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Visual Evoked Potentials (VEP) Elicited by Checkerboard Versus Foveal Stimulation in Multiple Sclerosis

A Clinical Study in 235 Patients*

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Summary. In 235 patients with suspected multiple sclerosis (MS) the diagnostic value of visual evoked potentials (VEP) elicited by checkerboard and central foveal stimulation was compared. No significant difference was found. Both methods are supplementary in diagnostic value. Foveal stimulation may provide an additional diagnostic clue. Normal VEPs do not exclude a prior retrobulbar neuritis.

Electronystagmography and examination of CSF are at least as essential for the diagnosis of MS as VEPs. The combination of these methods increases the accuracy of diagnosis.

Key words: Multiple sclerosis – Visual evoked potentials – Retrobulbar neuritis – Foveal stimulation – Checkerboard reversal stimulation – Electronystagmography – CSF

Zusammenfassung. Bei 235 Patienten mit klinischem Verdacht einer Multiplen Sklerose wurden durch Schachbrett und foveale Reizung evozierte visuelle Potentiale (VEP) verglichen. Beide Methoden sind für die Diagnostik der MS etwa gleichwertig, jede dieser Methoden erfaßt aber ca. 10% pathologischer Befunde, die mit der anderen Methode normal erscheinen. Normale VEP's können eine abgelaufene Retrobulbärneuritis nicht ausschließen.

Nystagmogramm und Liquoruntersuchungen sind ähnlich aussagekräftig und nur die Kombination aller Methoden gibt eine größtmögliche diagnostische Sicherheit.

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Table 1

Author	Normal range				Pathological responses (%)				
	Age (years)	P2 latency	Upper limit	Cases (*n*)	Definite MS	Probable MS	Possible MS	RBN	System type
Lowitzsch et al. (1976)	15–72	103.8 ± 4.3	112	135	82%	60%	65%		Mirror
Matthews et al. (1977)	17–56	91.1 ± 11.6	110	186	75%	58%	38%	81%	Mirror
Sharokhi et al. (1978)	16–68	102.3 ± 5.1	114	149	82%	52%	28%	96%	Mirror
Mastaglia et al. (1979)	19–64	No remarks		108	77%	27%	10%		Not indicated
Oepen et al. (1980)	11–73	98 ± 8.3	115	235	75%	51%	37%	81%	Checkerboard TV
		128 ± 13.1	155	235	76%	80%	54%	80%	Central foveal stimulation TV

Schlüsselwörter: Multiple Sklerose – Retrobulbärneuritis – Evozierte Potentiale – Schachbrettreizung – Foveale Reizung – Elektronystagmographie – Liquor

Introduction

Recording of visual evoked potentials (VEP) has become a popular method for measurement of visual defects in the course of nervous diseases. In the diagnosis of Multiple Sclerosis (MS), this method may help to detect demyelination in the visual pathways in advance of clinical symptomatology. The fact that the optic nerves are among the earliest and most frequently involved sites for plaques in MS enhances the usefulness of VEP [8, 11].

Reports on the percentage of pathologic VEP findings in MS differ considerably, as do the mean latencies of the normal pattern reversal evoked potentials. This is probably due to different technical equipment and patient selection (Table 1). These discrepancies demonstrate the need for each laboratory to collect its own reference values.

It was reported that VEPs elicited by central foveal stimulation should achieve a significantly better discrimination of optic nerve lesions than checkerboard reversal VEPs. These authors suggested that small demyelinating lesions mainly affecting optic nerve fibers originating from foveal ganglion cells cannot be detected by large visual angle checkerboard stimulation [3].

The report claiming that a higher percentage of pathologic responses is obtained with foveal VEPs as compared to checkerboard stimulation [3] is not supported by our experience or that of other authors [13]. The following study re-evaluates both methods in a larger number of patients and compares the diagnostic value of both VEP methods with other clinical data.

Patients and Methods

Forty healthy subjects with normal visual acuity and no history of visual disturbances, ophthalmologic disease, or central nervous system disease, served as controls. The age ranged from 20–66 years with a mean of 34 years (23 males, 17 females).

The VEPs recorded in our hospital during the last 3 years in 235 patients suspected of MS were evaluated. The patients were classified according to the criteria of McAlpine [11] into 87 definite Ms (37%), 35 probable Ms (15%) and 113 possible Ms (48%), by reference to the clinical documents. There were 84 male and 151 female patients, 11–73 years of age (mean age 38,3 years). The duration of the disease varied between several days and 38 years.

In all control subjects and patients visual acuity was normal or corrected by glasses.

All VEPs were recorded in the same laboratory under clinical routine conditions. The subjects sat relaxed in an armchair in a darkened room and viewed the signals with one eye at a distance of about 1.5 m. They were requested to fixate on a point in the middle of the upper border of the TV screen [6].

For checkerboard reversal stimulation a black and white checkerboard pattern was produced and viewed on a television monitor subtending 20 degrees of the visual field. Reversal of the checkerboard was performed by a time pulse generator. The overall luminance did not change. The luminance of the white squares was 51.3 cd/m^2, that of the black ones was 0.34 cd/m^2.

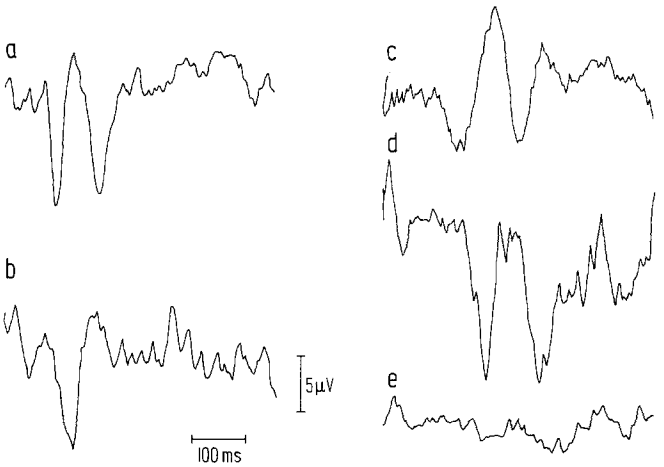

Fig. 1. *a)* Normal VEP (checkerboard), *b)* normal foveal VEP, *c)* pathological VEP (checkerboard), *d)* pathological foveal VEP, *e)* "absent" foveal VEP (for further details see text)

Central foveal stimulation was performed by offering a small bright rectangle in the visual axis subtending 45 min, which alternated with a black rectangle every 800 ms. The background luminance was constant.

Scalp potentials were recorded via Grass gold-plated electrodes. The recording electrode was fixed 6 cm above the inion in the midline and the reference electrode was placed on the left ear lobe. This location has been found to yield a maximal response to visual stimulation. The subjects were grounded to the right ear. EEG signals were amplified and fed to a Datalab 200 point averager triggered with the visual stimulus.

For each eye 64 responses were averaged over 500 ms for at least two successive series. The potentials were displayed on a storage oscilloscope and an x-y plotter (Fig. 1).

Recordings of electronystagmogram (ENG) were performed by routine methods [4]. Saccadic pursuit movements, all forms of spontaneous nystagmus, signs of internuclear ophthalmoplegia, nuclear ophthalmoplegia, and clear optokinetic disturbances were all regarded as pathological findings.

In lumbar CSF the level of gamma globulins was determined by cellulose-acetat electrophoresis and oligoclonal IgG by disc electrophoresis. Cytology was done by routine staining. Augmented gamma globulins, IgG, and the presence of plasma cells were regarded as abnormal findings [12].

Results

1. Control Subjects

For checkerboard reversal stimulation in normal subjects the major positive potential appeared after 90 ms ± 8.3 with a mean interocular difference of 2.93 ms ± 3.28. To be classified as a pathological response one of the following parameters must be fulfilled: a peak latency longer than the normal mean values plus two times the standard deviation (> 115 ms), an interocular latency difference over 10 ms ($\bar{x} + 2$ SD), or an absence of reproducible potentials within a least three recordings. If potentials were not detectable despite prolonged search (excluding technical difficulties), this was also considered abnormal since it never occurred in controls.

Table 2

Evaluation criteria	Definite MS ($n=87$)		Probable MS ($n=35$)		Possible MS ($n=113$)		All patients ($n=235$)	
	% of patients	% of eyes	% of patients	% of eyes	% of patients	% of eyes	% of patients	% of eyes
a. No response	8.1	6.9	5.7	4.3	7.1	5.3	7.2	5.8
b. Prolonged latency	59.8	50.6	48.6	35.7	24.8	19.9	41.3	33.6
c. Pathologic interocular difference	35.6		25.7		14.2		23.8	
d. Only unilateral prolonged latency	18.4		25.7		9.7		15.3	
e. Bilateral prolonged latency	41.4		22.9		15.0		26.0	
f. Only pathologic interocular difference	9.2		0		6.2		6.4	
g. RBN with abnormal response	82.0		69		100.0		81.5	
h. Abnormal checkerboard response with normal foveal response	11.5		8.6		9.7		10.2	

Table 3

Evaluation criteria	Definite MS ($n=87$)		Probable MS ($n=35$)		Possible MS ($n=113$)		All patients ($n=235$)	
	% of patients	% of eyes	% of patients	% of eyes	% of patients	% of eyes	% of patients	% of eyes
a. No response	48.3	44.3	45.7	38.6	31	28.3	39.6	35.8
b. Prolonged latency	28.7	22.4	28.6	22.9	22.1	18.1	25.5	20.4
c. Pathologic interocular difference	10.4		20.0		8.9		11.1	
d. Only unilateral prolonged latency	12.6		11.4		8.0		10.2	
e. Bilateral prolonged latency	16.1		17.1		14.2		15.3	
f. Only pathologic interocular difference	1.2		5.7		3.5		3.0	
g. RBN with abnormal response	79.0		77.0		86.0		79.6	
h. Abnormal foveal response with normal checkerboard response	12.6		37.0		26.5		23.0	

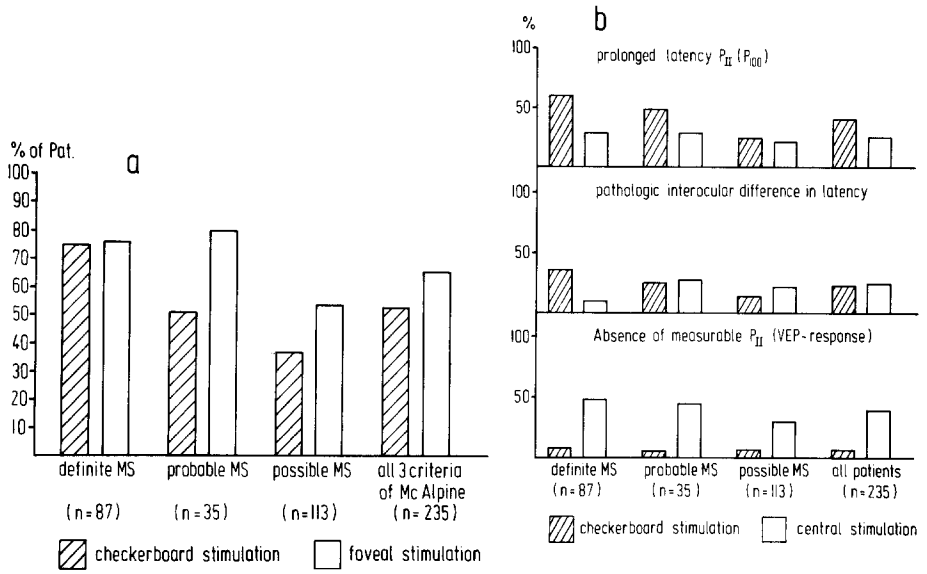

Fig. 2. a) Amount of pathological results. **b)** Pathological responses subdivided into prolonged latency, pathologic interocular difference and absence of measurable P2 (for details see text)

For foveal stimulation the mean latency of the major positive potential was 128 ms ± 13.1 with an upper limit of 155 ms ($\bar{x}+2$ SD). This major positive peak was often difficult to detect (Fig. 1). In 20% of control subjects no foveal VEPs were detected. The highest normal value (150 ms) did not exceed the upper limit ($\bar{x}+2$ SD = 155 ms). The mean value for latency differences (MLD) between the responses obtained by central foveal and checkerboard reversal stimulation was 28.7 ± 11.6 ms ($\bar{x}\pm$ SD), the upper limit 52 ms ($\bar{x}\pm 2$ SD), and the normal range 5–50 ms.

2. Patients Suspected of MS

A history of one or more complaints of visual disturbances was reported by 94 of 235 patients (53 with definite MS, 17 with probable MS and 24 with possible MS). In only 54 of 235 patients was a history of retrobulbar neuritis (RBN) confirmed clinically by neuroophthalmological examination.

Recordings were repeated in 14 patients, of whom seven were suspected of RBN prior to the first VEP recording. In three of these seven patients the latencies improved and reached normal values. In another patient the latency improved but remained prolonged.

In checkerboard reversal stimulation pathological responses were found in 75% of definite MS, 51% of probable MS, 37% of possible MS and in 53% of all 235 patients (for details see Table 2).

For central foveal stimulation abnormal responses (prolonged latency, interocular difference, or absence of VEP) were found in 76% of definite MS, 80% of

Table 4. Abnormal results from different methods in 235 patients suspected of MS

Method of investigation	Patients investigated (*n*)	Pathological results (%)	Detectable VEPs (%)
VEP by checkerboard stimulation	235	53.2	47.7
VEP by central foveal stimulation	235	66	28.5
VEP by checkerboard and central foveal stimulation	235	76.2	57.8
Only anamnesis of visual impairment	235	40	
Clinically diagnosed RBN	235	23	
Pathologic ENG	204	78	
Pathologically altered CSF:			
— IgG augmented	80	67.5	
— Globulins augmented	101	42.6	
— Plasma cells in cytology	82	36.6	

probable MS, 54% of possible MS, and in 65.5% of all patients. If absent VEP responses are excluded, this high percentage of positive results is restricted to 61% in definite MS, 54% in probable MS, 35% in possible MS, and 47% in all patients (for further details see Table 3). The comparison of pathological results obtained by both methods is illustrated in Fig. 2.

Pathological results from one method were not necessarily confirmed by the other method. Abnormal checkerboard responses were found in spite of normal foveal responses in 10.2% of all patients (11.5% in definite MS, 8.6% in probable MS, and 9.7% in possible MS), whereas abnormal foveal responses with normal checkerboard potentials appeared in 23% of all 235 patients—12.6% of definite MS, 37% of probable MS, and 26.5% of possible MS (see Tables 2 and 3).

Pathological VEPs elicited by a combination of both methods (89% probable and 64% possible MS) provided the first diagnostic clue of visual impairment in 45% of patients with either probable or possible MS (40% of probable and 46% of possible MS). With regard to foveal VEPs alone, we found pathological VEPs in 23% of probable and 20% of possible MS without known visual impairment.

In Table 4 the frequency of pathological findings obtained with the two different VEP methods are compared with laboratory and neurophysiological data. It seems that the diagnostic value of the electronystagmogram and cerebrospinal fluid analysis is at least as essential for the diagnosis of MS as visual evoked potentials.

In 178 patients investigated by VEP and at least one of the two other methods (ENG, CSF), normal VEPs with pathological ENG and/or CSF were found in 21% (6% in definite MS, 2% in probable MS, and 13% in possible MS). Pathological VEPs with normal ENG and/or CSF were found in only one patient (possible MS). All three investigations showed abnormal results in 79% (40% in definite MS, 14% in probable MS, and 25% in possible MS). No pathological results were found in only three patients with possible MS. A pathologic MLD (over 52 ms) was seen in 16% of definite, 26% of probable and 29% of possible MS

(in 24% of all patients); in only 3% of all patients, a pathologic MLD with normal checkerboard and foveal VEPs was found.

Discussion

The results confirm the generally accepted validity of the VEP test in the diagnosis of MS. However, the reported high sensitivity of VEPs elicited by central foveal stimulation should be considered with caution. There is no significant difference between the diagnostic value of checkerboard and foveal stimulation for most of the measured parameters, except for responses possibly not recognized. In nearly 40% of all patients and in 20% of controls a clear foveal response could not be elicited. An absence of foveal potential may in fact be due to technical difficulties. If only prolonged latencies or pathological interocular differences are compared, foveal VEPs are not superior to checkerboard reversal stimulation.

In Hennerici et al. [3] the standard deviations of mean values for latency and interocular difference are smaller than values reported by other authors (Table 1). This may be explained by different techniques and equipment. However an absence of VEP by foveal stimulation has not been described, although we observed it in 20% of our control subjects. Difficulties in recording detectable foveal responses have also been reported by others [13].

Difficulty in fixating on the small stimulus during the entire period of recording might be a possible explanation. The amplitude of P2 decreases rapidly with increasingly lateral fixation points, as shown for checkerboard stimulation [3]. The same is valid for foveal stimulation, for example at the time of small eye movements.

Nevertheless both methods mutually contribute to the diagnosis of MS, and the percentage of abnormal responses increases if both methods are combined (76% total abnormal responses compared to 53% for checkerboard and 66% for foveal stimulation). Therefore, if a normal checkerboard response is recorded, central foveal stimulation may give an additional diagnostic clue. In contrast, the measurement of MLD gives no additional information, as was reported elsewhere [13].

Although we were unable to confirm the very high incidence of pathological central VEPs in MS, the technique does provide a reliable method for detection of asymptomatic lesions of the visual pathways in about 21% of patients. Checkerboard reversal stimulation can be supplemented by recording central foveal responses, but seems to be superior, more stable, and less influenced by attention. Despite contrary reports [1, 2, 3, 5], not all patients with clinical RBN have abnormal VEPs. Moreover the assumption that prolonged VEPs remain pathological could not be confirmed. Thus, normal VEPs do not exclude a prior RBN.

For the clinical diagnosis of MS, VEP is a useful supplement, but the investigation of CSF or of oculomotor disturbances by ENG provides slightly higher diagnostic reliability. The combination of several clinical and neurophysiological tests increases the accuracy of diagnosis.

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