

# Electrophysiological Disorders in Multiple Sclerosis and Optic Neuritis

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**ABSTRACT:** Visual evoked response (VER), auditory brainstem evoked response (ABER), somatosensory evoked response (SSER), blink reflex and electronystagmographic (ENG) investigative methods were applied to a group of 89 patients with Multiple Sclerosis (MS) and Optic Neuritis (ON). The MS patients were classified as definite (n = 31), probable (n = 31) and possible (n = 27).

The aim of this study was to determine the diagnostic value of the five electrophysiological tests in MS. VER and ABER recordings were found to reveal the highest number of asymptomatic abnormalities (33 and 31 percent respectively). The combination of VER, ABER and ENG revealed all possible electrophysiological disorders. As these tests are completely non-invasive it is proposed, that a combination of two of these three tests is useful for the detection of a second silent lesion in patients with suspected MS showing purely spinal signs (VER, ENG, ABER) and/or a history of uncomplicated ON (ABER, ENG).

**RÉSUMÉ:** Nous avons examiné 89 patients souffrant de sclérose en plaques (SEP) et 25 patients souffrant de névrite optique (NO) à l'aide des tests: Potentiels Evoqués Visuels (PEV), Auditifs (PEA) et Somesthésiques (PES), Nystagmographique électrique (NGE) et le réflexe de l'orbiculaire de la paupière ("Blink" réflexe). Les observations de sclérose en plaques ont été classifiées suivant les critères cliniques habituels définis par McAlpine.

Le but de ce travail est d'aider à préciser l'apport de cette cinq tests au diagnostic neurologique le PEV et le PEA déterminée le plus moyen des anomalies asymptomatologique (33% et 31% respectivement).

La combinaison de PEV, PEA et NGE déterminée tous les anomalies électrophysiologiques. Le PES et le "Blink" réflexe n'était pas importante pour la diagnostic neurologique. Pour la détection d'une lésion seconde nous conseillons l'application de la combinaison de PEA et NGE dans une cas de névrite optique et la combinaison de PEV, PEA et NGE dans un patient avec une forme spinal de SEP.

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Multiple Sclerosis (MS) may give rise to a variety of clinical signs and symptoms. Electrophysiological investigations, such as visual evoked response (VER), auditory brainstem evoked response (ABER) and somatosensory evoked response (SSER), blink reflex and electronystagmography (ENG) may detect clinically asymptomatic lesions in the central nervous system (CNS) (Goodwill and O'Tuama 1969; Namerow and Etemudi 1970; Halliday et al 1972/1973; Kimura 1975; Asselman et al 1975; Lowitzsch et al 1976; Solingen et al 1977; Small et al 1978; Lacquaniti et al 1979; Mastaglia et al 1979; Matthews and Esiri 1979; van Vliet and van Lith 1979; Trojborg and Petersen 1979; Chiappa 1980; Prasher and Gibson 1980; Robinson and Rudge 1977/1980; Scarlapoz et al 1981; Green et al 1982; Shibusaki et al

1982; Yamada et al 1982; Kjaer 1983; Reulen et al 1983; Bartel et al 1983; Kayamari et al 1984; Chiappa et al 1985).

These methods may be helpful in demonstrating a possible second lesion in the early or monosymptomatic stages of MS, thus confirming the clinical diagnosis (which requires the detection of two separate lesions). All the fore-mentioned publications emphasized the existence of subclinical or silent lesions. However, only two of them (Matthews and Esiri 1979; Shibusaki et al 1982) provided pathological evidence that the electrophysiologically detected but clinically silent CNS disorder was due to a demyelinating plaque.

In the present study, five electrophysiological tests (VER, ABER, SSER, blink reflex and ENG) were applied to a group

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of 89 patients with MS and 25 with Optic Neuritis (ON). The main motive for application of these tests was the hope that they might provide information about the functioning of specific parts of the CNS. Pathological studies show that the optic nerve and the brainstem are frequently involved in MS patients. Demyelinating plaques tend to be located symmetrically in the pons and medulla oblongata near the fourth ventricle (Schob 1907; Anton and Wohlwill 1912; Fog 1965; Ikuta and Zimmerman 1976).

Since it is not always possible to gain information about visual and brainstem involvement in MS patients by another technique (Gyldensted 1976; Cala et al 1978; Young et al 1981), we were particularly interested in tests that could yield the desired information by alternative routes.

Another aim was to determine the contribution of these tests to the demonstration of the second lesion considered mandatory for the diagnosis of MS. Two groups of monosymptomatic patients were of particular interest: patients with clinical signs of spinal cord involvement only and patients with uncomplicated ON. Several studies have shown that ON can be an early sign of MS (Sandberg-Wollheim 1975; Hutchinson 1976; Cohen et al 1979; Nikoskelainen et al 1981).

In evaluating our data, we tried to answer the following questions:

1. how many of these electrophysiological tests are required to demonstrate a second (silent) lesion in a patient with suspected MS?,
2. are multiple electrophysiological test abnormalities always indicative of multiple lesions?

## METHODS

### Patients

All patients were examined during a one year period (1983/1984). Patients with known or suspected MS (or ON) were included in the present study. The clinical material comprised 89 MS patients (53 females and 36 males) and 25 ON patients (17 females and 8 males).

The MS patients were classified according to the clinical criteria of McAlpine et al (1965) into definite ( $n=31$ , mean age 48 years, mean duration of disease 14.5 years, mean Kurtzke DSS score 6.7), probable ( $n=31$ , mean age 41 years, mean duration of disease 7.6 years, mean Kurtzke DSS score 3.7) and possible ( $n=27$ , mean age 37 years, mean duration of disease 5.1 years, mean Kurtzke DSS score 1.6 years). The electrophysiological tests were performed shortly after the clinical examination. To find out which of these tests is helpful for the diagnosis in an early stage of the disease, the MS patients were classified according to age, duration of and disability due to the disease. Kurtzke's disability status scale (1961) was used to provide a measure of the last mentioned factor.

### Visual Evoked Response (VER)

VER recordings were obtained by a pattern-reversal method (Halliday et al 1972) with a black-and-white checkerboard pattern projection on a TV screen, subtending a visual angle of  $33^{\circ}2'$ . The luminance contrast of the pattern was 1/14. Silver-silver-chloride scalp electrodes were placed at the points  $O_1$  (left occipital) and  $O_2$  (right occipital) with reference on  $C_2$ . VER signals were measured by stimulation of both eyes simultaneously and for each eye separately. The signals passed a filter (bandpass 1-100 Hz) and the result was expressed as the aver-

age of 256 individual responses. The mean latency time of the P100 peak as measured in 15 healthy controls was 105 ms (SD 6.5). A latency of more than mean plus  $3 \times SD$   $105 + 19.5$  or an interocular difference of more than 13 ms ( $2 \times SD$ ) was judged as abnormal.

### Auditory Brainstem Evoked Response (ABER)

ABER recordings were obtained using an averaging method (Jewett and Williston 1971). Silver-silver chloride scalp electrodes were placed on both mastoids ( $A_1$ ,  $A_2$ ) and over the vertex (reference  $C_2$ ). Successive 'clicks' (frequency 15 Hz) were presented via a headphone (pulse duration 0.1 ms). The stimulus intensity was 70 dB above the normal hearing level. Stimuli were applied unilaterally, while responses were recorded bilaterally after passage through a band-pass filter (80-3500 Hz). Each ABER reading consisted of the average of 2048 responses. The parameters studied were the interpeak latencies between the I<sup>st</sup> and III<sup>rd</sup> and the III<sup>rd</sup> and V<sup>th</sup> peaks. Amplitude abnormalities were not covered in this study. Normal mean interpeak latencies obtained from a group of 15 control subjects were 2.10 ms (SD 0.18) for the interval I - III and 1.98 ms (SD 0.18) for that between III - V. The ABER was considered as abnormal when the interpeak intervals differed more than three times SD from the standard values (I - III and III - V) or a difference between these interpeak intervals for a patient's left and right side of more than three times SD were also considered as abnormal.

### Somatosensory Evoked Response (SSER)

The SSER was studied by unilateral stimulation of the median nerve at the wrist using repetitive current pulses of 0.1 ms duration and a frequency of 10 Hz. The stimulus intensity was chosen far enough above the motor threshold level of the thenar muscle to give an adequate response. The signals were picked up by scalp electrodes placed at the vertex (reference  $F_2$ )  $C_3$ ,  $C_4$  and  $C_7$  and were passed through a band-pass filter (80-3500 Hz) and averaged (512 sweeps) before being recorded.

The interpretation of the SSER was based on the difference in latencies between the  $N_{14}$  and  $N_{20}$  peaks. The  $N_{14}$ - $N_{20}$  delay is related to the transmission time of the response between the cervical spine via the brainstem to the cortex (Matthews et al 1974; Eisen and Odusote 1980). An absent  $N_{20}$  peak or a prolonged  $N_{14}$ - $N_{20}$  interval is probably a result of a lesion at brainstem level or higher. The normal mean  $N_{14}$ - $N_{20}$  interval obtained in 15 healthy control persons was 5.47 ms (SD 0.41). A time interval exceeding 5.47 plus three times the SD (6.70 ms) or a difference between left and right response of more than three times SD (1.23 ms) was judged to be abnormal. Amplitude information was not analysed, since  $N_{14}$  and  $N_{20}$  amplitudes are seldom reduced if latencies are normal in MS (Eisen and Odusote 1980).

### Blink Reflex

The latency of the blink reflex was measured by the method described by Ongerboer de Visser and Goor (1974) and Kimura (1975), involving stimulation of the supra-orbital nerves with a 400 mA pulse of 0.1 ms duration. The blink reflex for each eyelid was recorded using coaxial needle electrodes in the inferior orbicularis oculi muscle. The signals were passed through a band-pass filter (200 Hz - 10 Hz) and analysed over 100 ms, starting from the presentation of the stimulus. The latency time was measured from the start of the oscilloscope sweep to the initial deflection of the evoked muscle potential.

Normal latency values, obtained from 15 healthy controls, were between 10 and 12 ms for the R<sub>1</sub> response and between 21 and 40 ms for the R<sub>2</sub> response. A latency value of R<sub>1</sub> above 12 ms, or R<sub>2</sub> above 40 ms, or a combination of both was considered as abnormal. A difference between the left and right R<sub>1</sub> response of more than 1.5 ms and of more than 9 ms for the left-right R<sub>2</sub> response was also judged to be abnormal. This method is slightly more invasive than the others described in this paper but was well tolerated by all subjects.

**Electronystagmography (ENG)**

In this method (Reulen et al 1983) eye-movements were followed with silver-silver-chloride electrodes taped on the inner and outer canthi of both eyes. The visual stimuli for investigating horizontal saccadic eye-movements were provided by red light-emitting diodes ( $\lambda = 635$  nm) mounted on a horizontal cylindrical screen (radius 1 m), with the patient's eye situated at the centre of the curvature. Initially the patient was asked to look at the centre of the screen and the first stimulus appeared there. About fifty stimuli in all were presented in a random sequence at positions subtending angles of 10, 20 or 30 degrees to the left or right of the initial position. The parameters studied were 1. the saccadic latency (normal 205 ms, SD 22 ms) 2. the saccadic velocity (normal 220 deg/s, ampl. 10°; 300 deg/s, ampl. 20°, 400 deg/s, ampl. 30°) and 3. the saccadic accuracy. This method permits detection of an internuclear ophthalmoplegia (INO); INO's detected in this way will be designated ENG/INO in this paper. Both clinical and subclinical ENG/INO's have been observed. A subclinical ENG/INO is defined as an ENG recording indicative for an INO without any visible eye-movement abnormality (Reulen et al 1983).

Horizontal smooth-pursuit eye-movements were elicited by a target produced by a laser beam ( $\lambda = 630$  nm, power 0.1 mV), moving in simple harmonic motion (amplitude 12 deg/s) along a horizontal line through the fovea, stimulus frequencies were between 0.2 and 1.2 Hz. The eye-movement signals were displayed on an oscilloscope screen and simultaneously recorded on magnetic tape (Bell and Howell CR 3000). A complete eye-movement test lasted about thirty minutes and did not cause the patient any discomfort.

**Statistics**

Statistical analysis was performed with the SPSS computer program. Differences between sets of experimental data were tested for significance by the Wilcoxon, Chi-square or the Kendall's tB and tC tests. The statistical associations between the results of a given test and clinical data were examined with the aid of contingency tables.

**RESULTS**

**Electrophysiological responses**

The overall results of the VER, ABER, SSER, blink reflex and ENG tests are grouped according to the clinical status of the patients in Table 1.

As was to be expected, nearly all tests gave the highest percentage of positive (abnormal) results in the clinically 'definite' group of MS patients, while by far the fewest abnormalities were detected in the possible MS group.

For the ABER, SSER and blink reflex tests, the difference between the incidence of abnormalities in the 'definite' MS

**Table 1: Frequency of electrophysiological test abnormalities in different clinical categories of MS**

Test	Definite (n = 31) %	Probable (n = 31) %	Possible (n = 27) %	Total (n = 89) %
VER	68	68	45	61
ABER	84	74	59	73
SSER N <sub>14</sub> -N <sub>20</sub>	97	68	41	70
Blink reflex	81	65	56	67
ENG	84	80	63	76
Total	100	97	81	93

group and that in any other clinical group was highly significant ( $p < 0.005$ ). In the VER and ENG tests this difference was not statistically significant.

The ENG test data of table 1 include our previously reported results for 84 MS and 21 ON patients (Reulen et al 1983). Within the ENG group, the results indicative for an internuclear ophthalmoplegia (INO) were particularly interesting. All INO's (clinical and subclinical) detected by the ENG test are denoted by ENG/INO in this paper. The ENG test was particularly powerful in picking out subclinical INO's, which were found in 19 MS and 1 ON patients (unilateral 7 and bilateral 13). Most of the subclinical bilateral INO's (n = 8) were found in the 'definite' MS patients. All unilateral INO's recorded were subclinical.

**Relation between electrophysiological responses and clinical features**

Optic neuritis patients were excluded from evaluation of the statistical association between the results of the electrophysiological tests and the clinical signs and symptoms in order to get a statistically more homogeneous group. The MS patients were divided into those with and without clinical optic nerve, brainstem and spinal cord involvement and into those with and without a (past) history of ON. The contingency tables of Table 2 show the statistical significance level of the various possible associa-

**Table 2: Contingency tables showing the statistical relationships between the electrophysiological test results in MS patients and the presence (+) or absence (-) of clinical symptoms. ENG and SSER N<sub>14</sub>-N<sub>20</sub> showed no association with clinical brainstem involvement (not included in this Table)**

	ABER		Blink reflex		ENG/INO	
	+	-	+	-	+	-
Brainstem symptoms	30	6	29	7	20	16
No brainstem symptoms	35	18	31	22	9	44
	p = 0.05		p 0.05		p 0.005	
	VER		VER		SSER N <sub>14</sub> -N <sub>20</sub>	
	+	-	+	-	+	-
Visual loss	27	9	20	7	21	20
Normal vision	25	28	32	30	41	7
	p = 0.015		p = 0.08		p = 0.001	

tions between clinical symptomatology and electrophysiological test results.

Patient's ages and the duration of the disease were both quantified in five year periods, while the severity of the disease was measured in terms of the disability status scale (DSS) proposed by Kurtzke (1961). Statistical analysis revealed that of all tests only the number of blink reflex abnormalities increased with patient's age; with exception for the ENG, all other test abnormalities (including blink reflex recording) showed a significant increase with duration of the disease (0.001  $p$  0.05) and Kurtzke's disability scale (0.001  $p$  0.05, not shown in the tables).

#### Relations between electrophysiological parameters

We assume that the value of the investigative techniques used in this study is based on the spatial relation between certain electrophysiological signals and certain CNS pathways. From an anatomical point of view, some of these pathways lie close together at pontine or mesencephalic level. Thus, a single demyelinating plaque can simultaneously cause a combination of lesions in functional systems, such as the trigeminal tract (detectable by the blink reflex), medial lemniscus (SSER), lateral lemniscus (ABER), medial longitudinal fascicle (ENG) and paramedian pontine reticular formation (ENG). A statistical analysis pointed out that ABER abnormalities were associated with abnormal blink reflex recordings ( $p < 0.005$ ) and the total of electronystagmographically recorded INO's ( $p < 0.005$ ). A further correlation was that between clinical INO and blink reflex ( $R_1$ ) abnormalities ( $p < 0.05$ ), in agreement with a previous report by Kimura (1975). When subclinical INO's are included, bringing the total number of ENG/INO's up to 29, the association with  $R_1$  blink reflex abnormalities remains significant ( $p < 0.005$ ). An association between overall blink reflex disorders and ENG/INO was not found, however. Disturbed SSER recording showed no association with any of the other tests (ABER, blink reflex, ENG).

#### Monosymptomatic patients

As mentioned in the introduction, patients are generally only considered to have MS when at least two different lesions have been detected. For evaluation of the information about the second (silent) lesions revealed by our five electrophysiological tests, we distinguished between two groups of clinically monosymptomatic patients:

a. patients with unilateral or bilateral paresis of the lower limbs and Babinski reflexes, with or without sensory loss in one or both legs and bladder dysfunction and without symptoms above the cervical level, were classified as having spinal cord involvement. This group contained a total of 16 patients (11 with probable and 5 with possible MS). These 16 patients all showed an oligoclonal pattern on isoelectric focusing of the cerebrospinal fluid.

b. the 25 ON patients, in whom only one of the optic nerves was involved (although one patient did suffer a relapse of ON within a year, in the contralateral eye, this is not taken as definite evidence of bilateral involvement of the optic nerve in this patient; there is also the possibility of interaction in the optic chiasm). All affected ON eyes showed an abnormal delayed P100 latency on VER examination.

The test results for these two monosymptomatic groups are summarized in Table 3.

**Table 3: Distribution of electrophysiological test results in the two monosymptomatic groups and distribution of subclinical disorders detected by the various tests in the total MS and ON patients**

	spinal cord involvement	optic neuritis	all patients
Electrophysiological tests	n = 16 %	n = 25 %	n = 114 %
VER	38	28*	33
ABER	31	32	31
SSER N <sub>14</sub> -N <sub>20</sub>	31	20	14
Blink reflex	31	12	21
ENG	44	28	29

\* In 7 clinically unilateral ON patients the VER was bilaterally disturbed.

The combination of tests showed subclinical abnormal functioning in 56 percent of the spinal cord and 44 percent of the ON patients respectively, thus demonstrating their usefulness in the diagnosis of MS. The last row of Table 3 shows the total amount of clinically unsuspected CNS lesions as detected with each test separately for the whole patient group (n = 114).

#### DISCUSSION

The two main aims of our study were first to examine the correlation between clinical signs and symptoms and the results of the electrophysiological tests and secondly to compare the results of the various tests one with another, so as to select the smallest combination giving the maximum amount of diagnostic information.

#### Relation between clinical and electrophysiological findings

The percentage of test abnormalities in MS found in this study is comparable with that found by most authors, cited in the introduction.

Except for the ENG, the abnormal electrophysiological tests were significantly associated with signs and symptoms of that particular part of the CNS they are supposed to monitor (0.001  $< p < 0.05$ ). Notwithstanding these relevant associations all tests were able to detect subclinical lesions in different percentages, varying from 14 to 33 percent (Table 3).

The close association between clinical brainstem involvement and the three electrophysiological parameters (ABER, blink reflex and ENG/INO) is probably responsible for the pairwise association between 1) abnormal blink reflex ( $R_1$ ) and ENG/INO, 2) ABER disorders and ENG/INO and 3) ABER dysfunctioning and abnormal blink reflex ( $R_1$ ,  $R_2$ ). The only conclusion that can be reasonably drawn from these findings is that a single demyelinating plaque located in the brainstem can cause a combination of electrophysiological disorders.

It is highly unlikely that each abnormal electrophysiological response detected with these tests corresponds to a separate CNS lesion.

The number of the electrophysiological abnormalities detected in our 25 ON patients is of the same order as that reported by Feasby and Ebers (1982) in their 35 ON patients. They found 7 (20%) ABER and 5 (14%) blink reflex abnormalities as compared with 3 and 12 percent in the present study. These authors did not perform SSER N<sub>14</sub>-N<sub>20</sub> and ENG investigations.

Our overall data indicate the presence of one or more electrophysiological abnormalities in 11 ON patients, adding strength to the supposition that ON may be regarded as a possible early sign of MS. Only a prospective study of this ON patient group can give a definite answer to the question whether ON patients really run a higher risk of developing MS in the near future.

#### Diagnostic value of the tests

Detection of two CNS lesions is considered mandatory for the diagnosis of MS, but these two lesions will not always occur at the same time. For early detection of MS, it is desirable to have simple non-invasive screening tests which can be applied to patients who already show one symptom indicating the possibility of MS, to allow a second (subclinical) lesion to be detected without having to wait for it to produce clinical symptoms.

Table 3 shows that the ENG and ABER reveal the most asymptomatic lesions. The ENG test is the one which is least dependent on parameters such as a patient's age, disease duration or disability. Hence, the ENG is the most suitable diagnostic tool, especially in early stages of MS. According to a number of previous studies (mentioned in the introduction), the yield of detected electrophysiological abnormalities increases when two or more tests are combined (for this purpose our results are summarized in Table 4).

**Table 4: Increase in yield of detected electrophysiological abnormalities obtained by combining two or more tests (VER, ABER, ENG)**

Test or test combination	multiple sclerosis	optic neuritis	total
	% n = 89	% n = 25	% n = 114
VER	61	100	81
ABER	73	32	64
ENG	76	36	68
VER + ABER	80	100	90
VER + ENG	78	100	89
ENG + ABER	92	40	92
VER + ABER + ENG	93	100	95

As can be seen in Table 3, the combination yielding the highest percentage of asymptomatic lesions were the VER and ABER tests. This pair revealed a total of 102 (89%) abnormalities in the total patient group. It has to be said that the large diagnostic yield of the VER and ABER combination is partly due to the inclusion of the 25 ON patients who all had a VER disorder by definition.

The combination of all three tests (VER, ABER, ENG) yielded at least one electrophysiological abnormality in 108 (95%) of the 114 patients. Addition of SSER N<sub>14</sub>-N<sub>20</sub> and blink reflex results to Table 4 did not increase the diagnostic yield any further, because abnormalities of these two tests were always seen in combination with an ENG and/or ABER disorder.

#### CONCLUSION

In this study, five electrophysiological methods were tested for their value in the diagnosis of MS. Because of the statistical significant associations between the results of those tests, which

yield information concerning the brainstem function, it is not possible to draw definite conclusions about the existence of separate lesions in such a small anatomical region.

Investigation of which pair of tests gave most information about CNS involvement in MS and ON, showed that SSER N<sub>14</sub>-N<sub>20</sub> and blink reflex data do not contribute to the information already gained with the three other tests.

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