Acta Scientific Neurology (ISSN: 2582-1121)

Volume 5 Issue 12 December 2022

Research Article

Event Related Potentials and its Correlation with Cognitive Decline in Multiple Sclerosis Patients in a Tertiary Care Hospital in New Delhi

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DOI: 10.31080/ASNE.2022.05.0558

Received: August 16, 2022

Published: November 05, 2022

Abstract

Introduction: Multiple sclerosis is one of the common disabling neurological disorders. Cognitive deficits are emerging as the main cause of change in professional and social life. The P-300 event related potentials are delayed in latency in various disorders characterised by dementia. Here, we study the correlation of the event related potentials with cognitive decline in MS patients.

Aims and Objectives: To evaluate patients with multiple sclerosis clinically and electro physiologically measuring event related potentials in respect of latency and amplitude and to co-relate it with cognitive decline.

Material and Methods: 30 consecutive cases of multiple sclerosis were included in the study. All the patients were subjected to detailed neurological examination with MMSE, dementia score of Blessed et al and information-memory - concentration test. All the neurophysiologic tests were performed. Results: The mean MMSE score was 26.16 ($P < 0.01$). The mean dementia score was 5.43 ± 4.0 ($P < 0.01$). P300 latency was significantly ($P < 0.01$) higher in patients as comparison to control subjects. Dementia scores showed significant correlation with P300 latency when partially correlated.

Conclusions: Abnormal prolongation of P300 ERP latency had a high correlation with cerebral white matter involvement and with impaired cognition in multiple sclerosis.

Significance: The paper helps in identifying cognitive decline as a symptom of MS and strengthens how electrophysiology methods could be used to identify sub-clinical cognitive decline.

Keywords: Event Related; Potentials; Correlation; Cognitive Decline; Multiple Sclerosis

Introduction

Multiple sclerosis, an inflammatory, demyelinating illness of the central nervous system and is one of the common disabling neurological disorders of young adults. The random occurrence of lesions, both in time and space, accounts for the extreme variability of clinical presentation. Although motor disorders have the greatest influence on the evaluation of disability as measured by scales widely used for staging of MS patients, cognitive deficits are emerging as the main cause of change in professional and social life. In fact, cognition is the neurological function, which can be most strongly influenced by the accumulation of demyelinating lesions in the brain. Recent neuropsychological studies have indicated that cognitive dysfunction occurs in 54-65% of patients with multiple sclerosis [1]. The main pattern of neuropsychological impairment

observed in MS patients is characterised by deficits of attention, memory, particularly recent memory and semantic memory as evaluated by categorical verbal fluency, speed of information processing and problem solving, abstract reasoning disturbances. This Pattern has been considered compatible with sub cortical type of dementia. Typically cognitive impairment spares language function [2]. Most patients of multiple sclerosis do have concomitant cerebral hemisphere disease, the extent of which can be visualised with conventional MRI. Cerebral white matter plaques are visualised on MRI early in the course of the disease and are often apparent before the onset of substantial disability. While these plaques may occasionally cause motor, sensory or visual deficits; they usually appear to be silent; perhaps these are linked to subtle cognitive deficits, which are often missed on neuropsychiatric evaluations [3]. The P-300 event related potentials (also known as P-3) is an endogenous, stimulus independent wave related to cognitive processing of an unexpected stimulus is delayed in latency or diminished in amplitudes in various disorders characterised by dementia in comparison to normal persons. Recent reports have indicated an abnormality of P-300 in patients with multiple sclerosis [4-10]. The use of MRI Brain for evaluation and monitoring in patients with multiple sclerosis is under intense research. More so, nonconventional techniques of MRI i.e., magnetisation transfer imaging and T_1 weighted imaging are found to be better in assessment and definition of lesions in multiple sclerosis [11].

Aims and Objectives

To evaluate patients with multiple sclerosis clinically in respect of duration of disease, clinical disability and cognitive deficits, radiological evaluation, electro physiologically measuring P-300 event related potentials in respect of latency and amplitude and co-relate it with cognitive decline.

To correlate the above parameters with each other to define their role in evaluation of patients with multiple sclerosis.

Material and Methods

Thirty consecutive cases (15 males, 15 females) of multiple sclerosis meeting the diagnostic criteria proposed by McDonald's [12], attending neurology OPD or admitted in neurology wards were included in the study. After taking informed consent, historical details were recorded and all the patients were subjected to detailed neurological examination and graded on Kurtzke's expanded disability status scale(EDSS) [13] of 0 (normal) to 10 with steps of 0.5, Folstein's mini mental status examination(MMSE) [14] which spans from 30 (normal) to 0, dementia score of Blessed., *et al*. [15] which is scored from 0 (normal) to 28 and information-memory - concentration test of Blessed., *et al.* [15], which is strongly based on remote memory and general knowledge and is scored from 0 (normal) to 37. In addition clock drawing test (CDT) was also performed and scoring was done by method of Shulman., *et al.* (16), which scored from 1 (normal) to 6 (no reasonable presentation of a clock). The followings were done in all patients: Hemogram, blood sugar, liver function tests (LFT), kidney function tests (KFT), urine examination, electrocardiogram (ECG) and chest X-ray, Cerebrospinal fluid (CSF) examination for proteins, sugar, total and differential cell counts and oligoclonal bands testing by agarose gel electrophoresis was performed in 27 patients.

MRI was performed with a NT-Intera (Philips) (field strength 1.5 Tesla) imaging system. All patients underwent MRI of the brain and 12 patients also had MRI of the spinal cord in addition. In addition to conventional sequences (T1WI, T2WI, FLAIR), MTC images were also obtained in all patients. Post contrast T1W and post contrast MTC were also obtained. Axial brain images were obtained at 5 mm slice thickness with a gap of 0.5 mm with a turbo spin echo sequence and a 352*512 -pixel acquisition matrix. Overall scan time was 20.5 minutes. Contrast used was gadolinium (DOTAREM), in dose of 0.2 mmol/kg. Patient's images were scored with the Vanderbilt grading system (VGS) criteria on a scale of 0 (reflecting no abnormalities) and 1 to 4 based on increasing lesion size and extent [17].

All the neurophysiologic tests were performed on MEDELEC SYNERGY (oxford instruments, USA) EMG machine. Silver- silver chloride mounted cup electrodes were used. Results were compared with standard normal values. The upper and lower limits of normal were defined by mean ± 2.5 SD of the controls. VEP, BERA, SSEP, P300 and Blink reflex were done.

Statistical analysis

Appropriate statistical tests including student's t-test, $\chi 2$ test, Pearson's correlation coefficient and binary logistic regression analysis were applied for the analysis of the data. P values < 0.05 were considered as statistically significant.

Results

Thirty patients [Male 15 and Female 15] were included in this study. Male to female ratio was 1:1. All the patients were right-

handed except one female [3.3%] who was left-handed. The age group was 30.46 ± 10.33 years [varied from 17 to 57 years]. Majority (80%) of the patients had education of 10-19 yrs. Mean years of education in males were 11.93 yrs and in females 12.16 yrs. The control group consisted of 20 age and education matched healthy volunteers (m = 14, f = 6). The mean of age was 35.45 ± 9.75 (range, 17-55 yrs). All had normal physical and Neurological examination. The disease had its onset between 10-29 yrs of age in 19 patients (63.34%). The mean age at the onset of disease was almost comparable among the sexes.

21 (70%) patients had RRMS, 7 (23.33%) SPMS and 2 (6.67%) had PPMS. 22 (73.33%) patients had motor weakness, out of these 6 (27.27%) patients had hemiparesis, 14 (63.64%) had paraparesis and 2 (9.09%) had quadriparesis. 15 (50%) patients have sensory loss. Out of these 14 (93.33%) patients have impairment for all modalities of sensations while one patient had impairment of posterior column sensation only. 9 patients had a sensory level, out of these 1patient had cervical and rest of the patients had thoracic spinal cord level. 5 patients had band like sensations.

12 (40%) patients had positive sensory symptoms in the form of paresthesias. 9 patients had h/o lhemite symptoms. 6(20%) patients have diplopia. 14 (46.67%) patients had History of vision loss, out of these 5 patients had bilateral Vision loss. 7 (23.33%) patients had both limb & gait ataxia while 9 (30%) patients had only limb ataxia and 16 (53.33%) patients had only gait ataxia. 4 (13.33%) patients had Facial weakness, out of these 2 patients had LMN type and 2 patients had UMN type Weakness. In all 4 patients facial weakness was unilateral. 8 (26.67%) patients had spastic type of Dysarthria and 3 (10%) patients had dysphagia. bladder and bowel involvement were seen in 17 (56.67%) and 14 (46.67%) patients respectively. Bladder involvement was of spastic type, although 8 patients had retention of urine at the time of acute paraplegia. Majority of the affected patients had history of urgency, frequency, inability to hold urine and occasionally urge incontinence. Constipation was the complaint related to bowel involvement. 9 (30%) patients had history of Impotence.

5 (16.67%) had history of cognitive impairment. Cognitive impairment as reported by the patients was in the form of inability to recall recent events. Abnormal movements in the Form of flexor spasms were reported by 4 patients. EDSS scores ranged from 1 (minimal signs) to 8.5 (bed bound), with mean value of 4.23 (full activities precluded but able to ambulate 300 meters unaided). 18 (60%) patients had EDSS between 1-3.5, 10 (33.3%) patients had severe physical disability.

CSF for oligoclonal bands was positive in 15(55.55%) patients.

MRI lesion burden was graded on VGS grading score. The mean score was 2.77 ± 1.33 (range 0-4).11 patients had less severe disease on MRI (VGS score 0-2) while 19 patients had more severe disease on MRI (VGS score 3-4).

Evoked potentials were done in all the patients (Table 1). P100 latency was prolonged in 28 (93.3%) patients, 18 of these had bilateral prolongation. Abnormal auditory P300 (prolonged latency) was seen in 22 (73.3%) patients. Median SEP was abnormal (prolonged N20 latency) in 9 (30%) patients, out of which 3 had bilateral abnormalities and 6 had unilateral abnormalities. Central conduction time was prolonged in 5 patients, out of which 2 had bilateral prolongation. Tibial SEP was Abnormal (prolonged P37 latency) in 22 (73.33%) patients, out of which 16 patients had bilateral involvement. BAER abnormalities (prolonged latencies or not recordable wave forms) were seen in 15 (50%) patients, out of which 5 patients had bilateral involvement. Blink reflex was abnormal (prolonged latency or not recordable response) in 14 (48.28%) patients, 8 of these had bilateral abnormalities.

The MMSE and dementia score were comparable among sexes (Table 2). However, on IMCT, CDT scoring females scored better.

Patients were similar to control subjects with respect to age, sex ratio and years of Education. The mean MMSE score was 26.16 (range 14-30), significantly ($P < 0.01$) less than control mean of 29.5 (Range 27-30). The mean dementia score was 5.43 ± 4.0 (0-17), significantly ($P < 0.01$) higher than control subjects. The mean blessed IMCT score was also significantly ($P < 0.01$) higher than controls. However, there was no significant Difference between CDT scores of both groups (Table 3).

On comparing various waveforms of event related potentials among both groups, only P300 latency was significantly ($P < 0.01$) higher in patients as comparison to control subjects. There was no significant difference between amplitude among both groups (Table 4).

Evoked Potentials	Mean ± SD	No. of Patients with Abnormal Response
VEP (n = 30) Latency P100 Right Left Amplitude P100 Right Left	124.57 ± 24.45 (range, 97-217 ms) 119.51 ± 29.34 ms (range, 87-240 ms) 4.67 ± 2.84 µv (range, 0.32-13.2 µv) 5.19 ± 2.51 µv (range, 1.8-9.7 µv)	(>104 ms or NR) 25(83.3%) 21(70%)
Auditory P 300 latency	368.8 ± 36.45 (range 303-477)	(>345.5ms) 22(73.3%)
Median SEP Right N20 Latency Left N20 Latency CSCT (n = 8) Right Left	20.53 ± 4.35 ms (range, 16.2-38.2 ms) 20.0 ± 4.14 ms (range, 17.5-39.2 ms) 8.09 ± 3.79 ms (range, 4.7-15.7 ms) 8.57 ± 3.15 ms (range, 5.6-14.5 ms)	(> 21.5 ms or NR) 7(23.33%) 5(16.67 %) (>7.12 ms) 3(37.5%) 4(50%)
Tibial SEP (n = 30) P37 Latency Right Left CSCT (n = 21) Right Left	47.44 ± 10.61 ms (range, 35.75-74.25 ms) 46.40 ± 9.66 ms (range, 35-70 ms) 25.57 ± 10.57 ms (range, 16.05-50.8 ms) 25.57 ± 9.50 ms (range, 14.1-50 ms)	(>42.5 ms or NR) 19(63.33%) 19(63.33%) (>19.48 ms or NR) 12(57.14%) 14(66.67%)
BAER (n = 30) Wave 3 Latency Right Left Wave 5 Latency Right Left Wave 1-3 IPL Right Left Wave 3-5 IPL Right Left Wave 1-5 IPL Right Left	3.72 ± 0.22 ms (range, 3.24-4.12ms) 3.78 ± 0.37 ms (range, 2.83-4.46 ms) 5.68 ± 0.37 ms (range, 5-6.48 ms) 5.73 ± 0.39ms (range, 5-6.44 ms) 2.06 ± 0.15 ms (range, 1.7-2.48 ms) 2.2 ± 0.29 ms (range 1.59-2.88 ms) 1.96 ± 0.22 ms (range, 1.64-2.6ms) 1.94 ± 0.21 ms (range, 1.5-2.54 ms) 4.03 ± 0.29 ms (range, 3.64-4.68 ms) 4.15 ± 0.32 ms (range 3.63-4.82 ms)	(>4.03 ms or NR) 5 8 (>6.1 ms or NR) 5 8 (>2.26 ms or NR) 3 12 (>2.3 ms or NR) 5 4 (>4.38 ms or NR) 5 9
Parameter	Mean ± SD	No. of Patients with Abnormality (n = 30)
Facial Nerve Study (Latency) Right Left Ipsilateral Response (Latency) R1 Left Right R2 Left Right Contra lateral Response R2 (Latency) Left Right	3.51 ± 0.44 (2.35-4.4) 3.50 ± 0.34 (3-4.2) 10.68 ± 1.00 (8.75-12.3) 10.36 ± 1.06 (7.1-12.75) 33.46 ± 4.25 (26.8-46) 33.23 ± 5.10 (21.15-47.35) 35.57 ± 4.46(28.7-48.4) 35.98 ± 5.07 (28.05-50.15)	(>4.80 ms) 0 0 (>11.5 ms or NR) 7 4 (>34.53 ms or NR) 8 8 (>38.07 ms or NR) 7 5

Table 1: Evoked potentials in the patients.

Scales	Male	Female	Total
MMSE	25.93 ± 4.38	26.4 ± 4.28	26.16 ± 4.26
Dementia score	5.46 ± 4.70	5.4 ± 3.31	5.43 ± 4.0.
IMCT	7.53 ± 4.25	4.4 ± 4.32	5.97 ± 4.5
CDT	1.85 ± 1.83	1.35 ± 0.49	1.60 ± 1.34
EDSS	4.86 ± 1.83	3.6 ± 2.45	4.23 ± 2.23

Table 2: Dementia scoring in MS patients (males and females).

Comparison of patients with multiple sclerosis with control subjects			
Variable	**Patients (n = 30)**	**Controls (n = 20)**	**Significance**
Age, y	30.47 ± 10.34 (17-57)	35.45 ± 9.75 (17-55)	t = 1.7, df = 48, P > 0.05
Sex ratio (m: f)	1: 1	2.3:1	x2 = 1.23, df = 1, P > 0.05
Education, y	12.17 ± 4.33 (0-19)	12.8 ± 4.15 (0-17)	t = 0.51, df = 48, P > 0.05
MMSE score	26.16 ± 4.26 (14-30)	29.5 ± 0.95 (27-30)	t = 3.42, df = 48, P < 0.01
Blessed IMCT score	5.97 ± 4.5 (0-16)	0.65 ± 1.66 (0-7)	t = -5.03, df = 48, P < 0.01
Dementia score	5.43 ± 4.0. (0-17)	0.55 ± 0.68 (0-2)	t = -5.29, df = 48, P < 0.01
Clock drawing test	1.60 ± 1.34 (1-6)	1.1 ± 0.30 (1-2)	t = -1.65, df = 46, P > 0.05

Table 3: Comparison of MS patients with control subjects.

Variables	Patients	Controls	Significance
Latency (ms)			
N1	111.83 ± 18.94	110.30 ± 22.76	t = -0.25, df = 47, P = 0.79
P2	175.21 ± 30.79	173.3 ± 37.67	t = -0.19, df = 47, P = 0.84
N2	248.55 ± 47.73	227.75 ± 34.37	t = -1.67, df = 47, P = 0.10
P300	368.8 ± 36.45	318 ± 11	t = -5.99, df = 48, P = 0.00
Amplitude (μv)			
N1-P2	5.12 ± 2.49	5.38 ± 3.61	t = 0.30, df = 47, P = 0.76
N2-P3	9.16 ± 4.42	7.91 ± 3.45	t = -1.06, df = 47, P = 0.29

Table 4: Comparison of ERP among patient and controls.

Neither Control Subjects nor patients showed association of P300 latency with age, years of education and gender. Within the patient group there was no significant difference among sexes with respect to mean age, years of education, age of onset of disease, number of attacks, cognitive function scales (except IMCT score, which was higher in males, approaching to near significant level, P = .05), EDSS scores, P37 and P300 latencies.

Within the patient group, the cognitive function measures (MMSE score, IMCT score, DS and CDT score) were highly correlated with each other except no significant correlation between CDT score and DS. In addition, these measures partially correlated with VGS grade. In addition, IMCT and CDT were inversely correlated with years of education and DS and IMCT score showed significant correlation with EDSS score. However, these scores did not show any association with age, duration of disease, age of onset of disease, number of attacks.

P300 latency showed a highly significant correlation with MRI lesion burden as assessed by VGS score. P300 latency for patients with more severe disease seen on MRI (VGS score 3 to 4; 386.94 ± 30.15 ms) was significantly longer than that for patients with less severe disease seen on MRI (VGS score, 0to2; 337.45 ± 22.58 ms) (P = 0.000).

P300 latency did not showed any correlation with, EDSS score, age, age of onset, duration of disease, years of education, number of attacks, and type of MS.

However, P300 latency did not showed any significant correlation with MMSE, dementia score, IMCT, and clock drawing test when these tests were correlated individually but these scores showed significant correlation with P300 latency when partially correlated. P3 latency showed significant correlation with spinal cord lesions on T2WI. EDSS score did not showed any correlation with MRI lesion burden as measured by VGS score.

Discussion

Patients with multiple sclerosis exhibit increased latency of P300, long latency event related potentials. The P300 latency shows a direct relationship with cognitive dysfunction, cerebral disease seen on MRI and duration of disease but is independent of patient's age [18]. Concomitant with latency prolongation, P300 amplitude is also diminished in patients with greater cognitive dysfunction or MRI abnormalities. However, no such relationship is observed with early components of event related potentials, e.g., N1, P2, and N2. This is in concordance with the observations with cortical dementia of Alzheimer disease. Although multiple sclerosis is white matter disease, plaques may functionally disconnect cortex, causing electrophysiological dysfunction more akin to cortical disease than to the basal ganglia - associated dementias. In our study, the age of onset was 26.7 ± 10.56 years, which is comparable to previous Indian studies [19-22]. The female to male ratio was 1:1, which is similar to two other studies [20,22]. Remitting-Relapsing multiple sclerosis was the commonest type in our study, which is in agreement with the accepted notion.

Signs/symptoms at presentation of the disease were: pyramidal (43.3%), optic nerve involvement (26.6%) cerebellar (23.33%), which is consistent with other studies. In the signs/symptoms observed during course of illness, pyramidal (73.3%), cerebellar (53.33%), sensory (50%) involvement predominated and optic nerve involvement was seen in 46% cases. The above findings suggest that in the MRI era, there is occurring a deviation of the clinical spectrum from more classical Asian type of multiple sclerosis towards the Caucasian type and reemphasise the fact that the clinical spectrum in the two races is essentially similar.

In our study, BAER was abnormal in 50% patients, which is higher than reported previously (40.54%). Abnormal VEP were found in 93.3% cases, which is higher to other Indian studies (70-88%) [19-22].

Oligoclonal bands represent abnormal synthesis of gamma globulins in the CSF and therefore implicate an immuno-pathological process. It has been found that in Caucasians the CSF OCB's are found in a higher number of cases (90%), where as in Asian studies its incidence has been found to be ranging between 33 to 45% (58-60). Our study showed the positivity of CSF OCB's in 55.5% of patients.

In our study, 73.33% patients with multiple sclerosis had abnormally prolonged P300 latency with normal latencies of early components (N1, P2, and N2). Similar observations have been made by others (Tourtellotte., *et al*, Triantafillou., *et al*, and Honig., *et al*, Newton., *et al*. [4,7-9]. A decrease in P 300 amplitude had been reported by Polich J., *et al.* [26], Triantafyllou., *et al.* [8], while no decrement, as in our study, had been observed by Gil., *et al*. [27]. P300 latencies were significantly (P = 0.00) related to radiological measures of cerebral disease on (VGS grade), but only partially related to various cognitive measures. The standard dementia screening tests: folstein Mini-Mental state (MMSE) score, Dementia score (DS) of blessed., *et al,* and blessed' s Information Memory Concentration Test (IMCT) score were significantly (P < 0.01, P < 0.01, P < 0.01, respectively) impaired in patients as compared to control subjects. These measures (MMSE score, dementia score and IMCT) were correlating (P < 0.01) between each other but showed only partial correlation with VGS grade (P = .023, P = .002, P = .002, respectively) and P300 latency (P = .013, P = .001, P = .002, respectively). This could be due to the reason that standard dementia screening tests such as MMSE, DS and blessed IMCT, are relatively insensitive measures of cognitive dysfunction in multiple sclerosis.

MMSE score is prominently biased toward examination of orientation, registration and language.

The patients with low MMSE score, had faltered their total folestein MMS points on other nine MMS points: attention, recall & design copy items in 81% cases. Dementia score has bias for motor system integrity while Blessed IMCT score depends on acquired knowledge. Yoram Barak et al, reported significant correlation of CDT score with mental functional system score and duration of disease, but found no correlation with motor disability [28]. In our study, CDT score did not reveal significant difference among patients and control subjects. The patient population in our study had mean duration of disease less than 3 years in 63% of patients.

P300 latency did not show any correlation with EDSS, age at onset, duration of disease, years of education, number of attacks and type of multiple sclerosis. Similar results have been reported by Honig., *et al.* [9]. No correlation of EDSS score with P300 latency and VGS score is explained by the fact that EDSS score is adversely affected by spinal cord involvement, while VGS score primarily reflects the cerebral involvement. Cognitive dysfunction in multiple sclerosis as evident by P300 latency prolongation correlates with VGS score.

Conclusions

Abnormal prolongation of P300 ERP latency had a high correlation with cerebral white matter involvement and with impaired cognition in multiple sclerosis. The P300 latency as well as cerebral MRI findings showed no correlation with disability as measured by EDSS, because this scale predominantly reflects spinal cord disease involvement. More extensive cognitive testing batteries rather than standard dementia screening tests (Folesteins MMSE, IMCT, dementia score) needs to be evaluated for their correlation with P 300 test. Role of clock drawing test in evaluation of cognitive dysfunction in multiple sclerosis also needs further evaluation. The findings presented herein are consistent with a primary role for cerebral demyelination in the impaired cognition occurring in multiple sclerosis.

Conflict of Interest Statement

The authors and co-authors have no conflict of interest.

Acknowledgement

There are no study sponsors nor are there any acknowledgements to be made.

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