Subclinical optic neuropathy in multiple sclerosis¹

How early VER components reflect axon loss and conduction defects in optic pathways

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SYNOPSIS The pathological effect of multiple sclerosis in the visual pathways consists of axonal demyelination and axonal loss. These two consequences of the disease, even in its subclinical stages, are reflected in changes in the initial component of the visual evoked response (VER) affecting its latency, configuration, or both. These abnormal early components of the VER were recorded in 25 patients with multiple sclerosis, only 10 of whom had any indication of visual involvement that could be documented historically or by conventional ophthalmic investigations.

Electrophysiological changes occur in the optic pathways of multiple sclerosis (MS) patients in advance of clinical symptomatology. In 1971 Richey *et al.* reported that the average peak latencies of four occipital components of the visual evoked response (VER) were significantly delayed. Identical findings were soon reported by others (Namerow and Enns, 1972; Halliday *et al.*, 1972, 1973; Feinsod *et al.*, 1973). These investigators suggested that a major factor in the delay was demyelination of axons, as demonstrated experimentally in diphtheria toxin induced demyelination of cat spinal cord (McDonald and Sears, 1970).

Recently, Frisen and Hoyt (1974) reported funduscopic findings in the retinal nerve fibre layer indicating the presence of focal and diffuse axonal attrition in MS, even in patients without visual symptoms or signs. These findings in the eye supply a clinical analogue for the established pathological (Greenfield and King, 1936; Adams and Kubik, 1952) and experimental conclusions (McDonald and Sears, 1970) that the underlying

pathology in MS is a combination of axonal degeneration and demyelination, both of which may be insidious, as was also demonstrated in an epidemiological study by Kahana *et al.* (1973). This report documents and discusses the electrophysiological correlates of axonal loss and demyelination as recorded by us in the VER of a series of MS patients.

METHODS

PATIENTS Data in this study were obtained from 25 patients in whom a diagnosis of multiple sclerosis was established according to the criteria of McAlpine *et al.* (1972). In 15 patients there were no visual symptoms or signs. Four patients had had retrobulbar neuritis and six had signs of chronic bilateral optic neuropathy.

OPHTHALMOSCOPIC EXAMINATION This was performed with a modern battery-powered hand ophthalmoscope that provides an exceptionally bright red-free illumination of the peripapillary nerve fibre layer (Hoyt *et al.*, 1973; Frisen and Hoyt, 1974).

VISUAL EVOKED RESPONSES Our patients were examined with dilated pupils (Mydril 1%) in a darkened room. Grass gold plated electrodes were fixed to the scalp with Grass electrode paste. The visual evoked response (VER) was recorded between the active O₁ and O₂ electrodes, and the linked ears

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FIG. 1 A normal VER recorded from the left (LT) and right (RT) occipital regions.

FIG. 2 VER to stimulation of the left (OS) and right eye (OD) in a patient with spinal MS. Note the increased latency of the initial negative component (arrows).

FIG. 3 VER in a patient with brain-stem involvement due to MS. Note the break down of the initial negative component into 'subcomponents' (arrows).

served as reference (10–20 EEG international nomenclature). The resistance between the active and the reference electrodes was kept between 2 000 and 5 000 Ω . EEG signals were amplified by a Grass model VII electroencephalograph (band width 1–70 Hz) and fed to a Mnemotron CAT computer of averaged transients 1 000B with 1 MHz modulated cards. A standard calibration pulse was averaged at the beginning of each examination.

One hundred 1/s flashes at 20 cm from the dilated pupils were delivered by a Xenon discharge lamp activated by a Grass Photostimulator PS-2 at intensity 4. The photostimulator and the CAT were triggered by a Grass Physiologic Stimulator (S4) in such a way that each computer averaging cycle was initiated 25 ms before the flash. Analysis time was 250 ms. Auditory masking was not required. The average responses to monocular stimulation were displayed on a Tektronix 502 cathode ray oscilloscope and photographed with a Polaroid camera.

Our data in normal subjects coincided with those reported by Kooi and Bagchi (1964) and by Richey *et al.* (1971). The normal flash-evoked potential under these test conditions consists of an initial negative deflection with a peak latency of 40–50 ms, followed by a W-shaped wave (Fig. 1). The components are named according to their polarity and latency. Thus the first negative component is N_{45} followed by P_{65} , N_{90} etc.

RESULTS

In all 25 MS patients examined by us, latency and shape of the initial negative component of the VER with stimulation of each eye were abnormal. Three basic patterns were found. The first pattern was one with prolonged peak latency (45 ms in the normal), sometimes as much as

80 ms (Fig. 2). The second pattern was one showing breakdown of the first negative component into multiple subcomponents, usually two to four in number. The latencies of the first subcomponent sometimes fell within the range of normal, but the remaining subcomponents were delayed (Fig. 3). The VER recorded from some of our patients displayed combinations of the first and second pattern, delayed peak latency and breakdown of the initial component (Fig. 4). The third pattern was a very low amplitude

FIG. 4 VER in an MS patient with history of an attack of optic neuritis in each eye demonstrating the combined effect of delayed conduction and break down into 'subcomponents' of the initial negative wave (arrows).

FIG. 5 VER in MS patient with cerebellar signs. Note disappearance of all recognized patterns of the VER. (The patient had no visual symptoms.)

bizarre VER in which none of the usual single components was recognized (Fig. 5).

Examination of the peripapillary nerve fibre layer showed abnormality in 17 of the 25 patients. These abnormalities consisted of two patterns. The first was slit-like defects in the

arcuate nerve fibres combined with diffuse thinning of the nerve fibre layer (Frisen and Hoyt, 1974) (Fig. 6). The second was diffuse thinning of temporal peripapillary nerve fibre bundles with lesser degrees of thinning in the remaining sectors surrounding the optic disc. The latter pattern included mild temporal pallor of the disc. In several eyes of patients in whom we initially found no abnormality of the retinal nerve fibre layer, and in whom the VER was clearly abnormal, a second examination of the fundus revealed marginal signs of focal or diffuse thinning in the nerve fibre layer. However, we did not consider these changes definite enough to conclude that axons had degenerated from the retinae. In one young patient, who had characteristic symptoms of dim vision during exercise and hot baths, we found no sign of abnormality in the fundi, colour perception, visual acuity, or fields of vision. However, the initial component of the VER was clearly delayed.

While 17 of our 25 MS patients had nerve fibre layer signs of axonal atrophy, only six of the 17 had corresponding changes in their optic discs.

Thus, it was the VER that consistently provided evidence of abnormality. It demonstrated clear evidence of optic pathway involvement in seven patients in whom all objective ophthalmological criteria of normal, including the appearance of the retinal nerve fibre layer in red-free light, were satisfied.

DISCUSSION

The clinical value of the abnormal flash or pattern-evoked VER in the diagnosis of multiple sclerosis has been confirmed by Richey *et al.* (1971), Namerow and Enns (1972), Feinsod *et al.* (1973), and Halliday *et al.* (1973), though each of these groups of investigators has defined the abnormality by differing criteria determined by the technique employed by each for stimulation and recording. Of special importance is the frequent finding of abnormal VER in MS patients who have no historical or clinical signs of visual system involvement (Richey *et al.*, 1971; Feinsod *et al.*, 1973; Halliday *et al.*, 1973). Subclinical demyelination in visual pathways was proposed as a possible explanation, but how

FIG. 6 Retinal nerve fibre layer defects in a patient with spinal MS and no visual symptoms. Note multiple slit-like gaps in the arcuate nerve fibre bundles (arrows). These gaps indicate nerve fibre atrophy from retrograde degeneration.

such involvement alters latency and configuration of the VER has not been clarified satisfactorily.

Demyelination of peripheral or central axons slows conduction and alters the responsiveness of the affected pathways to various stimuli (McDonald and Sears, 1970; Davis and Schauf,

1974; McDonald, 1974). The electrophysiological correlate of slowed conduction is extended latency of the VER, as illustrated in Fig. 2.

A VER component may be regarded as the sum of electrical changes evoked by impulses ascending at varying conduction velocities along

FIG. 7 Schematic representation of normal (top) and abnormal (middle and bottom) VER components. Each VER component (shaded area) is the algebraic sum of multiple subcomponents. Drop out of a sub-component (dotted triangles) can distort the shape or shift the peak.

afferent fibres of varying calibre (Fig. 7). If fast conducting fibres in a sensory pathway are selectively affected, peak latency and form of the summated cortical activity will be changed (Fig. 7, middle traces). Loss of groups of axons of differing conduction velocities will produce a multi-peaked initial component in the VER (Fig. 7, lower traces), as was frequently recorded in our MS patients (Figs 3 and 4). Clinical evidence for axonal loss in visual pathways of patients with chronic demyelinating disease has been documented in red-free photographs of the retinal nerve fibre layer (Frisen and Hoyt, 1974). Experimental evidence for this attrition of axons with demyelinating lesions is provided in the report of McDonald and Sears (1970).

The effects of multiple sclerosis on the axons of the optic nerve are not uniform with regard to calibre of fibres involved, or severity. Accordingly, a variety of distortions in the form of the early VER component would be expected. We believe that most of the subclinical electrophysiological abnormalities that we and others record in visual evoked responses of MS patients can be explained satisfactorily by varying degrees of conduction delay in demyelinated axons and depletion of axons in the optic pathways. The possibility that delay in conduction and change in pattern of the VER could be caused in part by a humoral factor that impairs synaptic transmission in multiple sclerosis has been inferred from the tissue culture experiments of Bornstein and Crain (1965) but the existence of such a circulating factor in man remains entirely in the realm of speculation (McDonald, 1974).

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