

Diagnostic Value of Conventional Visual Evoked Potentials Applied to Patients With Multiple Sclerosis

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Key words: conventional visual evoked potentials; multiple sclerosis; neurological systems.

Summary. *Objective.* The aim of this study was to determine the sensitivity and specificity of this classical technique employed at the Hospital of Lithuanian University of Health Sciences for the patients with multiple sclerosis and to assess its possible correlations with affected neurological systems.

Material and Methods. Pattern shift visual evoked potentials were recorded in 63 patients with multiple sclerosis, 17 (27%) of whom had a history of optic neuritis, and in 63 control patients with other neurological diseases. The latencies and amplitudes of P100 were measured. In total, 126 patients were referred to the inpatient department of neurology for differential diagnosis of demyelinating disorders between January and December of 2007.

Results. Abnormalities of visual evoked potentials were observed by 73% more frequently in patients with multiple sclerosis than in control patients ($\alpha=0.05$, $\beta<0.01$). The combined monocular/interocular test showed a specificity of 90.5% and a sensitivity of 82.5%. The probability of an affection of the pyramidal system was 5 times greater (95% CI, 2.2–11.0; $P<0.01$) and the probability of the optic pathways involvement was 4.8 times greater (95% CI, 1.9–11.9; $P<0.01$) in patients with multiple sclerosis than in controls.

Conclusion. Conventional visual evoked potentials must be reappraised in light of their diagnostic value in multiple sclerosis given their high diagnostic efficiency, relatively easy, short, and cheap implementation, and easy availability in everyday clinical practice.

Introduction

The clinical utility of evoked potentials, first employed by Dawson in 1947, is based on their ability to demonstrate objectively abnormal sensory system conduction, to reveal subclinical involvement, to help define the anatomic distribution, to give some insights into pathophysiology of a disease, and to monitor the changes in neurological status (1, 2). At the Hospital of Lithuanian University of Health Sciences (former Kaunas University of Medicine), the technique of evoked potentials entered clinical practice in 1991, and approximately 500 patients are examined annually.

Paraclinical tests, including electrophysiological ones, are performed to increase the certainty of a clinically suspected diagnosis, and this is of particular importance in a disease of “no better explanation,” such as multiple sclerosis (MS), for which no specific test exists (3). Evidence suggests that the disease is present long before the first symptom (presymptomatic stage) appears and is also more widespread and continuous than previously thought

with the changes in gray as well as white matter and changes in normal-appearing white matter (4, 5). While information provided by neuroimaging techniques is essentially related to anatomy (structural abnormalities), the neurophysiological signal is strictly related to function and expresses a significant correlation with the clinical findings, disability status, and quality of life (6–13).

Although most of the various assessment techniques are predominantly used in research, the conventional visual evoked potentials (cVEPs) are the most commonly employed electrophysiological tests for early diagnosis of demyelinating diseases in clinical practice (14). In MS, “time is also brain” measured in weeks or months of irreversible damage leading to disability, which silently accumulates, even with the first event and continues to do so even in the absence of symptoms, which makes an early diagnosis especially important for the optimal time of treatment initiation (15). Demyelination has a predilection to occur in certain sites within the central nervous system (CNS) (16). The afferent visual

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pathway, which extends from the retina to the primary visual cortex and consists of four neuronal components, is often affected even without a history of optic neuritis and/or visual symptoms (16–18). Since a few diseases other than MS affect the CNS in noncontiguous areas, the demonstration of an optic nerve lesion helps define the disease (2). The electrophysiological assessment of the clinically unaffected (fellow) eye of patients with unilateral optic neuritis may reflect the status of normal-appearing white matter in the CNS (19). Thus, abnormal VEPs in unaffected eyes provide evidence that might help identify dissemination in space and hence help diagnose MS although they are only formally incorporated in the currently revised McDonald criteria for primary progressive MS (16, 20). Apart from VEPs, the other evoked potentials contribute little to the diagnostic process of MS (21).

MS has long been regarded as only a demyelinating disease, but evidence now suggests widespread damage to axons that may be more closely correlated with the progression of disability (4). Therefore, the pathological effect of MS in the visual pathways consists of both axonal demyelination and axonal loss (22–25). These two consequences of the disease, even in its subclinical stages, are reflected in the changes in the initial component of the visual evoked response affecting its latency, waveform configuration, or amplitude (2, 16, 22).

Neurophysiological pathological evidence may improve, worsen, remain the same, or in small percentage of cases, return temporarily to normal in time (14, 26). VEP latencies were found to decrease significantly during the first two years with the most marked changes occurring between 3 to 6 months suggesting that recovery processes involving remyelination and possibly ion channel reorganization proceed for at least two years in the background of concurrent effects of demyelination and/or axonal degeneration also occurring in the fellow eye optic nerve initially masked by the recovery process, but gradually becoming more evident (27). Thus, VEP measures can provide not only diagnostic, but also prognostic information during the evaluation of patients with MS (9, 19). Experts of the recent evidence-based review recommend that VEPs are probably useful in identifying patients who are at increased risk of developing clinically definite MS (21). VEP was considered to be a tier I test in patients with optic neuritis primarily to assess responses in the opposite eye (28). The predictive value of evoked potentials was documented by the correlation between the results of combined testing of VEPs and motor evoked potentials at baseline with the change in the Kurtzke Expanded Disability Status Scale (EDSS) scores over the next two years; repeated and combined testing was proposed, which

yielded objective numerical data helping identify patients at higher risk of rapid progression, represented the burden of dysfunctional lesions, and documented the course of the disease even in patients at an early stage (13).

The multifocal visual evoked potential (mfVEP) is a relatively new technique increasing research interest, which has to be established as a reliable diagnostic tool. It has been developed to examine conduction in the parts of the visual field that is not possible with the full field cVEPs (16, 29). According to one recent study, it was found that mfVEPs were more sensitive than cVEPs in patients with MS; however, the difference was less significant than expected, and thus, it seemed advisable firstly to test patients suspected of MS with cVEPs (14). The multichannel (256-channel) VEP, another new VEP recording technique, has been recently introduced in research area, demonstrated a higher diagnostic value than the conventional analysis (30).

Our aim was to determine the sensitivity and specificity of this classical technique employed at the Hospital of Lithuanian University of Health Sciences for the patients with MS in everyday clinical practice, to assess its possible correlations with the affected neurological systems, and to compare the results with the literature.

Material and Methods

It was a retrospective comparative study of the clinical records of 126 patients referred to a tertiary care inpatient department of neurology of the Hospital of Lithuanian University of Health Sciences for a differential diagnosis of demyelinating disorder. The cVEPs were performed during the period from January to December, 2007. From the history of every case, the following data were extracted: final clinical diagnosis, age, sex, first symptoms and duration of the disease, clinical course, prescribed medications or used therapeutic techniques, disability status, history of optic neuritis, other possible ophthalmological pathology (designated after a consultation with a neuro-ophthalmologist), and results of all paraclinical tests, which were employed for the diagnostic basis (brain and/or spinal cord magnetic resonance imaging (MRI) results, cerebrospinal fluid findings, and cVEPs). The MS diagnosis was confirmed according to the McDonald diagnostic criteria revised in 2005. Finally, the following disorders of the neurological system were collected from the objective neurological examination records of the same time when cVEPs were performed: 1) visual disorders characterized by the visual acuity, alterations of visual fields, and optic nerve disc atrophy in the fundi; 2) sensory disorders characterized by decreased or lost sensation of vibration, figure writing, touch, pain, and propriocep-

tive sensation; 3) pyramidal disorders characterized by the intensification of the deep tendon reflexes, detectable weakness of the muscles, appearance of the pathological signs, and increased muscular tone; 4) brainstem disorders characterized by nystagmus, diplopia, swallowing disorders, dysarthria, or detected pathological signs of other cranial nerves; 5) cerebellar disorders characterized by ataxia; 6) bowel/bladder disorders characterized by constipation, retention, hesitancy, urgency, and need of catheterization. Disability status evaluated in Kurtzke EDSS scores (from 0 to 10 points) was recorded for all the patients with confirmed MS diagnosis.

The standard pattern shift VEPs were recorded for all 126 patients under the circumstances of everyday clinical practice following the recommended standards (31). A routine diagnostic electrophysiological procedure was done in a darkened room with every patient comfortably seated with the head supported. Correcting lenses or spectacles were used for every subject if needed for the appropriate refraction. The electrodes were placed at 2.5 cm above the inion (active) and reference at Fz. A ground electrode was placed on the forehead. Impedances were reduced to $<5 \text{ k}\Omega$ by skin preparation. Subjects were seated at eye level at a distance of 1 m from a stimuli screen and were instructed to focus on the center of the screen indicated by a small red dot. Full field stimulation was performed monocularly, and during monocular stimulation one eye was occluded. The stimulus was a reversing checkerboard (checker size $12 \times 16 \text{ mm}$), LED screen, 3.9 times per s. The analysis time was 246 ms; 260 responses were averaged twice and overlapped. The peak latencies of P100 were measured; the peak amplitude of P100 was calculated as the amplitude from an isoline. Registration of cVEPs was done by the Evoked Potential Navigating System (Bio-Logic system, USA equipment). The responses were considered abnormal if the P100 latency was longer than 114 ms (i.e., 2 SD above the mean) or the amplitude was reduced by less than $3 \mu\text{V}$.

Statistical analysis was performed using the Microsoft Excel 2007 and Statistical Package for Social Sciences software (SPSS) version 16. For data description, the mean values for the symptoms under investigation, standard deviations (SD), and 95% confidence intervals (CI) were presented. The chosen significance level for statistical hypothesis testing was 0.05. The Student *t* test was used to compare the mean values of the two subject groups; the *Z* test was used for the comparison of probability. The Mann-Whitney and Kruskal-Wallis tests were used for the comparison of nonparametric variables; the Spearman test was performed for the estimation of possible correlations. In the presence of the type I error of $\alpha=0.05$, type II error β was assessed in order

to determine the magnitude of the difference between the parameters. The magnitude of the difference was considered to be significant when $\alpha=0.05$ and $\beta \leq 0.2$. Sensitivity was defined as the proportion of patients with MS with abnormal cVEPs, and specificity was defined as the proportion of patients without MS and with normal cVEPs.

The study was approved by the Kaunas Regional Ethics Committee.

Results

Based on medical data from all 126 patients enrolled into the study, clinically definite MS was diagnosed in 63 patients, and other neurological diseases were confirmed in other 63 cases. In the latter cases, cranial MRI scans did not demonstrate abnormalities characteristic of demyelinating diseases. These patients constituted the MS and control groups. The clinical diagnoses of the patients in the control group were as follows: vestibulopathy of various etiology in 17 patients (27.0%), myelopathy of unknown origin in 8 patients (12.7%), migraine and other primary headaches in 7 patients (11.1%), cerebrovascular diseases (transitory ischemic attack and cerebral infarction) in 7 patients (11.1%), cerebellar ataxias of various etiology in 7 patients (11.1%), epilepsy in 3 patients (4.8%), depression in 3 patients (4.8%), other psychiatric disorders in 3 patients (4.8%), hemisindrome of unknown cause in 3 patients (4.8%), neuromuscular disease (myasthenia and spinal atrophy) in 2 patients (3.2%), meningitis in 1 patient (1.6%), polyneuropathy in 1 patient (1.6%), and parkinsonism in 1 patient (1.6%). Detailed characteristics of the MS group are shown in Table 1. The mean age of the patients in the control group was 37.4 years (SD, 2.6; range, 18 to 71 years); there were 25 males (39.7%) and 38 females (60.3%).

The frequencies of affected neurological systems in both MS and control groups are presented in Table 2. The data showed that the frequency rates of visual disorder were higher by 41.3%, sensory by 36.5%, motor by 52.4% ($\alpha=0.05$, $\beta<0.01$), and bladder and bowel by 19% ($\alpha=0.05$, $\beta<0.1$) in the MS group as compared with the respective values of the control group. The differences in the frequency rate of brainstem and cerebellar disorders were not significant between the two investigated groups.

In the MS group, 17 patients (27.0%) had a history of an optic neuritis episode (Table 3). Further analyzing MS patients with previous optic neuritis, it was found that 5 (29.5%) of them had normal VEP responses, and 12 (70.6%) had abnormalities of the P100 wave parameters. However, no statistically significant relation was found between visual abnormalities and the history of visual pathway involvement ($P>0.1$).

Table 1. Characteristics of 63 Patients With Multiple Sclerosis Analyzed Retrospectively

Characteristic	Patients, No. (%)
Women	50 (79)
Age, mean (SD) [range], years	36.3 (10.8) [17–74]
Disease course	
Relapsing-remitting	58 (92.1)
Secondary progressive	4 (6.3)
Primary progressive	1 (1.6)
Time since the first symptom, mean (SD) [range], years	6.2 (5.6) [1–22]
Time since diagnosis, mean (SD) [range], years	2.6 (2.4) [0–11]
First symptoms	
Motor weakness	41 (65.1)
Dysesthesia, paresthesia, pain	32 (50.8)
Visual	18 (28.6)
Urination/defecation problems	20 (31.8)
Ataxia (limb, gait)	24 (38.1)
Fatigue	29 (46)
Other	9 (14.3)
EDSS, mean (SD) [range], score	2.7 (1.4) [0–7]
Disease-modifying drugs	
Beta interferon-1a SC	11 (17.5)
Beta interferon-1a IM	5 (7.9)
Beta interferon-1b IM	18 (28.6)
Glatiramer acetate	3 (4.8)
Azathioprine	1 (1.6)
Mitoxantrone	3 (4.8)
Glucocorticoids given before/simultaneously with VEPs recording	46 (73)
Plasmapheresis performed before/simultaneously with VEPs recording	23 (36.5)

Values are number (percentage) unless otherwise indicated. EDSS, Expanded Disability Status Scale.

Table 2. Frequencies of Affected Functional Neurological Systems and Their Differences Comparing Multiple Sclerosis (MS) and Control Groups

Neurological Functional System Affected	MS Group (N=63)	Control Group (N=63)	Frequency (Rate) % Difference	P	β^*
Visual	54.0	12.7	41.3	<0.0001	0.0005
Sensory	58.7	22.2	36.5	0.0001	0.0085
Pyramidal	93.7	41.3	52.4	<0.0001	0.0000
Brainstem	42.9	30.2	12.7	0.1414	–
Cerebellar	36.5	22.2	14.3	0.2701	–
Bowel/bladder	20.6	1.6	19.0	0.0009	0.061

*Calculating β , $\alpha=0.05$.

Table 3. Neuro-Ophthalmological Characteristics of All the Patients Under Investigation (N=126)

Ophthalmological Description	MS Group (N=63)	Control Group (N=63)
Visual functional system affected	34 (54)	8 (12.7)
unilateral	10 (29.4)	–
bilateral	24 (70.6)	–
History of optic neuritis	17 (27)	0 (0)
Visual acuity, mean (SD)		
right eye	0.54 (0.41) (<i>visus</i> =1 for 20 cases)	0.65 (0.3)
left eye	0.54 (0.41) (<i>visus</i> =1 for 16 cases)	0.64 (0.31)
cVEPs measures with history of ON		
abnormal	12 (70.6)	–
normal	5 (29.4)	–
Absent response of VEPs of one eye or both	16 (25.4)	0 (0)

Values are number (percentage) unless otherwise indicated. MS, multiple sclerosis.

Table 4. Comparison of the Conventional VEP Parameters Between the Two Investigated Groups (N=126)

cVEP Parameters	MS Group (N=63)		Control Group (N=63)		Mean Difference		P	β^*
	Mean	SD	Mean	SD	Abs. No.	%		
P100 latency of the right eye, ms	122.76	14.00	103.94	11.70	18.82	15.3	0.000	0.000
P100 latency of the left eye, ms	122.60	12.52	104.53	10.93	18.06	14.7	0.000	0.000
P100 amplitude of the right eye, μ V	3.68	2.66	5.74	2.44	2.05	-55.8	0.000	0.006
P100 amplitude of the left eye, μ V	3.65	2.66	6.15	2.55	2.51	-68.7	0.000	0.000

*Calculating β , $\alpha=0.05$; Abs. No., absolute number. MS, multiple sclerosis.

The P100 values (latency and amplitude) and their differences are shown in Table 4. Significant differences were observed comparing the P100 wave latencies and amplitudes of the right and the left eye of the MS patients with those in the control group.

From clinical aspect, correlations between EDSS scores, symptom duration, medications, and therapeutic techniques given and the estimated values of cVEP P100 latencies and amplitudes of each eye were tested separately. A significant correlation was found between the symptom duration and prolongation of the P100 latencies of both eyes (Spearman correlation coefficient, 0.25; $P=0.048$), and pathological findings in latencies if amplitudes were abnormal, and vice versa ($P<0.0001$).

It was relevant to detect the sensitivity and specificity of the cVEP employed in our department with the intention to evaluate their diagnostic efficiency and to compare with the results published by other authors. The combined monocular/interocular test had a specificity of 90.5% and a sensitivity of 82.5%. The analysis of results revealed cVEPs overall abnormality rates (both in P100 latencies and amplitudes) of 52 patients (82.5%) missing in 11 cases (17.5%) in the MS group. In the control group, 6 patients (9.5%) had abnormalities of cVEPs. Pathological cVEP parameters were detected at the frequency rate higher by 73% in the MS group compared with the control group, which differed significantly ($\alpha=0.05$, $\beta<0.01$). A significant relationship was detected between cVEP pathological values and affection of the visual system ($P<0.01$) as well as between cVEP pathological values and motor neurological functional systems ($P<0.01$). When cVEP values were abnormal, the probability of having motor disorders increased by 5.0 times (95% CI, 2.2–11.0) and that of visual disorders by 4.8 times (95% CI, 1.9–11.9).

Discussion

The analysis of our study revealed a high diagnostic value of cVEPs in terms of both sensitivity and specificity (90.5% and 82.5%) for the MS patients when employed in everyday clinical practice, which was similar to the results provided in the recent scientific literature. Historically, when the

VEPs were first introduced into clinical practice, the method was found to detect abnormality in up to 95% of individuals who would eventually receive a diagnosis of clinically definite MS; in one recent British audit of 273 referrals, 92.5% of patients who eventually received a diagnosis of multiple sclerosis were found to have VEP abnormalities (1). According to the latest evidence-based review, VEP sensitivities ranged from 25% to 83% in large studies, which proved to be reliable (21). When a combined monocular/interocular criterion was employed, the cVEP test had a sensitivity of 84.2% and a specificity of 90%, compared with mfVEP with the highest sensitivity of 94.7% and specificity 90% (14).

Encompassing 1950 patients with all MS classifications, the average abnormality rate of cVEPs was 63% with the greater likelihood of optic nerve lesions with more definite clinical diagnoses (2). Our results indirectly support the latter finding as a significant correlation was found between the duration of MS symptoms and prolongation of P100 latencies. It has to be noted that more than half of the investigated MS patients developed visual system affection, majority of them had bilateral involvement, and quarter of them had totally absent VEP responses both unilaterally and bilaterally.

It was impossible to compare the results directly as the differences between the studies existed and could be explained basically by the different definitions of MS used, variations in the course of a disease, some studies being composed of a predominance of one class of the patients, and different technical factors. Some studies have suggested that the sensitivity of the technique may be as low as 25% in some circumstances, when, for example, computer monitors are used as stimuli, and can be normal in 40% to 50% of patients initially (1, 32). The incidence of cases with abnormal cVEPs was also lower reported from Asia than that reported from Europe and the United States, and this difference was explained possibly due to racial differences and the use of different criteria (33).

VEPs were recognized and emphasized as the most sensitive studies since after optic neuritis, they disclosed in about 93% changes as sequels of de- and remyelination, which was helpful for the clinician

in order to prove a previous clinical event (34). It should be noted that there was a large proportion of the patients (one third) who had a history of a previous optic neuritis episode at the time of neurophysiological evaluation of our study. It could be under favor for the higher rates of the cVEP abnormalities and, thus, calculated chances of having visual system affection. Previous studies have also shown that VEPs may have a superior sensitivity to detect clinically silent lesions even though their diagnostic sensitivity in MS may be lower than evoked potential modalities. In the study of Beer et al., VEPs had a greater chance to detect subclinical lesions than had MEPs and SSEPs because fewer patients complained about visual disturbances, and even though VEP abnormalities were considerably less frequent than MEP or SSEP abnormalities, they led to a greater relative number of reclassifications (3).

VEPs showed abnormal results in 54.4% of patients in the first study evaluating a population of visually asymptomatic patients with MS, and P100 latency was the most diffuse parameter most often used to detect optic nerve involvement, but it was not very sensitive in the diagnosis of postchiasmatal localizations (18). The diagnostic value of the new measures for MS reached a sensitivity of 72% and a specificity of 100% for the VEPs when using multi-channel recordings (30).

In one survey on the subject of VEP appraisal, 5000 neurologists managing patients with MS were questioned whether they would order an evoked potential analysis in a patient with the first demyelinating event. A mixed opinion was expressed: 30% would not, while 48.8% were neutral, and only 21% would order this test, which showed underestimation of the valuable neurophysiological technique (28).

Limitations of Our Study. An obvious limitation of our study was the retrospective design of the analysis of the measurements performed. The quality of the data depended on the quality of medical documentation. A relatively small sample could be assessed as a disadvantage of the study too. The sample of our patients was heterogeneous as in everyday clinical work, but the predominance of relapsing-remitting clinical course and longer duration of the disease should be emphasized.

Conclusions

Conventional visual evoked potentials must be reappraised because of high diagnostic value in multiple sclerosis given their high diagnostic efficiency, relatively easy, short, and cheap implementation, and easy availability in everyday clinical practice.

Statement of Conflict of Interest

The authors state no conflict of interest.

Standartinių regos sukeltų potencialų diagnostinė reikšmė sergantiesiems išsėtine skleroze

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Raktažodžiai: standartiniai regos sukelti potencialai, išsėtinė sklerozė, neurologinės sistemos.

Santrauka. *Tyrimo tikslas.* Nustatyti šio klasikinio metodo, taikomo universitetinėje ligoninėje sergantiesiems išsėtine skleroze, jautrumą ir specifiškumą bei galimą ryšį su pažeistomis nervų sistemos funkcijomis, radus patologinių pokyčių.

Tyrimo medžiaga ir metodai. Atliktas retrospektyvusis 126 pacientų, atsiųstų į neurologijos stacionarą diferencinei demielinizuojančių susirgimų diagnostikai, 2007 m. sausio–gruodžio mėn. ligos istorijų tyrimas. Rašto poslinkio regos sukelti potencialai atlikti 63 pacientams, kuriems diagnozuota išsėtinė sklerozė, 17 (27 proc.) iš jų yra sirgę optiniu neuritu, ir 63 kontrolinės grupės asmenims, kuriems nustatyta kita neurologinė patologija. Išmatuota P100 bangų latencija ir amplitudės.

Rezultatai. Sergančiųjų išsėtine skleroze grupėje pokyčiai standartiniuose regos sukeltuose potencialuose nustatyti 73 proc. dažniau palyginus su kontroline grupe ($\alpha=0,05$, $\beta<0,01$). Monokulinis/interokulinis regos sukeltų potencialų tyrimo specifiškumas – 90,5 proc., jautrumas – 82,5 proc. Esant pokyčių regos sukeltuose potencialuose, galimybė, jog yra pažeista piramidinė sistema, padidėja penkis kartus (95 proc. PI 2,2–11,0, $p<0,01$), jog pažeisti optiniai takai – 4,8 karto (95 proc. PI 1,9–11,9, $p<0,01$) palyginus su kontroline grupe.

Išvados. Atsižvelgiant į nustatytą tyrimo efektyvumą ir į tai, jog jį sąlyginai lengva atlikti, didesnę prieinamumą kasdienėje klinikinėje praktikoje ir pigumą, trumpesnę atlikimo laiką, standartinių regos sukeltų potencialų diagnostinė reikšmė sergantiesiems išsėtine skleroze turi būti įvertinta iš naujo.

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