Visually evoked responses in multiple sclerosis

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SUMMARY Visually evoked cerebral responses (VERs) from the occipital and central areas were compared between 50 patients with multiple sclerosis and 50 control subjects. The average peak latencies of four occipital components (OII-OV) and two central ones (CIV and CV) were significantly delayed. In no instance was the amplitude significantly different. Routine EEGs were either entirely normal (16) or showed only minor findings (10) in 26 patients. Of this group, nine showed abnormal VERs. Seventeen patients had clinical symptoms or signs which pointed to spinal cord involvement only; nonetheless, eight in this group had abnormal responses. Inasmuch as changes in visually evoked potentials are not directly dependent upon the presence of a demonstrable field defect, the technique may be useful in detecting otherwise occult cerebral lesions.

Because multiple sclerosis frequently produces visual defects, it is natural to anticipate concomitant changes in visually evoked cerebral responses. However, a preliminary study of a small group of patients revealed that, while there were evident changes in some patients, they were not necessarily those having signs of involvement of the visual system. In the present study, an expanded sample of patients with multiple sclerosis was examined in order to ascertain (1) the effect of the disease upon the latencies and amplitudes of visually evoked waves, (2) the proportion of patients who have clearly abnormal responses, (3) the clinical correlates, if any, of the alterations, and (4) their relation to routine electroencephalographic findings.

SUBJECTS AND METHODS

Visually evoked responses (VERs) were obtained on 50 patients with multiple sclerosis (35 females, 15 males) and 50 normal subjects (35 females, 15 males). The two samples were matched with respect to age (averages of 40-2 years each). Control subjects were in good health, without neurological illness, and not on any medication. All patients were hospitalized during a period of exacerbation of their disease. The final diagnosis of multiple sclerosis was made in each case by the Neurology Service.

The same procedure was followed in all subjects and patients. A resting EEG was obtained along with the evoked response study. The face of a Grass PS-2 photic stimulator lamp enclosed in a double walled box was placed 5 cm before the open eyes. No responses were detectable in control runs with the light covered. Background light intensity was adjusted to approximately one foot candle.

Routine EEGs were run on a Grass Model III Electroencephalograph. The evoked responses were summed with the Mnemotron Computer of Average Transients. Three computer runs were obtained. The averaging period for the first two runs was 250 msec and for the third was 125 msec. Light flashes were randomized and given one every 4 to 6 sec to a total of 50 for the first two runs and one every 0.5 to 1 sec to a total of 300 for the third run.

During the first run, data were obtained from the following electrode positions: left and right frontal, central, occipital, and temporal areas. The reference was joined-ears. Occipital electrodes were placed 3 cm above and 3 cm lateral to the inion. Central electrodes were placed 4 cm from the midline in the interaural plane. Data from the second and third computer runs were used to substantiate the initial observations and further to assess possible ocular and myogenic artefacts. The summed responses were displayed on a Tektronix cathode ray oscilloscope and photographed with a Hathaway oscilloscope camera.

Individual components of the evoked responses from the occipital and central regions were used for analysis. Both left and right-sided measurements were obtained with the left-sided values being used for statistical analysis (Kooi, Güvener, and Bagchi, 1965). The first five major occipital waves in either a negative or positive direction after the stimulus were studied. The vertex sharp wave

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(CV), a surface-negative deflection, was evaluated from
the central response. The preceding positive wave (CIV)
was also studied. Ranges for latencies and amplitudes of
these occipital and central components are based on
previous studies by Kooi and Bagchi (1964) and Kooi
et al. (1965), and the control data obtained from the
present study. CIV and CV were not measured if the
eye blink artefact extended into the central regions.

Amplitude orders were established for the major com-
ponents of the occipital and central response in the
patient and control groups. Waves having the greatest,
second greatest, and third greatest amplitudes in both
negative and positive directions were identified and their
latencies plotted (Fig. 1A and B and Fig. 2A and B).

The first major wave of the normal occipital VER is a
surface-negative deflection (OI) having a general latency
range of 30-70 msec. As seen from Fig. 1A, 2 clusters of
latencies fall within the general range of OI. The inter-
mediate wave previously described by Richey, Kooi, and
Waggoner (1966) is responsible for the second of these.
The next major deflection is a surface-positive one (OII)
with a latency of 50-100 msec, a second surface negative
deflection (OIII) with a latency range of 70-125 msec,
then a second surface-positive component (OIV) having
a latency range of 100-150 msec, and, finally, a surface-
positive deflection (CV) with a latency range of 125-190
msec. Later occipital components were not measured and
evaluated statistically. Latency ranges of CIV and
CV are 95-115 msec and 110-165 msec respectively. These
2 deflections are seen in Fig. 2A. Earlier central com-
ponents were also not evaluated statistically.

Latency was determined by measuring the interval be-
tween the instant of the stimulus and the peak of the
appropriate major deflection within each range. Amphi-
tude for the first occipital component was measured from
the averaged base line to the peak of OI. For each suc-
ceeding component, in both occipital and central regions
amplitude was determined by measuring from the peak
of the preceding wave to the peak of the wave being
measured. In a few instances, one or more components
could not be identified. Measurements of selected waves
in occipital and central regions have shown high orders
of reliability in earlier test-retest studies with correlation
coefficients of .91 to .96 for latencies and of .87 and .97
for amplitudes. Reproducibility is enhanced through the
use of eyes-open technique which reduces variance from
'background' activity as well as factors related to the
structure of the eyelids.

The VER was classified as abnormal if there was (1)
absence of discernible response, (2) a unilateral absence
or a left-right voltage difference of greater than 75% of
one or more waves in homologous areas, or (3) a distinct
left-right asymmetry of form confirmed by a difference
in peak latency of the wave of more than 15 msec in
homologous areas, or (4) in the case of CV, an absolute
latency exceeding 170 msec (Kooi and Bagchi, 1964;
Kooi et al., 1965). Three of the normal controls had
responses which met these criteria, all because of asym-
metries of form.

RESULTS

Twenty-six of the 50 resting EEGs in the patient
group were either entirely within normal limits or
showed only borderline non-specific findings. Twenty EEGs showing primarily theta or theta-
delta patterns in the temporal regions were classified
as mildly abnormal. Three records were interpreted
as moderately abnormal because of an excess of slow
components in the background pattern plus
temporal theta-delta transients. One record was
markedly abnormal because of a slow background
pattern (7-8 Hz) plus delta activity shifting between
the temporal regions. In no case were spikes or
spike-wave discharges seen.

Figures 1 and 2 show the peak latencies of the
major waves in occipital and central regions selected
according to relative amplitude in control and
patient groups. By inspection there is more vari-
ability in the patient group with a resultant lack of
definition of the clusters representing each of the
major components previously described.

Table 1 shows the analysis of average latencies
for the five occipital and two central components.
Every component shows a statistically significant
delay in the patient group with the exception of OI.
Further statistical evaluation revealed that the
latency of OI was not significantly different in the
patients and controls when the patient group was
restricted to the 18 cases with visual signs—central
scotomata (11), enlarged blind spots (four), homono-
ymous field defects (three), optic atrophy (two),
bilateral nonhomonymous field defects (one).

Although there was considerable variation in
amplitudes throughout the patient group and many
individual cases showed definite left-right amplitude
asymmetries of one or more components, in none
of the statistical comparisons of either the right or
the left side were average amplitudes of the five
occipital or two central components statistically
different from comparable components in the
control population. When patients with and without
visual system damage were compared, no significant
differences emerged between average latencies or
amplitudes of any of the seven components studied.

Figure 3 shows typical central and occipital
responses in a normal subject.

Figures 4 to 6 are examples of the evoked response
in the central and occipital regions of three multiple
sclerosis patients.

Table 2 shows a comparison between all cases of
multiple sclerosis versus cases by neurological
categories in respect to incidences of normal VERs.
The proportion of deviant responses was not signi-
ificantly different in the group of 18 patients who had
evidence of visual system damage as compared with
the group as a whole. The 10 brain-stem dysfunction
cases showed primarily dissociative nystagmus. Of
five patients presenting with an organic mental
Visually evoked responses in multiple sclerosis

FIG. 1. Amplitude orders and latencies of major waves in the occipital region, three surface-negative and three surface-positive for each subject. A: control subjects, N = 50. B: patients with multiple sclerosis, N = 49. Note that the individual components (latencies given in text) are not well delineated in the patient group.

FIG. 2. Amplitude orders and latencies of major waves in the central region, three surface-negative and three surface-positive for each subject. A: control subjects, N = 46. B: patients with multiple sclerosis, N = 49. (See under Fig. 1.)
TABLE 1
AVERAGE LATENCIES OF VERs IN PATIENT AND CONTROL GROUPS

<table>
<thead>
<tr>
<th></th>
<th>OI</th>
<th>OII</th>
<th>OIII</th>
<th>OIV</th>
<th>OV</th>
<th>CIV</th>
<th>CV</th>
</tr>
</thead>
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<td></td>
<td>(msec)</td>
<td>(no.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>52.5</td>
<td>44</td>
<td>81.8</td>
<td>45</td>
<td>105.5</td>
<td>46</td>
<td>132.8</td>
</tr>
<tr>
<td>Control</td>
<td>51.3</td>
<td>50</td>
<td>75.3</td>
<td>49</td>
<td>95.3</td>
<td>49</td>
<td>118.0</td>
</tr>
<tr>
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<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
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</table>

1 No. of individuals.

**FIG. 3.** Typical responses in the central and occipital regions of a normal subject (F26). The seven waves evaluated in this study are indicated.

**FIG. 4.** The two central components in this multiple sclerosis patient (F30) were normal. Note the delay of OIII on the left side.

**FIG. 5.** This patient (M45) shows considerable delay of the two central components with CV occurring at 200 and 207.5 msec on the left and right sides respectively. There is also a slight latency and amplitude asymmetry of OIII. This patient had a mild organic mental syndrome.

**FIG. 6.** In this patient (F26) there is an asymmetry in culmination of CV with the delay occurring on the right side. Also, note asymmetry of OIII with this component being delayed on the left side.

syndrome, four had deviant responses. One of the four, who also had bilateral optic atrophy, had no detectable evoked response but showed a normal resting electroencephalogram and a normal retinogram. The remaining three had delayed culmination of CV. It is noteworthy that eight patients who had spinal cord signs only showed abnormal evoked patterns. Three patients of the
eight had normal resting electroencephalograms. The EEG results are compared with the VERs in Table 3.

**TABLE 2**

| VERs in multiple sclerosis | Categories by neurological signs  
|----------------------------|---------------------------------|
|                           | All cases  
|                           | (n = 50)  
|                           | Visual dysfunction  
|                           | (n = 18)  
|                           | Brain-stem dysfunction  
|                           | (n = 10)  
|                           | Organic mental syndrome  
|                           | (n = 5)  
|                           | Spinal cord signs only  
|---------------------------|---------------------------|
| VERs                      | Normal  
|                           | 30  
|                           | 10  
|                           | 8  
|                           | 1  
|                           | 9  
| Abnormal                  | 20  
|                           | 8  
|                           | 2  
|                           | 4  
|                           | 8  
| Types                     | Absent VER  
|                           | 1  
|                           | 0  
|                           | 1  
|                           | 0  
| L-R amplitude difference > 75% | 3  
|                           | 1  
|                           | 1  
|                           | 1  
| Latency CV > 170 msec     | 6  
|                           | 0  
|                           | 1  
|                           | 3  
|                           | 5  

1 Not mutually exclusive.

earlier results, taken together with the present findings, suggest that cortical responses elicited by diffuse binocular photic stimulation are more likely to be distorted by central than by peripheral lesions of the visual pathway. In keeping with this is the fact that both patients in the present series with homonymous field defects had deviant VERs. Questions remain, however, as to the importance of such factors as size of the visual defect and its location within the visual field.

It is evident from our data that alterations of the VER occur commonly in patients who have no evidence of visual pathway damage whatsoever, suggesting that conduction defects within non-specific cerebral or, more strictly, non-primary pathways may be responsible for some of the observed deviations. In this connection, however, it is pertinent to consider another line of reasoning which offers an alternative explanation for the dissociation between the clinical signs and electrical phenomena. It has been shown in cases recovering from an acute exacerbation of the illness in which the somatosensory system has been affected that the configuration of the cerebral response to nerve stimulation may continue to improve after sensory function has returned to apparent normality (Baker, Sances, and Larson, 1966; Namerow, 1968), suggesting the presence of mechanisms that compensate for disturbances of nerve transmission attendant upon lesions directly within the primary sensory pathway. Without prejudice to this theory, which may well be applicable in certain instances, our group data would not seem to be satisfactorily viewed in this light, inasmuch as no appreciable differences were found between patients with and without overt signs of involvement of the visual pathway.

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