A Comparison of Visual, Brainstem Auditory, and Somatosensory Evoked Potentials in Multiple Sclerosis

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SUMMARY: *Multimodality evoked potentials testing including PVEPs, SEPs and BAEPs was done in 112 patients who were known or suspected to have multiple sclerosis. The incidence of abnormal evoked potential findings in each of these systems was considered in patients in the different diagnostic categories of M.S. Results were also evaluated with respect to the presence of abnormal clinical visual, somatosensory, or brainstem signs. The PVEP was found to be the most frequently abnormal even in patients without clinical involvement in the visual system (45% of patients with definite, probable, or possible M.S.), the SEP was less frequently abnormal in the absence of clinical signs (35% in patients with M.S.), and the BAEP showed the lowest frequency of abnormalities in patients without brainstem signs (14% in patients with M.S.). Combining the three types of evoked potentials significantly increased the percentage of M.S. patients having abnormal findings, compared to any of these tests alone, with 97% of "definite" M.S. patients, 86% of "probable" M.S. patients and 63% of "possible" M.S. patients having at least one of these EP tests abnormal.*

RÉSUMÉ: *Nous avons étudié, chez 112 patients au diagnostic connu ou présumé de sclérose en plaques, les potentiels évoqués multimodaux, incluant les PVEP, SEP et BAEP. Nous avons étudié l'incidence de potentiels évoqués anormaux pour les différentes catégories diagnostiques de sclérose en plaques. Ces résultats furent également évalués par rapport à la présence de signes cliniques anormaux visuels, somatosensitifs ou du tronc cérébral. Le PVEP fut trouvé le plus fréquemment anormal, même chez des patients sans atteinte clinique du système visuel (45% des patients avec sclérose en plaques certaine, probable ou possible). Le BAEP, par contre, montra la plus basse fréquence d'anomalies chez les patients avec des signes du tronc cérébral (14% des patients avec sclérose en plaques). Lorsque l'on combine les 3 types de potentiels évoqués, ceci augmente le pourcentage des patients avec sclérose en plaques qui sont anormaux: ainsi 97% des patients "certains", 86% des "probables" et 63% des "possibles" ont au moins un test anormal.*

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The patterned visual evoked potential (PVEP) has become a widely accepted test as an aid to the diagnosis of multiple sclerosis (MS) in its early stages. Halliday et al., (1972) first demonstrated that the latency of the PVEP was prolonged in patients with M.S. who did not have clinical evidence of a lesion in their optic nerves, thus providing objective evidence of multiple lesions at a time when the patient's presenting symptoms could be attributed to CNS involvement at a single location. This finding was received with great interest in many centers and numerous reports have appeared confirming the prolongation of the PVEP in patients with early M.S. (Halliday et al., 1973; Milner et al., 1974; Asselman et al., 1975; Hennerici et al., 1977; Zeese, 1977; Bynke et al., 1977 Purves & Low, 1978; Collins et al., 1978; Shahrokhi et al. 1978). All of these later reports found somewhat lower percentages of abnormal responses than the 96% that Halliday had reported in his 51 patients. The results varied from a low of 57% in the patients with no history of optic neuritis in the series of Shahrokhi et al., (1978) to a high of 75% in Zeese (1977) and 76% in Bynke et al. (1977) reports. The variability appeared related to the types of patients included in each series.

Robinson and Rudge (1975) reported that the brainstem auditory evoked potential (BAEP) was similarly effective in demonstrating lesions in the brainstem auditory pathways of M.S. patients and this finding was confirmed and the types of abnormalities were further defined by others (Chiappa and Norwood, 1977; Robinson and Rudge, 1977; Stockard and Rossiter, 1977; Chiappa, 1980).

Short latency somatosensory evoked potentials (SEPs) for upper limb (Eisen and Nudleman, 1978;

Small et al., 1978; Eisen et al., 1979; Chiappa et al., 1980) and recently for lower limb stimulation (Eisen and Odusote, 1980) have also been shown to be delayed in multiple sclerosis patients with and without clinical involvement of this system. Documentation in an autopsy study of the sensitivity of the SEP in revealing a small plaque of demyelination that had not resulted in any clinical symptoms was reported by Matthews and Esiri (1979).

There have been a few reports of combining two or more of these evoked potential tests in individual patients. Mastaglia et al., (1976) combined SEPs and PVEPs to increase the abnormal percentage from 83% with PVEP alone to 94% with both tests in "definite" patients, and from 33% to 59% in the "possible" patients. Trojaborg and Petersen (1979) also reported improvement with combining PVEP and SEP tests. Chiappa (1980) was the first to provide a combination of all three types of sensory EPs in some of the patients from a large series.

This report outlines the results of the application of a uniform battery of evoked potential (EP) tests in a series of 112 patients studied in our laboratory over a 12 month period because of known or suspected M.S. (January 1, 1979 to December 31, 1979). The EP tests included the PVEP, short latency SEPs for median nerve stimulation, and BAEPs. The results were evaluated with consideration given to the diagnostic classification of M.S. for each patient by the McDonald and Halliday (1977) criteria, and also with respect to whether the patient had clinical signs or symptoms in any of the three systems tested.

METHODS

There were 112 patients referred for testing because of known or suspected M.S. A full neurological history and examination were available at the time of the referral, and on the basis of this information the patients were classified according to the criteria of McDonald and Halliday (1977). No patient with onset of symptoms after 50 years of age was included. There were 33 classified as clinically definite, 21 as early probable, 16 as suspected, 13 as progressive possible (progressive spinal paraplegia with other causes excluded) and 29 patients for whom M.S. was reasonably included in the differential diagnosis of their signs or symptoms, but who did not fall into any of the previous categories. This group we called "possibility". As described by McDonald and Halliday (1977), a patient classified as "suspected" had had a "single episode suggestive of M.S." with or without evidence of a single lesion. Patients with neurological symptoms that were not necessarily clearly episodic, or not typical for M.S., or for whom other causes were still being considered were included in our "possibility" group. Also 5 patients with first episodes of optic neuritis, and 3 patients with transverse myelitis were included in this "possibility" group.

The clinical presentation for each patient was classified as positive or negative for each of the three systems tested by the evoked potentials. Decreased corrected visual activity, an afferent pupil defect, visual scotoma, or a clear history of optic neuritis for either eye was classified as positive clinical evidence for optic nerve involvement (questionable optic disc pallor was not). Objective sensory changes, weakness or spasticity (but not a reflex asymmetry alone) in the upper limbs were considered as positive clinical evidence for a lesion that could be in the same areas tested by the SEPs and diplopia, internuclear ophthalmoplegia, cerebellar signs or marked nystagmus were all considered as clinical evidence of a possible brainstem lesion in the area tested by the BAEPs.

The EP testing was done with a Z-80 microprocessor-based system developed in our laboratory. This system incorporates a Grass S44 stimulator, and a 23 inch Electrohome television monitor for presentation of stimuli. The EEG was recorded with Grass P511J amplifiers and digitized (to 8 bit precision) at a rate of 200 points/epoch. No specialized averaging or math hardware was used. All EPs were replicated at least once.

PVEPs were elicited with a reversing checkerboard pattern generated on a T.V. screen. 100 trials were averaged with a stimulus rate of 1/second. The pattern consisted of 1 cm checks viewed from 1 metre, and the total field size subtended 26°. The overall screen luminance was 12 ft-lamberts. The EEG was recorded with a bandpass of 1-300 Hz from an electrode (Grass gold disc) placed 5 cm above the inion at the midline referred to F_z. In 20 normal subjects, the mean latency of the major positive peak (called P100 by most investigators) was 93.6 ± 3.25 msec, and the mean interocular latency difference was 2.0 $\pm$ 1.43 msec. The upper limit of normal (mean plus 3 SDS) used was 103 msec for the P100 and 6 msec for the interocular difference.

The SEPs were elicited with an electrical stimulus of .2 msec duration controlled by a Grass constant current stimulator. It was applied over the median nerve at the wrist and adjusted to just below the thenar muscle twitch threshold. The stimulating current was usually in the 3-7 mA range. The electrical activity for averaging was recorded on 3 channels: from the ipsilateral Erb's point, over the second cervical spine, and at the C_3 or C_4 site on the scalp (contralateral to the stimulated wrist), all referred to a reference placed on the mid forehead. Five hundred trials with a stimulus rate of 5/second were averaged. A bandpass of 3-1000 Hz was used. Interpeak latencies were measured between the negative peak recorded at the Erb's point and the N_{14} recorded over the cervical spine (nomenclature described by Eisen et al., 1979), and between the Erb's point negative peak and the first negative peak (N_{20}) recorded over the contralateral scalp electrode. Normal studies conducted in our laboratory in 20 subjects showed a mean interpeak latency of $3.6 \pm .45$ msec from Erb's point to the cervical spine peak, and $9.2 \pm .6$ msec from Erb's point to the first negative peak (N1) at the scalp. For this study inter arm differences were not considered. The upper limit of normal (mean plus 3 SDs) used was 5.0 msec for the latency to the cervical spine peak, and 11.0 msec for the latency to the N1 peak recorded at the scalp.

Brainstem auditory evoked responses were elicited by .2 msec click stimuli at 65 dB above the patient's subjective threshold presented to the right and left ear separately. Two thousand trials with a stimulus rate of 10/second were averaged. BAEPs were recorded from Cz referred to ipsilateral ear lobe with a bandpass of 100-3000 Hz. The I-III and I-V interpeak latencies were measured and the amplitude ratio of I:V calculated for each ear. The normal values for these interpeak latencies determined in 20 subjects for our laboratory were similar to those reported by others (Rowe, 1978), i.e. for I-III the mean was $2.16 \pm .11$, and the upper limit (mean + 3 SDS) used was 2.6 msec, for I-V the mean was $4.15 \pm .15$ and the upper limit (mean + 3SDS) used was 4.6 msec and the I/V amplitude ratio was considered abnormal if it was less than 1. Inter-ear latency differences do not appear useful because of the frequent occurrence of different configurations (and absolute latencies) of the peaks between ears in the normal subjects (Chiappa, 1979).

All of these tests could be completed in less than two hours for most patients. Once the patient was prepared, the PVEP

required about 20 minutes, the SEPs another 30 - 40 minutes and the BAEPs 40 - 50 minutes of examination time. Waveforms were displayed on a monitor (or oscilloscope) and the peak latencies and amplitudes were measured with a digital cursor system. They were then written on an X-Y plotter for later re-examination and filing.

RESULTS

The percentages of abnormal tests for the patients in each of the diagnostic categories are indicated in Table I. Some of the patients had more than one abnormal test and so the final column does not necessarily represent a summation of the three. The PVEP showed the highest abnormal rate with the SEP second and the BAEP the lowest rate in all of the diagnostic classifications.

In order to determine how frequently the EP tests detected lesions that were not evident from the clinical examination or history, a further

TABLE I:

Results of Multimodality Evoked Response Testing on 112 Patients

	n	Mean Age	Abnormal PVEP	Abnormal SEP	Abnormal BAEP	At least one test abnormal
Definite	(33)	39	91% (30)	67% (22)	45% (15)	97% (32)
Probable	(21)	37	76% (16)	52% (11)	14% (3)	86% (18)
Suspected	(16)	36	38% (6)	50% (8)	25% (4)	63% (10)
Progressive	(13)	47	38% (5)	46% (6)	31% (4)	54% (7)
"Possibility"	(29)	33	14% (4)	10% (3)	7% (2)	28% (8)

TABLE II:

Evoked Potential Results Considered in Conjunction With Individual Clinical Information

	Positive	Confirmatory	Paradoxical	Negative
DEFINITE (33)				
PVEP	42% (14)	48% (16)	3% (1)	6% (2)
SEP	39% (13)	27% (9)	3% (1)	30% (10)
BAEP	12% (4)	33% (11)	30% (10)	24% (8)
PROBABLE (21)				
PVEP	67% (14)	10% (2)	0% (0)	24% (5)
SEP	29% (6)	24% (5)	19% (4)	29% (6)
BAEP	5% (1)	10% (2)	38% (8)	48% (10)
SUSPECTED (16)				
PVEP	25% (4)	12% (2)	0% (0)	62% (10)
SEP	44% (7)	6% (1)	0% (0)	50% (8)
BAEP	19% (3)	6% (1)	12% (2)	62% (10)
PROGRESSIVE (SPINAL) (13)				
PVEP	38% (5)	0% (0)	0% (0)	61% (8)
SEP	23% (3)	23% (3)	8% (1)	18% (6)
BAEP	31% (4)	0% (0)	0% (0)	69% (9)
POSSIBILITY (29)				
PVEP	7% (2)	7% (2)	0% (0)	86% (25)
SEP	3% (1)	0% (0)	0% (0)	96% (28)
BAEP	3% (1)	0% (0)	3% (1)	93% (27)
Total (112) PVEP	34% (39)	20% (22)	1% (1)	45% (50)
(112) SEP	27% (30)	16% (18)	5% (6)	52% (58)
(112) BAEP	11% (13)	12% (14)	19% (21)	57% (64)

POSITIVE: Abnormal EP with no definite history or findings in the system tested by this EP.
CONFIRMATORY: Abnormal EP with history and/or findings in the system tested by this EP.
PARADOXICAL: Normal EP with history and/or findings in the system tested by this EP.
NEGATIVE: Normal EP with no history or findings in the system tested by this EP.

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analysis of the individual patient's results was made. The results of each of the three EP tests were classified as positive if the EP did detect an abnormality that was not indicated by the clinical examination (as defined in the methods section), confirmatory if an abnormal EP only confirmed positive findings from the clinical examination, paradoxical if the EP was normal in the presence of abnormal clinical signs in the same system and negative when both the EP and clinical exam were normal. The results of this classification for each of the diagnostic categories are shown in Table II.

These figures indicate that of the three, the PVEP most frequently detects subclinical lesions (34% abnormal in the total group of patients). The SEP appeared to be slightly less sensitive for subclinical lesions (27% of the patients) and the BAEP was abnormal in the smallest percentage of the patients (11%). This relationship was present in nearly all of the diagnostic groups (with the exception of the progressive-spinal group where the BAEP detected subclinical lesions in a slightly higher percentage of patients than the SEP). If the "possibility" patient group is excluded from the overall total (since the likelihood of subclinical lesions existing in this group is much lower) the frequency of detecting subclinical lesions in the remaining patients is increased to 45% for the PVEP, 35% for the SEP and 14% for the BAEP. Table II also shows that the incidence of "paradoxical" findings for the PVEP is extremely low, with only one patient in the entire series showing a normal PVEP in the presence of a definite history of optic neuritis. There was also one other patient who presented with transverse myelitis, was noted to have a normal PVEP at that time, but who developed optic neuritis within a few weeks following testing. Repeat testing several months later following recovery from the episode of optic neuritis showed an abnormal PVEP, but repeat examinations on the same patient were not included in this series.

DISCUSSION

The observation that the PVEP is more sensitive for subclinical lesions, and more frequently abnormal in the total group of patients is in agreement with the study of Trojaberg and Petersen (1979). Chiappa (1980) and Mastaglia et al. (1976) reported that the SEP was abnormal in a slightly higher percentage of M.S. cases than the PVEP. The differences between these studies and ours are not large however, and may be due to variations in the patient series. In this study and also in those of Chiappa (1978) and Mastaglia (1976) the latency differences between right and left side were not included in the normal criteria for SEPs. Eisen (1979) has suggested that these symmetry differences should be considered and that this would significantly increase the rate of abnormal SEP findings in M.S. patients.

The relatively low percentages of abnormal BAEPs in these patients and the high increase of "paradoxical" results with the BAEPs may be due to several factors. Because the pathway tested by the BAEP is a very short one it is perhaps less likely to contain demyelinating plaques than the longer myelinated tracts tested by the PVEP and SEP. The clinical signs that may result from lesions in the vicinity of the brainstem auditory pathways are not necessarily specific to this location; for example signs such as nystagmus or cerebellar ataxia may result from lesions in the brainstem or cerebellum and this may account for the high incidence of "paradoxically" normal BAEPs.

The diagnostic classification of patients with M.S. is sometimes difficult. We choose to use the criteria laid out by McDonald and Halliday (1977) because they are slightly broader than those of McAlpine (1972). Since one of the important questions is whether these EP tests are useful in the assessment of patients in very early stages of M.S., it seems essential to have some way of classifying all of the patients who are tested with the possibility of this diagnosis under consideration. This inclusion of the group of patients we have called "possibility" in this series makes it unique. The EPs in these patients can serve to provide objective evidence of mild neurological symptoms difficult to document with clinical examination, and may also provide evidence of lesions otherwise not suspected, thus indicating a more widespread disease process. The abnormality rate in this particular group in our series was found to be very low. The percentage of these patients that eventually prove to have multiple sclerosis in spite of normal findings at the initial examination will be determined with a later long-term followup study.

This multimodality evoked potential approach appears to show abnormal results in a larger number of patients with known or suspected M.S. than any of the EP tests used alone. A comparison of the individual EP results shows that with our current techniques PVEP provides the highest yield for detecting subclinical demyelinating lesions with the SEP slightly lower and the BAEP showing the lowest detection rate.

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