Original Article

Role of Visual Evoked Potentials in Multiple Sclerosis

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Abstract:

Background: Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system (CNS) affecting young adults and is considered as the leading cause of non traumatic neurological disability of young adults affecting nearly 2 million people worldwide. The pathogenesis of MS is at best incompletely understood. There are several proposed mechanisms that may be important in the production of MS plaques: autoimmunity, environment and heredity. Deviation of immune responses in a genetically susceptible patient plays a central role in its pathogenesis. Electrophysiological, spinal tap and Radiological tools are important laboratory investigations and have added so much to the clinical diagnosis and for the classification of MS. It was found that visual function and conduction has been changed in patients with multiple sclerosis.

Objectives: The aims of the study is to estimate and evaluate the visual evoked potential (VEP) parameters in patients with MS and its relation to their disability degree (using the expanded disability status scale score "EDSS") and visual presentation of them in comparison with healthy individuals.

Patients and Methods: 112 patients with multiple sclerosis and 50 subjects without any neurological or psychiatric diseases as control group were recruited in this study. The cases were collected from Baghdad teaching hospital, MS center, Baghdad, Iraq at the period from May 2012 to April 2013, and studied at the unit of electrophysiology in Al-Shaheed Ghazi Al-Hareri Hospital in the Medical city. All patients and control groups were tested for VEP.

Results: The present study showed a significant increase in the P100 latency and inter-ocular (IO) latency difference and non statistical significant decrease in the IO amplitude difference in patients group than the control group. Also among patients group there was positive linear correlation between the severity of the disease measured by EDSS score and P100 latency while negative linear correlation with the amplitude.

Conclusion: There was a higher percent of patients with defective VEP parameters and so their visual pathway even if it was asymptomatic, in addition to their relation with patients` disability than the control group, making it easy to quantify and predict MS disability objectively.

Keywords: Multiple sclerosis, Expanded Disability Status Scale, VEP.

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Introduction:

Multiple Sclerosis (MS): is an inflammatory disease in which the fatty myelin sheaths around the central nerves of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. Disease onset usually occurs in young adults, and it is more common in women. It has a prevalence that ranges between 2 and 150 per 100.000 (1). MS was first described in 1868 by jean- martin Charcot (2). Till now MS is not easy to be detected, and a definite diagnosis can take several months or even years. And there is neither a single neurological or laboratory test that can definitively confirm or rule out MS, nor does any produce results in all patients. There are some supplementary tests (Paraclinical tests) that can help to aid the diagnosis and are playing an increasingly important role with technology advancement. Those tests are used in documenting multi-centric CNS lesions (in time and place), eliminating alternative diagnosis, and eventually making the ultimate diagnosis (3). These tests basically include electrophysiological test (Evoked Potentials), Spinal tap (Cerbrospinal Fluid Analysis) and Neuroimaging (MRI) tests (4 and 5). An evoked potential (EP) is a change in the electrical activity of the nervous system in response to an external stimulus. It may be produced in any neural structure, sensory or motor, central or peripheral by any perceivable input (6). Studying the evoked potentials are added by some scientists as a diagnostic or research tools to fulfill some diagnostic criteria for better understanding of the disease (7). As visual evoked potentials (VEPs) has been very useful in evaluating the visual function and conduction along the visual pathway, its usefulness in the diagnosis of MS is derived from the frequency with which the optic pathway is affected, with or without relevant symptoms and the usual persistence of the evoked potential abnormality (8).

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Patients and methods:

This is a case – control, study included 112 patients with multiple sclerosis (MS) 35 males and 77 females, ranging in

age from 14 to 51 years with a mean age of (33.48 ± 8.09) years. They were recruited from the multiple sclerosis clinic at Baghdad teaching hospital, Baghdad, Iraq, collected during the period from May 2012 to April 2013. They have definite MS who were diagnosed according to the famous MacDonald`s criteria, with different neurological signs and symptoms from motor, sensory, visual, cerebellum sphincter, brainstem and others according to their percentages. A control group of fifty individuals (17 males and 33 females) with no neurological or psychiatric diseases were also enrolled in this study, their age ranged from 15 to 52 years with a mean of (33.54 ± 8.4) years. Both patients and control groups have been examined at the unit of electrophysiology unit in Al-Shaheed Ghazi Al-Hareri Hospital in the Medical city, and were tested for Visual Evoked Potentials (VEP). A written consent from the patients was taken. Severity was calculated according to the famous Kurtzke, expanded disability scale status (EDSS). The parameters of VEP analysis in the right and left eye including duration and amplitude of NPN (N75, P100 and N145) were studied in all subjects included in this study. The percent of patients with VEP abnormalities expressed as prolongation in Latency of P100, and Inter-Ocular Difference of P100 latency, were calculated as 2SD above the mean of the normal values of control group and reductions in N75-P100 amplitude were calculated as 2SD below the mean of the normal values of control group.

Statistics: All statistical analysis was obtained using Statistical Package for Social Sciences (SPSS) version 17.0 and Microsoft Excel (2007) softwares used for data entry and analysis. Results were expressed in simple statistical terms such as means, percentages, and standard deviations. Data from each patient and control group were compared using ANOVA tests to calculate differences between groups. Finding of p value less than 0.05 was considered significant.

Results:

The study included 112 patients with clinically definite multiple sclerosis with relapsing remitting (87.5%), secondary progressive (5.4%), primary progressive (2.7%) and clinically isolated syndrome (4.5%) courses attended MS clinic in Baghdad teaching hospital in the medical city complex and 50 individuals without any neurological or psychiatric diseases served as control. The patients group comprised 77 (68.8%) females and 35 (31.2%) males having MS. There was a female predominance with female: male ratio = 2.2:1. The control group comprised 33 (66%) females and 17 (34%) males, there was a female predominance with female: male ratio = 1.9:1 the age of the patients with multiple sclerosis was ranged between 14 and 51 years. The age of subjects in the control group was between 15-52 years. The ages of the patients were classified into three groups: less than 30, 30-40 and more than 40. With a specifically more percent between (20-39) year`s subgroups (77.67 %) of total patients, which shows that this disease is mainly affecting middle age group, which is similar to nearby reports of Benamer etal (2009); Etemadifar and Abtahi (2012) as well as to other countries (9 and 10).

Table (1) explores the distribution of the MS patients according to their disability manner by using the most popular Kurtzke, Expanded Disability Status Scale (EDSS) score, showing that the highest percent (66.96 %) of patients had EDSS score of about (2- 4), while (18.75%) with a score below 2 and the lowest percent (14.29%) for those who had the EDSS of (> 4).

Table (1): Distribution of patients according to the Expanded Disability Status Scale (EDSS) score.

EDSS	Patients No.	Patients Percent (%)
≤ 2	21	18.75
2- ≤3	35	31.25
3- ≤4	40	35.71
> 4	16	14.29
Total	112	100

EDSS=Expanded Disability Status Scale

The mean and standard deviation of the P100 latency of the control group was (102.37 ± 5.94) msec, with a mean interocular difference of latency between the right and the left eyes of (2.88 ± 1.52) msec, while the mean latency of P100 wave in the MS group was (141.95 ± 28.89) msec, and the mean interocular difference (IOD) latency was (7.73 ± 4.93) msec. These results indicate that there is a statistically highly significant delay in the mean value of P100 latency of MS group as compared to the control group ($p< 0.001$), as well as, for each eye (Rt. and Lt.) individually. Similarly, there is a significant higher mean value for interocular difference of P100 latency of MS group as compared to control ($p< 0.001$). Additionally, there is a statistically significant decrease in the mean values of both N75-P100 amplitude and each right and left N75-P100 amplitude in the MS group when compared to those for the control group ($p< 0.001$), however, there is no significant difference in the (IOD) of amplitude between the control and MS patients for both sides ($p>0.05$) (Table 2).

Table (2): Comparison of VEP latencies and amplitudes between patients and control groups.

Parameters	Control N=50 mean±SD	Patients N=112 mean±SD
P100 Lat. For both sides (msec)	102.37±5.94	141.95±28.89**
Rt P100 Latency (msec)	101.6±4.76	140.02±27.28**
Lt P100 Latency (msec)	102.45±5.43	143.88±30.06**
IOD P100 Latency (msec)	2.88±1.52	7.73±4.93**
N75-P100 Amp. For both sides (µv)	4.94±1.01	3.57±1.57**
Rt N75-P100 Amplitude (µv)	4.95±1.06	3.55±1.52**
Lt N75-P100 Amplitude (µv)	4.93±0.95	3.58±1.61**
IOD N75-P100 Amplitude (µv)	0.96±0.69	1.05±1.0

* significant difference with control $p <0.05$, ** significant difference with control , $p < 0.001$

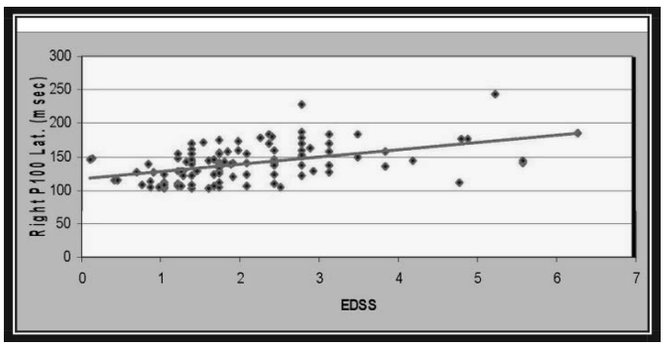
The evaluation of the VEP mean value results between the control group and MS patients subgroups with and without visual involvement, shows that there is a statistically highly significant differences in the mean value of P100 latency, (IOD) latency and N75-P100 Amplitude between the control and the two subgroups of patients with and without visual involvement subgroup ($p< 0.001$), while there are no statistical differences in the mean value P100 latencies and amplitudes between the two MS subgroups themselves (Table 3).

Table (3): Comparison of VEP latencies and amplitudes between control and MS patients with and without visual involvement.

Parameter	Control M ± SD No.=50	Visual symptoms M ± SD	
		Present No.=77	Absent No. =35
Rt. P100 Latency (msec)	101.6 ± 4.76	140.82±28.34**	138.25±25.1**
Lt. P100 Latency (msec)	102.45 ± 5.43	145.82±31.89**	139.59±25.47**
IOD P100-Latency (msec)	2.88 ± 1.52	8.35±5.02**	7.75±4.52**
Rt. N75-P100 Amplitude (µV)	4.95 ± 1.06	3.4±1.37**	3.6±1.79**
Lt. N75-P100 Amplitude (µV)	4.93 ± 0.95	3.27±1.59**	3.39±1.65**
IOD N75-P100 Amplitude (µV)	0.96±0.69	1.07±1.01	1.0±1.01

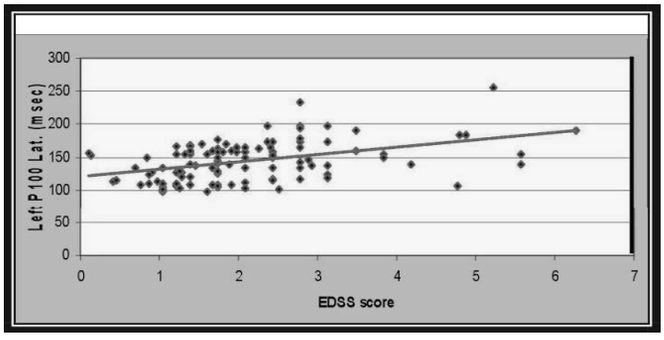
No=Number, M=Mean, SD=Standard deviation.

There is a positive linear correlation between the EDSS score and the mean values of (P100) latencies, i.e, as the EDSS score increases, the mean values of (Right and Left P100) latencies increase (figure- 1 and 2). While the mean values of (Right and Left P100) amplitude showed a reversed linear correlation (negative) with the EDSS score (figure 3 and 4). In the same time, this study reveals that there is a positive linear correlation between the duration of the disease and the progress of the disease's disability (EDSS) score, i.e., if the MS disease duration increases, there is meanwhile an accompanying progression and increment in the patients` disability with the time.



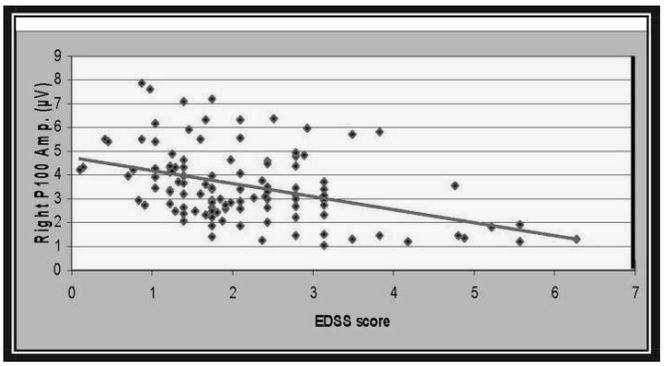
(r= 0.470----------p<0.0001)

Figure (1): Correlation between right P100 latency and EDSS.



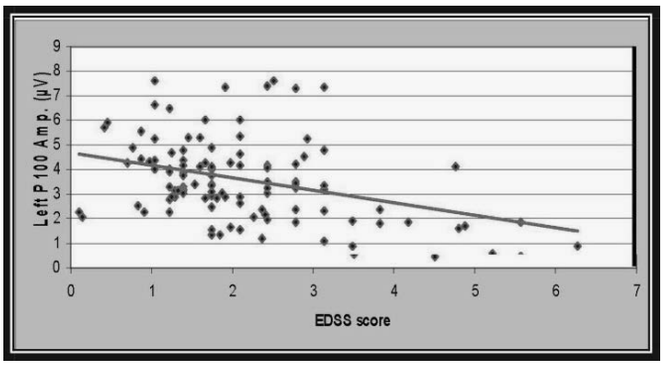
(r=0.435----------P<0.0001)

Figure (2): Correlation between left P100 latency and EDSS.



(r=-0.421----------P<0.0001)

Figure (3): Correlation between right P100 amplitude and EDSS.



(r=-0.366----------P<0.0001)

Figure (4): Correlation between left P100 amplitude and EDSS.

Discussion:

The present results showed prolonged mean values of P100 latency in MS patients as compared to control values, and these changes are present in both sexes in both eyes. These findings are in agreement with the studies of Movassat etal (2009); Ko (2010) and Balnytė etal (2011) (11, 12 and 13). The mean of P100 latency of (141.95 ± 28.67 msec), is nearly similar to

the range of others (122-151 msec), as the mean P100 latency obtained by Ko, 2010 (133.7) and Balnytė etal, 2011 (122.68 ± 12.36) msec. It has been shown that large areas of myelin loss in the central nerve fiber will produce complete conduction block over the demyelinated zone, whereas normal conduction at an unreduced velocity persists in the still myelinated portions of the nerve on either side of the lesion. In smaller or less complete lesions, the conduction persists in many fibers and recording has established that the conduction velocity of the impulse is reduced as it traverse a partially demyelinated zone and is normal in histological normal portion of the same fiber. There is also a reduction in the ability of partially demyelinated fibers to conduct high frequency trains of impulses in the normal way, which is an effect of the prolongation of the refractory period in the damaged nerve. These three defects; (1) conduction block, (2) slowed conduction and (3) a reduced high frequency response are reflected in the EP abnormalities encountered in demyelinating disease (11). The measurement of Inter-Ocular latency difference of the P100 wave is practically important because even the smallest increase in latency in one eye, is likely to be of significance when accompanied by an excessive difference between the two eyes. Our results demonstrated a significantly higher mean IO latency difference of P100 wave (7.73 ± 4.93 msec) in comparison with the control mean values (2.88 ± 1.52 msec). Accordingly, the IO difference is another sensitive marker in VEP study, and it`s shown that Mesaros etal, (2003) (14) recorded it as more than (8 msec) and Taş etal, (2013) (15) also documented its importance as a less variable index as compared to P100 latency. Regarding the N75-P100 complex amplitude, this study showed that the mean values were significantly reduced in MS patients as compared with that of the control group. However, it was found that the amplitude of the VEP is more variable than the latency, since it is affected by a number of factors including; electrode position, visual acuity, refractive errors, lack of fixation in addition to the individual variability reported from one subject to the other (11 & 16). Although all subjects in this study were appropriately examined and with spectacles when needed, but in Ko, (2010) and Balnyte, (2011) studies (12 & 13) have reported similar findings and concluded that the amplitude have little diagnostic yield. However, the reduction in the N75-P100 complex amplitude, suggested an axoplasmic pathology, where the underlying pathophysiological axonal dysfunction, causes loss of some active nerve fibers, and on stimulating the remaining fibers, a low amplitude action potential will be generated (17). The non-significant IO amplitude difference between the MS and control mean values, can be explained by the high variability of the amplitude recorded in the subjects, however, it has been shown that IO amplitude difference measurement is probably not proved to be very useful clinically (18).

In addition to the latency abnormalities, the evaluation of amplitude and waveform morphology can provide a useful information in the diagnosis and assessment of patients e.g. prolonged latency can occur in both MS and compressive or ischemic lesions of the visual pathway, however, in MS, VEP amplitude is usually normal whereas in compressive and ischemic lesions, the amplitude may be reduced and the VEP waveform may be grossly distorted (11). These abnormalities in the waveform, could be related to the inhomogeneous involvement of the optic pathway, in addition to the possibility that, the edema resulting from the inflammatory process of the demyelinating lesion outside the visual pathway can cause pressure effect especially in regions of tight constriction such as the optic nerve in the scleral and optic canal, which leads to distortion in the waveform (19). It was also noted in the current study, that there is a positive linear correlation between the physical disability score (EDSS) of the MS patients and the P100 latency value, while an inverse correlation between the EDSS score and the N75-P100 complex amplitude value, and this finding goes with other findings of Kallmann etal, (2006) and Schlaeger etal, (2011) (20 & 17) , in which, it's may be due to the adding of the duration factor with the advancement of the demyelination with or without the secondary axonal degeneration pathologies, growing in the whole CNS pathways including the sensory, motor tracts beside the visual pathways, and some researchers conclude the adding of the VEP test as a predictor and prognosting factor of the MS patient's disability, especially in the relapsing remitting type of MS (17). This study showed also, the lesion in MS patients without visual symptoms could be as severe as in patients with visual complaint, as the mean value of P100 latency and IO latency difference are delayed significantly for the affected and non-affected eyes more than the normal eyes of the control, and at the same time there was no statistical differences between the P100 latency mean values and IO latency difference between the MS patients subgroups with or without visual involvement. The permanent latency delay therefore, suggests a demyelinating lesion of the optic nerve. The high reliability of the latency delays related to an acute or an old attack of optic neuritis, independent on verified visual disturbances. It was noted, that delays in VEP latencies persist in definite MS cases after an attack of acute optic neuritis, even after the visual acuity had return to normal, which makes the VEP method important, especially if it is used in the early course of the disease (21).

Conclusion:

In visual evoked potential, the mean P100 wave latency and the mean IO latency difference, are significantly prolonged in patients with MS, while, the mean N75-P100 complex amplitude was significantly reduced, however, the mean IO amplitude difference did not show statistical change between the patients and control groups. The abnormal delayed P100 wave latency had the highest incidence, then the IO latency difference, while N75-P100 complex amplitude, IO amplitude difference and waveform are the least. Therefore, the most reliable VEP parameter is the prolonged P100 latency values in the diagnosis of MS, while the changes in N75-P100 amplitude and waveform had no such diagnostic values. The VEPs study has the ability to quantify the unsuspected clinically silent lesions, hence, allows confirming the vague deterioration of visual functions. VEP changes serve as a predictor for the

progressive deterioration of the patients` disability (EDSS increment).

Authors Contributions:

Dr. Ammar Thamer: Preparation, Performing and doing the tests of the research.

DR. Najeeb Mohammad: Supervision & support, as it is derived from PhD thesis.

Dr. Akram Ibrahim: Supervision & provide patients for this research.

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