impairments in contrast sensitivity, consistent with the findings of previous studies.⁶ Despite the fact that neither VEP nor contrast sensitivity findings contributed to the selection of patients, when the two are taken together 95% of the patients had abnormalities. The relatively high incidence of abnormalities may reflect a possible bias towards the selection of patients with ophthalmic complaints, because only about half of the patients who were asked to attend for ophthalmological examination did in fact do so.

It is interesting that the patients with abnormal contrast sensitivity and normal VEPs were significantly younger than those with normal contrast sensitivity and abnormal VEPs. One possible explanation is that contrast sensitivity declines with age as the many ocular and retrobulbar deficiencies to which it is susceptible start to take effect. In the young, whose eyes have yet to show the effects of aging, the deficits in contrast sensitivity resulting from retrobulbar pathology may be more apparent than in the elderly in whom ocular factors play a relatively important role. There is a far less marked change in the VEP with age, perhaps because the conventional form of VEP stimulus is not very sensitive to ocular impairments. The VEP is therefore more likely to detect optic neuropathy in the middle-aged and elderly. It is also possible that the differences in the spatial frequencies used in the two examinations could play a role.³⁸

Both contrast sensitivity and visual evoked potentials were superior to fundus and visual field examination in demonstrating minimal visual disturbance in patients with normal acuity. In our sample of 41

patients only 27% had abnormalities in fundus and 37% in visual fields.

Despite the fact that only one spatial frequency and one orientation was examined, the test of contrast sensitivity was the only investigation able to detect impairments of visual function in all nine patients with a well-documented history of optic neuritis. The history of optic neuritis was unocular in seven of the patients, five of whom nevertheless demonstrated bilateral loss of sensitivity. Abnormalities in the fellow eyes of patients with unilateral optic neuritis have already been reported.^{4, 11} Of the 26 patients who complained of visual symptoms, 20 (77%) had impaired contrast sensitivity and 23 (88%) had delayed VEPs. The more conventional ophthalmological examinations failed to reveal the deficits of which 26 patients complained. None of the patients had impaired Snellen acuity, only 10 (38%) had impaired visual fields, and eight (31%) fundus abnormalities, indicating that contrast sensitivity may provide the only measurement of those aspects of visual function that have remained undetected by previously available ophthalmic tests.⁶

Psychophysical testing has been criticised for being subjective and for depending on "excellent patient cooperation".²⁵⁻²⁷ The test we have described places minimal demands on patient cooperation and is criterion free, which eliminates many of the problems associated with subjective measurement.

The gratings used by Arden,^{4, 39} Vaegan and Halliday²⁷ and Ginsburg³³ are reproduced using complex techniques that keep the price of the tests rather high. The forced choice between gratings with different orientations used by Vaegan and Halliday and by Ginsburg suffers from two obvious disadvantages. (1) It is subject to variability introduced by meridional anisotropies; (2) it is not ideally suited to the measurement of contrast sensitivity over a range of different orientations. Recently deficits in contrast sensitivity in patients with multiple sclerosis have been shown to be orientation-specific, and in some patients it may be necessary to examine more than one orientation in order to detect a deficit.⁴⁰⁻⁴²

The present test is inexpensive, portable and easy to score, and it can examine contrast sensitivity in any orientational meridian. It has the potential disadvantage of measuring contrast sensitivity at only one spatial frequency. On rare occasions sensitivity loss can be more marked for some spatial frequencies than others,^{2, 6} and any test that examines only one spatial frequency may therefore in principle be less sensitive than those that examine the entire frequency spectrum. In some patients the deficits are more marked at higher spatial frequencies than low, and in others the reverse is the case. There are certain patients who show a focal loss at low spatial frequencies (3/48 in

Regan's series)² and a few have normal contrast sensitivity elsewhere in the frequency spectrum (1/22 in a series by Kupersmith *et al.*)⁶ Despite these rare exceptions, diffuse loss is the most consistent pattern.³⁴ Our test, which measures contrast sensitivity at 4 cycles/degree, would therefore be expected to reveal deficits in the majority of patients, as has been demonstrated in this study. The test is designed to be given to patients who have normal Snellen acuity, although this restriction is less of a disadvantage than it might appear, given that it is designed to detect deficits that are not measureable by other clinical methods. The test is very simple to administer and to undertake. It takes less than 5 minutes. A new version of the test using related techniques is now available from Clement Clarke International Ltd.

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