Visual Evoked Potential Study in Multiple Sclerosis Disease

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Abstract

Purpose: To demonstrate visual evoked potential (VEP) changes in multiple sclerosis (MS) disease

Methods: A case series study of VEP changes in forty-nine patients with definite, probable and possible diagnoses of MS referred to electrophysiology ward from January 2002 to December 2005. Pattern VEP was done for those with good visual acuity (VA), and flash VEP was done for those who did not have central fixation or good VA. Characteristics of P_100 wave in pattern VEP and P_2 wave in flash VEP were evaluated.

Results: The implicit time of P_100 and P_2 waves in pattern and flash VEP, demonstrated severe abnormalities in 84.5% of definite MS. In probable MS, implicit time increased in 81.8% cases. In possible MS cases, increased implicit time was seen in more than 50% of patients. Decrease in amplitude alone, was seen in a few cases. Combined changes of implicit time and amplitude were prominent.

Conclusion: VEP is an invaluable electrophysiological test in MS for both diagnosis and follow-up of the patients. Concurrent with magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis, VEP can help neurologists and ophthalmologists for better evaluation of MS patients.

Keywords: Visual Evoked Potential, Multiple Sclerosis, Implicit Time, Amplitude, P_100 Wave, P_2 Wave

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurologic disease characterized pathologically by multiple areas of central nervous system (CNS) white matter inflammation, demyelination and glial scarring (sclerosis).1,2,3

The optic chiasm, brainstem, cerebellum and spinal cord are commonly involved.1,2,4,5 Visual symptoms include diplopia, blurred vision which at first is for color vision, diminution or loss of vision, and visual field defects such as central or cecocentral scotoma, field contraction and homonymous hemianopia.4-6 The main pathophysiological effects of demyelination are reduced conduction velocity, conduction block and impaired ability to conduct fast trains of stimuli due to an increased refractory period.1,2,5,7

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It is well known that because of variable course of the disease and multi-sites involvement of it, the perfect diagnosis is not easy. Magnetic resonance imaging (MRI) of the central nervous system (CNS) is an important diagnostic method, but its results may be vague and not so precise in many cases especially at the beginning of the disease.\textsuperscript{1,2,6,8}

The current diagnostic criteria for MS are variable and in some clinics the visual evoked potentials (VEP) findings are considered the main document for diagnosis.\textsuperscript{9,10} In most cases, involvement of visual pathways especially optic nerve is the first sign of disease, demonstrating the importance of VEP test for diagnosis of MS.\textsuperscript{7,11-13}

The VEP test is a paraclinical method by which the electrical changes of visual pathway after light stimulation can be recorded. In patients with good vision and good central fixation, pattern VEP and in patients with severe visual loss and no good central fixation, flash VEP is indicated.\textsuperscript{8,14}

The most important part of pattern VEP is $P_{100}$ wave with implicit time of about 100-106 millisecond and amplitude about 10 microvolts. The most prominent part of flash VEP is $P_2$ wave with implicit time of about 110 millisecond and amplitude of about 9 microvolts.\textsuperscript{14}

The use of small checks (10 to 30 minute) has usually been found to increase sensitivity of the test and likelihood of abnormality detection.\textsuperscript{14} If grating stimulus is used instead of check stimulus, high spatial frequency is the best method.\textsuperscript{4,14}

A hemifield stimulation helps to detect chiasmal or retrochiasmal dysfunction.\textsuperscript{14}

In patients without visual symptoms, 60 minute checks at highest luminance is more distinctive.\textsuperscript{14}

An attack of optic neuritis usually starts with a sudden loss of visual acuity (VA) even to light perception at the end of the first week. At this acute stage, the pattern VEP is found to be flat or non-recordable. When VA is less than 20/2000, flat VEP is a rule. Recordable but delayed VEP is found in those with visual acuities of more than 20/100. Delayed VEP recovers with time, concurrent with recovery of VA but with a lag. VEP recovery is incomplete after multiple relapses of the disease.\textsuperscript{5,14,15}

During the course of MS, an acquired red-green color vision defect is frequent. Tsukamoto and Adachi-vsami demonstrated that in chronic optic neuritis, impaired color vision test with pseudoisochromatic plates (PIP) and panel D-15, was more frequent than delayed VEP, but Engell et al showed that VEP is more sensitive than color vision test in this condition.\textsuperscript{2}

Moreover, there are many diseases other than MS which can cause delay in VEP; among these, anterior ischemic optic neuropathy, tumoral compression of optic nerve, sarcoidosis, hereditary degeneration of CNS as ataxia, toxic neuropathy and Parkinsonism are to be mentioned.\textsuperscript{1,2,6}

It should be emphasized that even in thoroughly normal clinical situation, VEP may show delay due to some technical errors or patient condition.\textsuperscript{4,14} In low luminance and low contrast due to small pupil size, lens or vitreous opacity, defocused stimuli, and small or large check sizes, VEP can show some degrees of delay without pathologic changes in CNS.

The goal of this study is to show the changes of VEP in MS disease and to compare it with clinical examination and paraclinical (MRI) methods usually used in this disease.

**Methods**

This is a case series study in forty-nine cases with definite, probable and possible diagnoses of MS, whom were referred to electrophysiology ward of Farabi Eye Hospital for VEP study from January 2002 to December 2005. From these, 26 were definite, 11 were probable, and 12 were possible MS cases (Table 1).

Complete ocular examinations of anterior and posterior segments were done for all patients, and then patients went under VEP test. In patients with poor VA and no good central fixation, flash VEP by a flash light with luminance of 100 Cd/m\textsuperscript{2} and frequency of 60 produced by monitor was used. In patients with good VA and good central fixation, pattern reversal stimulus with check size of 30 minutes was used. Pattern stimulus was presented on a monitor with a pattern contrast of 98% and mean luminance of 50 Cd/m\textsuperscript{2}. 
Table 1. Criteria for clinical diagnosis of multiple sclerosis

<table>
<thead>
<tr>
<th>Clinically definite</th>
<th>Possible</th>
</tr>
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<tbody>
<tr>
<td>Consistent course</td>
<td>History of relapsing, remitting symptoms without documentation of signs objective signs insufficient to establish more than one lesion of central white matter</td>
</tr>
<tr>
<td>Relapsing, remitting course; at least two bouts separated by at least 1 mo slow or stepwise progressive course for at least 6 mo</td>
<td>No better explanation</td>
</tr>
<tr>
<td>Documented neurologic signs of lesions in more than one site, of brain or spinal cord white matter</td>
<td>Mortality</td>
</tr>
<tr>
<td>Onset of symptoms between ages 10 and 50 yr</td>
<td>Documented single bout of symptoms with signs of more than one white matter lesion; good recovery, then variable symptoms and signs no better neurologic explanation</td>
</tr>
<tr>
<td>No better neurologic explanations</td>
<td>Mortality</td>
</tr>
<tr>
<td>History of relapsing, remitting symptoms but signs not documented and only one current sign commonly associated with MS</td>
<td>Mortality</td>
</tr>
<tr>
<td>Documented single bout of symptoms with signs of more than one white matter lesion; good recovery, then variable symptoms and signs no better neurologic explanation</td>
<td>Mortality</td>
</tr>
</tbody>
</table>

Results

In 13 cases (definite, probable, possible) the best corrected visual acuity (BCVA) was 20/20 in both eyes and patients were referred because of complaints other than ocular problems. In 14 cases ocular complaints were only in one eye and other eye was entirely normal, and in the rest of patients both eyes had visual problem. The demographic and ocular characteristics of patients are shown in table 2.

Altogether, in 23 cases (46.9%), the only change of VEP was prolongation of implicit time; in 20 cases (40.8%), both decrease of amplitude and prolongation of implicit time were seen. In four cases (8.2%), the only change was decrease in amplitude and in two cases (4.1%), VEP test was totally normal bilaterally.

In 26 cases (52 eyes) with definite MS, 23 eyes had normal vision and 29 eyes had some degrees of decrease of vision due to optic neuritis. VEP was completely normal in only six eyes (11.53%). Delay of P100 or P2 wave was seen in 24 eyes (46.15%). Delay and low amplitude were observed in 20 eyes (38.46%) and low amplitude without delay was seen in 2 eyes (3.84%). In fact, of 23 eyes with normal vision, 17 eyes had abnormalities of VEP test.

In 11 cases (22 eyes) with probable MS, 7 eyes had normal vision and 15 eyes had subnormal vision. Of these eyes, four eyes (18.18%) had normal VEP, 14 eyes (63.63%) had prolonged implicit time, and four eyes (18.18%) had both decrease of amplitude and prolongation of implicit time. Of seven eyes with normal vision, 3 eyes showed VEP abnormalities.

In 12 cases (24 eyes) with possible MS, 10 eyes had normal vision and 14 eyes had subnormal BCVA. 10 eyes (41.66%) had normal VEP, one eye (4.16%) showed decrease of amplitude, 10 eyes (41.66%) showed prolonged implicit time, and in 3 eyes (12.50%) both decrease of amplitude and prolongation of implicit time were seen (Table 3) (Figures 1-5).

<table>
<thead>
<tr>
<th>Table 2. Ocular and demographic characteristics of the patients</th>
</tr>
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<tbody>
<tr>
<td>Age Range</td>
</tr>
<tr>
<td>15-58 year</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male: 15</td>
</tr>
<tr>
<td>Female: 34</td>
</tr>
<tr>
<td>Family history of multiple sclerosis</td>
</tr>
<tr>
<td>Yes: 5</td>
</tr>
<tr>
<td>No: 25</td>
</tr>
<tr>
<td>Unknown: 19</td>
</tr>
<tr>
<td>BCVA Range: V1/100 – V2/20</td>
</tr>
<tr>
<td>Normal: 42</td>
</tr>
<tr>
<td>Blurred: 1</td>
</tr>
<tr>
<td>Pale: 6</td>
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</tbody>
</table>
Table 3. Overall VEP changes in all patients

<table>
<thead>
<tr>
<th>VEP changes</th>
<th>Cases</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Low amplitude</td>
<td>4</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Prolonged implicit time</td>
<td>23</td>
<td>46.9</td>
<td></td>
</tr>
<tr>
<td>Low amplitude and prolonged implicit time</td>
<td>20</td>
<td>40.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Normal PVEP: 60 pattern/reversal stimulations of checks with 30° size and constant average luminance of 50 Cd/m² and contrast of 98%. Potential VEP: PVEP
Normal values of P₁₀₀ wave: IT: 103±3ms, Amplitude: 16±7μv

Figure 2. Delay of P₂ wave in RE and more severe delay and decrease of amplitude in LE in a patient with definite MS. (RE: Right eye, LE: Left eye)

BCVA:
\[
\begin{align*}
\text{RE:} & \quad \frac{20}{50} \\
\text{LE:} & \quad \frac{20}{200}
\end{align*}
\]
Figure 3. Nearly normal VEP in RE and severe delay and amplitude decrease of P100 wave in LE of a patient with definite MS, with normal vision bilaterally. (RE: Right eye. LE: Left eye)

BCVA: \[
\begin{align*}
\text{RE: } & 20/20 \\
\text{LE: } & 20/20
\end{align*}
\]

Figure 4. Severe decrease of amplitude and mild delay in P2 wave in RE and nearly normal VEP in LE in a patient with probable MS. (RE: Right eye. LE: Left eye)

VA: \[
\begin{align*}
\text{RE: } & \text{CF3m} \\
\text{LE: } & 20/20
\end{align*}
\]

Figure 5. Severe delay of P100 and reduction of its amplitude in RE and mild delay in LE of a patient with possible MS. (RE: Right eye. LE: Left eye)
Discussion

Due to variable clinical course and several episodes of exacerbation and remission in MS disease, the precise diagnosis is not so easy in all patients. In fact, MS suspect populations are heterogenous including patients with single clinical CNS lesion presenting with isolated optic neuritis, as well as those meeting clinical criteria for possible and probable MS.\(^3\)\(^,\)\(^6\)\(^,\)\(^17\)

As pathologic confirmation of the MS lesion is impossible, the diagnosis is clinical based, however, many patients do not have adequate symptoms or signs confirmative for definite MS.\(^17\)

MRI has 84-100% sensitivity for detecting of optic neuritis in cases in which optic nerve fibers show tissue changes,\(^5\)\(^,\)\(^8\)\(^,\)\(^15\) but in mild inflammation, the results of MRI are not so distinctive. In other parts of CNS, T\(_2\) weighted MRI can show multiple white matter lesion (demyelinated plaques) in about 90% of cases.\(^1\)\(^,\)\(^2\)\(^,\)\(^6\)\(^,\)\(^8\)\(^,\)\(^10\)\(^,\)\(^16\) Although conventional MRI appears sensitive for detecting changes due to MS, it has limitation by poor pathological specificity. Magnetization transfer (MT) imaging technique may provide information relating to tissue structure and myelin integrity by indirectly assessing protons bound to rigid macromolecules.\(^18\)

On the other hand as Mowry and colleagues have shown, asymptomatic involvement of optic nerve may occur in MS disease, which can be detected by VEP, leading to make the precise diagnosis and also to monitor the progression of disease.\(^11\)\(^,\)\(^13\) Also lee et al showed 60.7% sensitivity and 80.5% specificity for VEP test in MS disease. They believe VEP is useful to identify patients at increased risk for developing definite MS.\(^17\)

Fuhr and colleagues found objective numerical data by VEP test that can help to identify patients at higher risk of rapid progression.\(^19\)

Halliday and colleagues showed delayed pattern-reversal VEP in a high percentage of MS patients with no symptoms or signs of optic nerve involvement. He presented 51 MS cases, 24 of whom had a past history suggestive of optic neuritis in one or both eyes; all of them proved to have delayed pattern responses.\(^20\) From 27 other patients with no history of visual impairment, 25 have been shown delayed responses.\(^20\) In other reports, 82% to 100% of MS cases with visual impairment and 36% to 93% of MS cases without visual impairment showed delayed pattern responses.\(^5\)\(^,\)\(^7\)\(^,\)\(^6\)\(^,\)\(^14\)

Salmi reported high percentage of delayed VEP in longstanding MS disease.\(^2\)

On the other hand, in another study, it was shown that implicit time of waves in VEP decreased in 3-6 months after optic neuritis.\(^21\) Beer and colleagues showed multimodal evoked potential have a reclassification specificity of 87% while specificity of clinical examinations is 89%.\(^22\) They also mentioned that the incidence of nonspecific MRI abnormalities is greater after the age of 50.\(^22\)

However, Pinckers and Verriest demonstrated concordant results of VEP test and color vision in 71% of MS cases.\(^2\)

On the whole the sensitivity of VEP test in MS disease with a history of optic neuritis is about 77 to 100% and it remains abnormal in 81% of cases after a year.\(^10\)\(^,\)\(^11\)\(^,\)\(^13\)\(^,\)\(^16\) In 25-30% of MS cases the first symptom and sign is related to ocular abnormalities and VEP test is abnormal in about 90% of these cases.\(^2\)\(^,\)\(^6\)\(^,\)\(^14\)

Although cerebrospinal fluid (CSF) analysis can give supportive information by finding increased IgG fraction in CSF\(^1\)\(^,\)\(^8\)\(^,\)\(^23\) but due to its aggressive method, it is not a routine procedure for many of neurologist.

As our results show, positive pathologic abnormalities in implicit time and amplitude of P\(_{100}\) wave in pattern VEP, or P\(_2\) wave in flash VEP, are found in about 84.50% of definite, 81.80% of probable and 54% of possible MS cases. Our findings are comparable with Holiday’s et al who demonstrated delayed responses in a high percentage of patients whether with definite, probable or possible MS.\(^20\)

Also our results are nearly similar to Mowry, Beer and their colleagues findings that showed sensitivity of VEP test in MS is about 90%.\(^11\)\(^,\)\(^22\)

Although it seems that sensitivity of MRI and VEP are neck and neck in MS disease\(^12\)\(^,\)\(^13\)\(^,\)\(^23\) but we believe VEP test is easier to do and interpretation of it is far from vagueness, a condition that is often encountered in MRI reports in mild and initial episode of disease.
Of course abnormalities in VEP test can occur in many optic nerve diseases other than MS, as in Behçet, Wagner, syphilis, Lyme, HIV infection, tumors of optic nerve and CNS trauma and so on, but differential diagnosis is not so difficult. Our results show changes in implicit time are more prominent than amplitude, specially in cases with good vision, and this is in accordance with Atilla et al’s report that say VEP amplitude decrease is more significant in ischemic optic neuropathy, while changes of latency period is seen more in optic neuritis.

**Conclusion**

In conclusion, we believe the VEP test, pattern or flash, can be used in MS cases as a reliable method both, for diagnosis of new cases or revealing of recurrence of disease and follow-up. We suggest, in any case of MS suspect, besides the clinical examination, to do both CNS MRI and VEP, considering that VEP has more value in patients with vague and borderline signs and symptoms, but MRI has advantage in cases with multisystem involvement and also for evaluation of severity of disease.

**References**

17. Gronseth GS, Ashman EJ. Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-


