Hospital Topics

Visual Evoked Response in Diagnosis of Multiple Sclerosis

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British Medical Journal, 1973, 4, 661–664

Summary

The diagnostic value of the pattern-evoked response has been assessed in 73 patients referred because of suspected multiple sclerosis. Altogether 52 had delayed responses. Fifty-one patients in the group satisfied McAlpine's criteria for diagnosing definite, probable, or possible multiple sclerosis. Of these, all but two had delayed responses in one or both eyes, while only three of the remaining 22 patients had delays. In those patients with multiple sclerosis but without any history of optic neuritis the incidence of delayed responses was only slightly less. Of 51 patients with delayed responses 23 had normal discs. Thus subclinical lesions of the visual pathways can be readily detected with this test. The high incidence of abnormal pattern responses, even in patients with no other ocular signs or symptoms, suggests that the test is of value in establishing the diagnosis.

Introduction

When light falls on the retina a volley of nerve impulses is set up, and these are transmitted via the optic nerve, tract, and radiations to the occipital cortex. The electrical response produced in the cortex can be recorded by using scalp electrodes and appropriate averaging techniques. While it is relatively easy to record a response after the eye is stimulated with a bright flash, the latency and waveform of the potential evoked in this way are variable. A more reproducible response with a small range in peak latency between different normal subjects can be produced by a checkerboard pattern of light and dark squares which are reversed (so that the black squares become white and vice versa) at a frequency of two per second.[1 2] In a recent paper we showed that the latency of the major positive component of this pattern-evoked response was increased in 17 out of 19 patients with acute unilateral optic neuritis.[3] The delay persisted despite the subsequent return visual acuity to normal; we reported delays persisting five years after a single attack and have since seen cases with delays after 15 years. It thus seems that this method of assessing visual function provides a useful objective test of optic nerve damage.

A common source of difficulty to the neurologist in the diagnosis of multiple sclerosis is the absence of objective evidence of neurological damage at more than one site in the nervous system. The optic nerve is one of the commonest sites for plaques in multiple sclerosis.[4] We have therefore examined the frequency of delayed pattern-evoked responses in this condition.

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Patients

Patients were referred because of a suspected diagnosis of multiple sclerosis. In this report we have included all patients referred during the period of the investigation who were under the age of 60 at the time of recording and whose symptoms began before the age of 50. The only exception to this was that patients with clinical abnormalities of the anterior segment of the eye or of the retina were excluded. Altogether 73 patients were studied. Of these 40 were investigated as inpatients. The 73 cases were divided into two groups, those with multiple sclerosis and those either undiagnosed or with other diagnoses.

MULTIPLE SCLEROSIS

There were 51 patients in this group. The diagnosis was made on a basis of the clinical and laboratory assessment of the patients, including examination of the cerebrospinal fluid and myelography in appropriate cases. By using the diagnostic criteria of McAlpine the cases were classified as definite (34), probable (5), or possible (12) multiple sclerosis. The following is a summary of McAlpine's criteria. Further details are given by McAlpine *et al.*[5]

Definite.—(*a*) A history of an acute neurological episode with improvement but one or more relapses in association with other signs indicative of multiple lesions in the central nervous system. (*b*) A gradual onset of paraplegia later followed by relapses and signs indicative of disease in brain stem, cerebrum, or optic nerve.

Probable.—(*a*) During the original attack clinical evidence of multiple lesions followed by a good recovery. During a lengthy follow-up no clear-cut relapses but with a tendency to variability in the original signs or the occasional late appearance of new signs. (*b*) A history of one or more attacks of acute optic neuritis accompanied or followed by other signs, usually mild, with no clinical evidence of subsequent relapse.

Possible.—(*a*) A history similar to that described under Probable (*a*) but with unusual features or few signs or insufficient follow-up information. (*b*) A history of progressive paraplegia without evidence of relapse or remission or of a lesion outside the spinal cord, appropriate investigation, including myelography, having excluded other causes of progressive paraplegia.

CASES NOT YET DIAGNOSED OR WITH OTHER DIAGNOSES

A breakdown of the 22 cases in this group is given in table I.

TABLE I—*Cases with Diagnosis other than Multiple Sclerosis or Not Yet Diagnosed*

Diagnosis	No. of Cases	History suggesting Optic Neuritis	Delayed V.E.R.
Progressive spastic paraplegia:			
Cervical spondylosis	1	0	0
Cause unknown	6	1	2
Isolated brain-stem lesion, cause unknown	6	0	0
Vestibular neuronitis	1	0	0
Vertigo, cause unknown	1	0	0
Hemisensory loss, cause unknown	1	0	0
Partial cord lesion, cause unknown	1	0	0
Incontinence:			
Lesion of bladder neck	1	0	0
Cause unknown	1	0	0
Subacute progressive encephalopathy with optic atrophy and dementia	1	1	1
Optic atrophy with pyramidal signs, cause unknown	1	0	0
Anxiety	1	0	0
Total	22	2	3

V.E.R. = Visual evoked response.

Method

The details of the method of stimulation by pattern reversal were given in our previous paper.[3] Since that study we have developed an improved stimulator, incorporating a lighter, faster mirror which eliminates an instrumental delay of 15 msec. The mirror movement takes less than 10 msec, as compared with 35 msec in the old stimulator. In the present study 25 patients were tested only by the older method, 32 by both methods, and 6 only by the older method. That the results obtained by the two different methods may be compared simply by adding or subtracting 15 msec was validated on a group of 18 normal subjects tested with each method at the same session. The mean latencies for the group were 103·8 ± 4·3 msec using the newer, faster stimulator and 118·3 ± 4·6 msec with the old, slower stimulator. We have adopted as a working clinical criterion of *delayed* responses latencies of more than 115 and 130 msec for the fast and slow stimulators respectively—that is, a latency increased by more than two and a half times the standard deviation of the normal mean latency.

The age range for the 18 healthy subjects was 18 to 42 years. Though we have found that the latency of the responses in some healthy subjects over the age of 60 may be increased by a few msec we have not recorded any responses with latencies more than 12 msec above the mean in normal subjects below this age. Even if an alternative value of three times the standard deviation (13·8 msec) were to be accepted as defining the upper limit of normal only two cases regarded as "delayed" in the present series would turn out to be misclassified.

Results

In the whole series of 73 cases the pattern response was delayed in 52 (71%). Among the 51 patients with definite, probable, or possible multiple sclerosis only two had a normal latency in both eyes, one from the group of definite cases and one from the group of possible cases (table II). By contrast there were only three patients with an increased latency in one or both eyes among the 22 patients with other diagnoses or who were not yet diagnosed (table I).

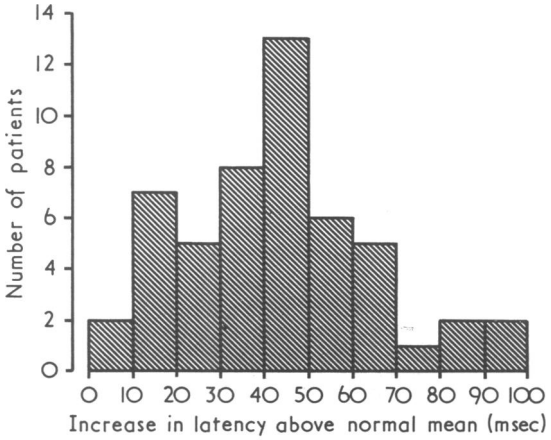
MULTIPLE SCLEROSIS

The range of the increase in latency found in the multiple sclerosis patients is shown in the histogram. In all except two patients the latency was greater than the upper limit of normal as defined above. Delays were uniocular in 14 cases and binocular in 35. Each patient is represented in the chart by the longer of the two latencies.

TABLE II—*Incidence of Delayed Pattern Responses in 51 Patients with Multiple Sclerosis*

	Definite M.S.	Probable M.S.	Possible M.S.	Total
No history of optic neuritis	16/17*	4/4	5/6	25/27
History of optic neuritis	17/17	1/1	6/6	24/24
Total	33/34	5/5	11/12	49/51

*First figure is number of cases with delayed pattern-evoked response; second figure is total number of cases in group.



Range of increase in latency found in 51 patients with multiple sclerosis.

Relation of Latency to Evidence of Optic Neuritis

Optic nerve damage was thus disclosed by the delayed response in more than 90% of the patients with multiple sclerosis. It was interesting to try to determine with what success this damage could have been detected by ordinary clinical methods. A history suggestive of optic neuritis was present in 24 cases (table II). A history alone of visual disturbance, however, is rarely adequate to allow the confident recognition of a previous neurological episode. We therefore turned to the physical signs. Because the patients were referred from several different sources they did not all have an equally detailed clinical assessment. It is therefore not possible to give an accurate estimate of the number of cases in which optic nerve damage could have been established clinically at the time the pattern-evoked response was recorded. The state of the optic discs was, however, recorded in all the cases (table III). One or both optic discs were pale in 28 patients whereas in 23 both optic discs were normal. We decided to re-examine the latter.

Of this group 16 attended. Since their previous examination five patients had developed disc pallor, leaving 11 patients for

TABLE III—*Incidence of Normal Optic Discs in 51 Patients with Multiple Sclerosis*

	Normal V.E.R.	Delayed V.E.R.	Total
No history of optic neuritis	2/2*	12/25	14/27
History of optic neuritis	0	9/24	9/24
Total	2/2	21/49	23/51

*First figure is number of cases with normal optic discs; second figure is total number of cases in group.
V.E.R. = Visual evoked response.

further assessment, 10 of whom had delayed responses. The reassessment included examination of the pupils, colour vision (Ishihara), and visual fields (Goldmann perimeter and Friedman analyser). In only three of the 11 cases could damage of the optic nerve be recognized with certainty—case 1, isolated uniocular colour defect; case 2, uniocular colour defect and field defect with the Goldmann apparatus; case 3, field defects with both methods. Three further patients had doubtful abnormalities—case 4 missed two plates on the Ishihara test and had a slightly increased paracentral stimulus threshold on the Friedman analyser; case 5, similar increase in threshold alone; case 6, slightly increased size of the blind spots. Five cases showed no abnormality with any of the tests used. The single case in the group with a normal latency (case 5) showed a slightly increased stimulus threshold on the Friedman analyser.

Though the number of completely documented cases is small it is clear from this group and from the notorious difficulty in assessing the significance of slight disc pallor that the latency of the pattern-evoked response is the single most reliable index of persisting damage to the visual pathways.

CASES NOT YET DIAGNOSED OR WITH OTHER DIAGNOSES

The composition of this group is shown in table I. Two of the patients with delays had progressive spastic paraplegia of unknown aetiology beginning in early middle life. Among the multiple sclerosis cases (diagnosed without reference to the pattern-evoked response) there were eight cases of progressive spastic paraplegia (six definite, one probable, and one possible multiple sclerosis). Five patients had normal discs but all eight had delayed pattern-evoked responses. From our experience of the multiple sclerosis group as a whole probably the two patients with undiagnosed progressive spastic paraplegia with delayed pattern-evoked responses will eventually turn out to have multiple sclerosis. The third patient with delayed responses had an as yet undiagnosed progressive subacute encephalopathy with optic atrophy and dementia.

Discussion

The outstanding finding reported in this paper was the very high incidence of delayed evoked responses in the patients with multiple sclerosis, even where the clinical picture justified only a probable or possible diagnosis (5/5 and 11/12 respectively; see table II). The high incidence is in accord with Lumsden's necropsy finding of optic nerve plaques in all of 36 unselected cases of multiple sclerosis.[4] Even in those patients with normal discs and without a history of optic neuritis the overall incidence of delayed responses was still 86% (12/14; see table III).

No other studies of the pattern response in multiple sclerosis have so far been reported. Studies of the flash response have yielded a lower incidence of delays. Richey *et al.*[6] found a significant increase in latency of most components of the flash response in their group of 50 patients with multiple sclerosis which was sufficiently large to be considered abnormal in 40% of the cases; however, 6% of their group of normal controls also had abnormal records on the same criteria. Namerow and Enns[7] confirmed the existence of a significant delay in the mean latency of the later components of the flash response in a further group of 20 patients, all with a history of at least one attack of retrobulbar neuritis, compared, in matched pairs, with 20 healthy subjects. The magnitude of the mean delay increased with the degree of impairment of visual acuity. The authors commented on the much greater variability of the latencies of the flash-evoked response compared with that of the somatosensory response, studied by them earlier. Our own experience in recording the flash-evoked responses in cases of optic neuritis confirms this variability of the flash response.[3 8] Not only did we find a much lower incidence of significant delays with this method but the intersubject comparisons were rendered difficult by the variability of the waveform, which often made it impossible to identify a particular component with certainty. Flash stimulation is very much less satisfactory than pattern stimulation in this respect. The major positive component of the pattern response is easily recognizable and has a small range of latencies in the normal population, which renders the recognition of a delayed response unequivocal in most cases.[3]

A prominent feature of our data was the high incidence of delayed pattern responses in the absence of clinical evidence of damage to the visual pathways. Richey *et al.*[6] made a similar observation using the flash response. They attributed delays in these circumstances to indirect effects of lesions lying outside the primary visual pathways. In view of our finding that delays persist indefinitely after an attack of acute optic neuritis, even after the visual acuity returns to normal,[3 9 10] we think it more probable that the delays in patients with no history of visual impairment are indicative of the high incidence of clinically silent plaques in the primary visual pathways themselves. The routine clinical tests of vision are relatively crude. It is a commonplace that observant patients who have had optic neuritis but whose Snellen value and reading acuity have returned to normal, and who have normal fields to a small object of low luminance, may nevertheless complain of subtle distortions of central vision.

The very high incidence of delayed responses in multiple sclerosis, even in the absence of other clinical evidence of optic nerve damage, means that measurement of pattern response latency is a valuable test in the early diagnosis of multiple sclerosis, particularly in cases presenting without signs of a lesion above the foramen magnum.

How specific is the delay in the evoked response to multiple sclerosis and optic neuritis? In addition to the 73 cases reported here we have examined some 120 with other types of neurological disorder. While multiple sclerosis and optic neuritis are by far the commonest causes of delay, other conditions may be associated with an increased latency of the pattern response. We have observed delays in some cases of spinocerebellar degeneration with optic atrophy, some cases of dominantly inherited isolated optic atrophy, and some cases of compressive lesions of the optic nerve. Delayed pattern responses have also been reported in glaucoma.[11] The latency of the pattern response is influenced by the intensity of illumination used.[10] Thus a delayed response is in no way specific to a particular disease or to an alteration at any particular site in the visual system. Provided disease of the cornea, lens, media, and retina is carefully excluded, however, it is reasonable to conclude that a delayed response is due to a lesion affecting the optic nerve or more posterior parts of the visual pathways. In patients, therefore, the delayed evoked response assumes the status of an objective physical sign. It provides evidence of neural damage but its exact interpretation depends on the clinical context. Since delays are not invariably present in multiple sclerosis a normal latency cannot exclude this condition. Nevertheless, the very high incidence of delays means that the finding of a normal latency in a case of suspected multiple sclerosis with an established neurological deficit should lead to a careful reconsideration of the diagnosis.

The mechanism of delay in the pattern response in multiple sclerosis and optic neuritis will be considered in another paper but slowed conduction through demyelinated regions must contribute to the delay.[3 12] Whether local slowing is the whole explanation of the very long delays in some cases of multiple sclerosis remains to be determined.

We thank the phvsicians and surgeons of Moorfields Eye Hospital and the National Hospitals who referred patients to us, and Mr. J. R. Pitman for technical help.

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Medicine in Old Age

Diseases of the Motor System

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British Medical Journal, 1973, 4, 664–666

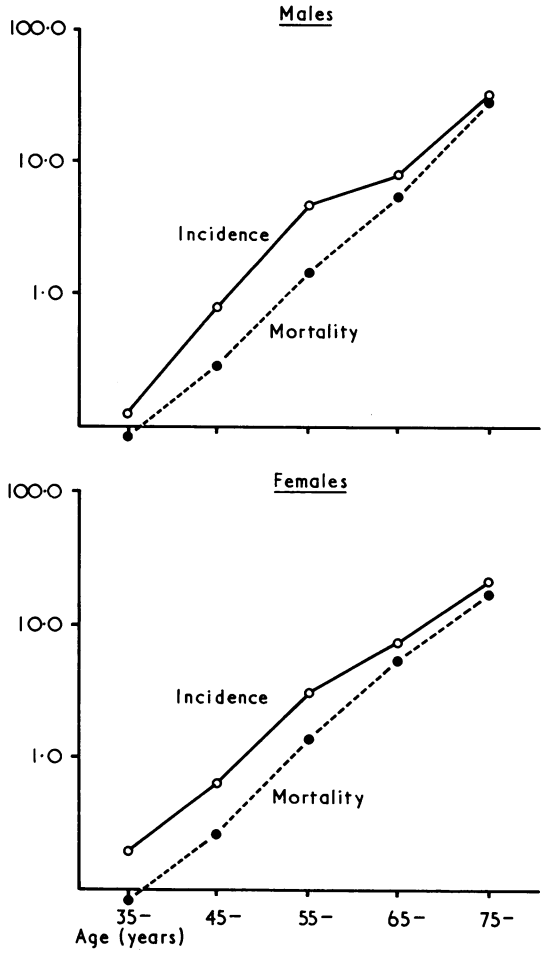
The Registrar General's *Statistical Review of England and Wales for the Year 1970* shows that 19% of all deaths in the over-65s were directly attributed to diseases of the nervous system. In addition, the 4% of all deaths in the same age group attributed to diseases of the arteries must include a proportion with central nervous system involvement. Mortality figures reflect morbidity (see fig.); every geriatric department contains more patients in this disease category than in any other. Though patients over 65 constitute only 12% of the total population, they occupy over one-third of the total N.H.S. beds—or a total of roughly 80,000 excluding psychiatric hospitals. Taken together, these facts indicate that elderly patients with diseases of the central nervous system must make formidable demands on the resources of the N.H.S. Moreover, with an annual rise of 100,000 in the over-65s this demand must continue to increase.

Disease of the Pyramidal System

By far the commonest disease of the central nervous system encountered is a stroke, varying from a disabling hemiplegia to a transient ischaemic cerebral episode with rapid recovery. A stroke with paralysis warranting admission to hospital is more common than acute appendicitis; a general practitioner with a list of 3,000 will see five new strokes each year and will have a similar number of disabled stroke survivors on his list. The annual stroke incidence is about two per 1,000 of the total population—which means 110,000 new stroke presentations each year in England and Wales. Three-quarters of all stroke patients are over the age of 65. In the United Kingdom 130,000 patients have appreciable impairment from a stroke and 93,000 of these are severely handicapped.[1]

The onset of a stroke due to cerebral thrombosis or embolism is usually first noticed after a period of sleep or rest. The patient may rise from bed to go to the lavatory and promptly falls owing to paresis of the leg. Relatives may become alarmed because the patient is vacant and confused after an afternoon nap; when the doctor arrives the patient appears normal again. This latter episode is typical of transient ischaemic cerebral episodes, which may recur with frequency.

The patient with a major stroke has motor weakness of both the arm and leg; initially there is flaccid muscle tone with



Semilogarithmic plot by age and sex of estimates of incidence and mortality in the Oxford Record Linkage area in 1963 for all types of stroke combined. (Acheson, R. M., and Fairbairn, A. S., *British Medical Journal*, 1970, **2**, 621.)

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