Original Article

Effect of Multiple Sclerosis Disability Status on Cognitive Functions

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic, progressive, inflammatory, demyelinating autoimmune disorder caused by autoantibodies and immune cells destroying the myelin sheath. A prevalent and incapacitating symptom of all MS patient profiles is cognitive impairment.

Objectives: To assess cognitive functions in Multiple Sclerosis patients, and analyze the association between cognitive affection and its relation with disease severity and disease duration.

Methods: In this study, sixty adult MS patients participated. Each participant underwent a comprehensive medical history, a basic audiological assessment, the expanded disability status scale (EDSS), event related potentials P300, mini mental state examination (MMSE) and symbol digit modality test (SDMT).

Results: The Multiple Sclerosis patients group had lower MMSE, SDMT scores, longer P300 latencies and decreased P300 amplitudes when compared to controls. Significant correlations were observed between MMSE, P300 latency, P300 amplitude and the EDSS scores.

Conclusions: Most of Multiple Sclerosis patients have poor cognitive abilities. Findings of the present study reveal the deteriorating effect of Multiple Sclerosis on cognition..

Key Words: Cognitive Impairment, Expanded Disability Status Scale, Multiple Sclerosis.

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INTRODUCTION

The chronic, progressive, inflammatory, demyelinating autoimmune disease known as multiple sclerosis (MS) is brought on by immune cells and autoantibodies that destroy the myelin sheath. Due to the extensive development of myelin degradation, multiple sclerosis (MS) causes a wide spectrum of symptoms, including motor, cognitive, and neuropsychiatric problems[1].

A prevalent and incapacitating symptom of all MS patient profiles is cognitive impairment (CI). Age, duration of disease, and increased physical handicap has been identified as the primary risk factors for CI[2]. In clinical practice, a variety of neuropsychological testing batteries have been created to address the primary areas of MS cognitive dysfunction; however, their application is restricted because of their lengthy administration times and physical limitations[3].

In addition to neuropsychological tests, P300 event-related brain potentials (ERPs) have been employed as neurophysiological indicators in the evaluation of cognition in multiple sclerosis. The steps of cognitive processing, including encoding, selection, memorization, and decision-making, can be illuminated by measuring them[4]. Numerous brain regions, including the hippocampus, medial temporal lobe, frontal lobe, inferior parietal lobule, and other limbic structures, are associated with P300 generation. ERPs are occasionally a component of a diagnostic battery of electrophysiological tests[5].

As a result, event-related potentials may be a more useful diagnostic tool for MS-related CI. Early detection of potential CI may enable both the patient and medical professionals to take action, attempting to decrease the rate of cognitive decline and significantly improve the quality of life for MS patients[6]

A paper-based test called the Mini-mental State Examination (MMSE) has a maximum score of 30, with lower results denoting CI. The MMSE is frequently used in clinical practice for cognitive screening and in assessing the degree of CI. Twenty separate tests make up the internal structure of the MMSE, which covers eleven domains such

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as orientation, registration, attention or computation, recall, naming, repetition, verbal and written comprehension, writing, and construction[7].

A screening tool frequently used in clinical and research settings to evaluate neurological impairment is the Symbol Digit Modalities Test (SDMT). Both written and oral formats are available for administering the test. These days, a variety of neurological and neuropsychiatric conditions are evaluated using this activity to gauge CI. Performance on the SDMT is supported by attention, perceptual speed, motor speed, and visual scanning, just like on other substitution tasks[8].

Thus, the purpose of this study is to determine whether event-related potentials can be a useful diagnostic tool for MS cognitive impairment. For MS patients who must continuously cope with the social and personal burden of the illness, especially the stigma attached to cognitive impairment, a positive response to this question can result in a significant paradigm change.

AIM OF THE STUDY

The objective of this study is to assess cognitive functions in MS, and analyze the association between cognitive affection and its relation with disease severity and duration.

PATIENTS AND METHODS

Subjects

The study was designed as an observational case control study conducting on 30 patients diagnosed with MS disease to be compared to age and gender matched normal subjects. The study was conducted from June 2024 to October 2024. Informed consent was obtained from all participants. Research protocol was approved by the XXX Research Ethics Committee, the approval number: (N-293-2024).

It included 60 adult subjects of both genders that were co-operative, alert and of average intelligence that were able to understand and perform tests, fulfilling the inclusion criteria.

Inclusion criteria of study group

1. Patients fulfil Diagnostic criteria of MS according to Macdonald diagnostic criteria[9].
2. Age between 18-55 years.
3. Both genders are involved.
4. Bilateral within normal peripheral hearing threshold levels.

Exclusion criteria of study subjects:

1. Individuals age less than 18 years or more than 55 years.
2. History or presence of any other otological or neuromuscular diseases.
3. Abnormal tympanometry.
4. History of ear trauma or surgery.
5. History of ototoxic medications.
6. Patients with hypertension, and diabetes mellitus.
7. Neurological disease other than MS disease.
8. Any disease that affects cognition.

METHODOLOGY

Equipments

- Sound treated room (Amplisilence Model E).
- Tympanometry: Zodiac 901 (Madsen Corporation, USA). callibrated according ISO standards.
- Two-channel audiometer (Grason-Stadler Inc, Milford, New Hampshire) calibrated to American National Standards Institute S3.6-1996 specifications.
- Evoked potentials system: Neuro-Audio (Neurosoft Ltd, Russia).

Procedure

All subjects in this study were subjected to the following:

A) Full history taking: including; including the age, sex, residency, disease manifestation and duration.

B) Assess MS severity: according to the expanded disability status scale (EDSS)[10] determined by a neurologist within 6 months of audiological testing.

C) Otological examination: to exclude any external or middle ear pathologies.

D) Basic Audiological Assessment, including:

- Pure tone audiometry (PTA): for octave frequencies 250-10000 Hz for air conduction and 500-4000Hz for bone conduction, using pulsed stimulus.

- Speech reception threshold (SRT): using Arabic spondaic words. Word discrimination score (WDS), using Arabic phonetically balanced words[11, 14].
- Immittancemetry: single-frequency tympanometry with a probe tone of 226 Hz with testing of the acoustic reflex threshold (ipsilateral and contralateral) at frequencies 500, 1000, 2000 and 4000 Hz.

E) Mini-Mental State Examination (MMSE): It is a screening tool used to detect and classify cognitive impairment[12]. The MMSE is a fully structured scale that consists of 30 points which are grouped into 7 categories: orientation to the place (state, country, town, hospital and floor), orientation to the time (year, season, month, day and date), registration (immediately, repeating three words), attention and concentration (serially subtracting 7, beginning with 100, or, alternatively, spelling the word world backward), recall (recalling the previously repeated three words), language (naming two items, repeating a phrase, reading aloud and understanding a sentence, writing a sentence, and following a three-step command), and visual construction (copying a design). Scoring was done as follows: scores ≥ 27 are considered normal cognition, scores 21–26 are considered mild cognitive impairment, scores 11–20 are considered moderate cognitive impairment, and scores ≤ 10 are considered severe cognitive impairment[13].

F) Symbol Digits Modality Test (SDMT): It presents a series of nine different symbols, corresponding to the numbers 1 through 9 in a key at the top of a standard sheet of paper. The key is available to the subject throughout the test. A sequence of 120 symbols, each printed in a square, is presented below the key. Empty squares are located below the squares containing the symbols. Patients are asked to practice writing the correct number under the corresponding symbol as rapidly as possible for 90 sec. The number of correct substitutions within the 90-second interval is recorded out of 120 (total score)[8].

G) Electrophysiological event related potential *P*300: The subjects were asked to identify the rare stimulus by pressing on button. The time of recording for each individual was about 10-15 minutes.

Electrode Montage

After preparing the scalp with a cleaning gel, the recording of neuro-electrical activity was accomplished with positive electrode at Fz site, referred to mastoid electrode (M1) and ground electrode (M2). The electrode impedance was kept below 5 K Ohms. Cortical auditory evoked potential (P300) evoked potential were recorded using the Neurosoft evoked potential system. Subjects were resting comfortably on a chair. The waves with better morphology were chosen for analysis.

Stimulus parameters

We used tone burst stimuli presented to right ear via an insert phone, in frequency of 2kHz for rare stimulus, presented randomly in likelihood of 20%, mixed with frequent tone burst of 1kHz, presenting likelihood of 80%. One hundred stimuli were delivered. The intensity of the stimulus was 70 dBnHL and with a presentation rate of 1 pulse/ sec.

Recording parameters and response analysis

One hundred stimuli were delivered, with a 1-30 Hz filter.

Time window: 500 msec.

The *P*300 was identified as a large broad positivity in the wave of deviant stimulus (rare stimulus) with latency of about 300-400 milliseconds post stimulus onset.

The response parameters measured were: Latency which was measured from the stimulus onset to the maximum positive peak of the wave and Amplitude which was measured from the highest point of the *P*300 waveform to the following most negative excursion.

Statistical Methods

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired *t* test[15]. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5[16]. Correlations between quantitative variables were done using Spearman correlation coefficient[17]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of *P*300 latency, amplitude, MMSE and SDMT for detection of cases. *P-values* less than 0.05 were considered as statistically significant.

RESULT

This study is a cross sectional case control study involving 60 subjects. They were divided into 30 MS patients and 30 normal subjects. The mean age in the MS group was 36.6±5 years and ranged from 25 to 45 years, while in the control group the mean age was 35.3±8.3

years and ranged from 22 to 55 years. The mean disease duration in the MS group was 9.37±8.83 ranging from 1 to 20 years. The EDSS mean value among the MS group was 1.65±1.27 ranging from 0 to 4.5. There was no statistically significant difference between case and control regarding age. There was a significantly lower average of *P*300 amplitude in cases than in controls; however, there was a significantly higher average of *P*300 latency in cases than controls. Although some patients with MS had normal MMSE and SDMT scores, the mean score was statistically lower in MS patients when compared to control group (*p value* <0.001) (Table 1)

Table 1: Sociodemographic characteristics and neuropsychological test results of the participants:

	Cases				Control				*P* value
	Mean	**SD**	**Minimum**	**Maximum**	**Mean**	**SD**	**Minimum**	**Maximum**	
age in years	36.60	5.00	25.00	45.00	35.33	8.30	22.00	55.00	0.239
disease duration (years)	9.37	5.83	1.00	20.00	.	.	.	.	-----
EDSS	1.65	1.27	0.00	4.50	.	.	.	.	-----
MMSE	26.53	1.25	25.00	29.00	29.17	0.87	27.00	30.00	<0.001
P300 latency	406.44	36.79	348.00	480.00	313.82	10.72	300.00	340.20	<0.001
P300 amplitude	3.63	0.81	2.30	5.60	4.85	0.94	2.90	6.50	<0.001
SDMT	35.10	3.07	28.00	40.00	50.47	2.54	46.00	55.00	<0.001

Among the MS cases, the P300 latency increased with increased EDSS scores and increased disease duration in a strong positive correlation, while P300 latency increased with decreased MMSE scores in a strong negative correlation. Regarding *P*300 amplitude; it decreased with increased EDSS in a strong negative correlation (Table 2, Figures 1, 2).

Table 2: Correlation between MMSE, EDSS, duration, SDMT and *P*300 latency, amplitude in cases:

		***P*300 latency**	***P*300 amplitude**
MMSE	**Correlation Coefficient**	-0.575-	0.263
	P value	**<0.001**	0.161
	N	30	30
SDMT	**Correlation Coefficient**	0.118	-0.004-
	P value	0.533	0.984
	N	30	30
EDSS	**Correlation Coefficient**	0.553	-0.392-
	P value	**0.002**	**0.032**
	N	30	30
Disease duration (years)	**Correlation Coefficient**	0.635	-0.293-
	P value	**<0.001**	0.116
	N	30	30

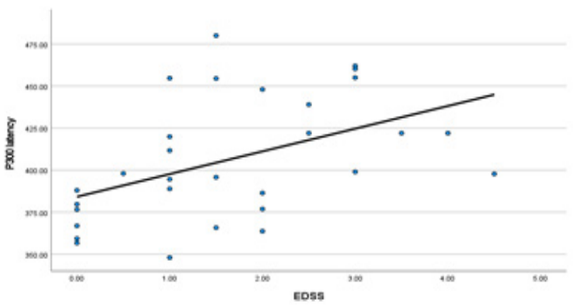

Fig. 1: scatter plot showing strong positive correlation between *P*300 latency and EDSS

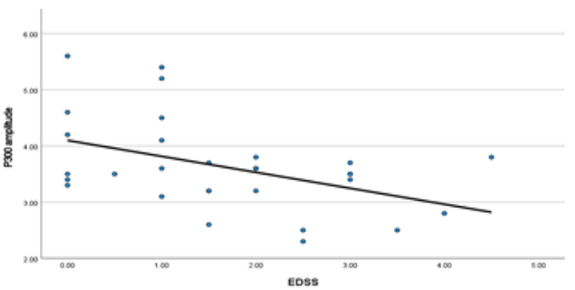

Fig.2: scatter plot showing strong negative correlation between *P*300 amplitude and EDSS

Regarding the cognitive tests in MS group, there was a strong negative correlation between the MMSE score and the EDSS and the disease duration, while there was no significant correlation between SDMT scores and EDSS, disease duration (Table 3).

Table 3: Correlation between MMSE, SDMT and EDSS, duration in cases:

		MMSE	SDMT
EDSS	Correlation Coefficient	-0.607-	0.102
	P value	<0.001	0.590
	N	30	30
disease duration (years)	Correlation Coefficient	-0.653-	-0.006-
	P value	<0.001	0.976
	N	30	30

Regarding the predictive abilities of the tests included in this study in diagnosing cognitive impairment, it was found that *P*300 latency and SDMT had the highest sensitivity score followed by MMSE, *P*300 amplitude, with sensitivity scores of (100%, 80% and 70% respectively). While regarding tests specificity, it was found that SDMT test had the highest specificity score followed by MMSE, P300 amplitudes and P300 latency with specificity scores of (100%, 96.7%, 93.3% and 53.3% respectively) as illustrated in (Table 4, Figures 3,4).

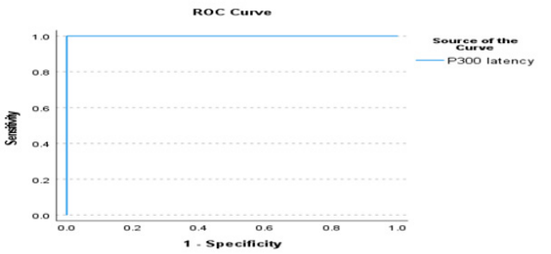

Fig. 3: ROC curve for prediction of CI in cases using p300 latency

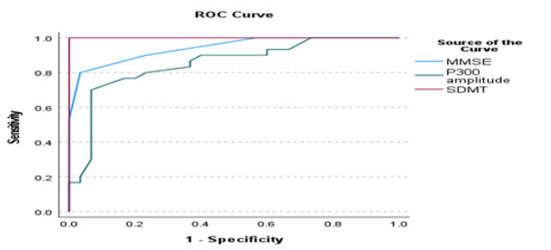

Fig. 4: ROC curve for prediction of CI in cases using *P*300 amplitude, MMSE and SDMT

Table 4: Predictive value of MMSE, *P*300 latency and amplitude in predicting diagnosis of cognitive impairment:

	Area under the curve	P value	95% Confidence Interval		Cut off	Sensitivity %	Specificity %
			Lower Bound	Upper Bound			
*P*300 latency	1.000	< 0.001	1.000	1.000	312.15	100	53.3
*P*300 amplitude	0.851	< 0.001	0.750	0.951	≤ 3.75	70	93.3
MMSE	0.942	< 0.001	0.888	0.997	≤ 27.5	80	96.7
SDMT	1.000	< 0.001	1.000	1.000	≤ 43	100	100

DISCUSSION

Cognitive impairment is a hallmark of multiple sclerosis (MS) that has a substantial impact on patients' quality of life. Cognitive impairment, characterized by deficits in processing speed, learning and memory, visuospatial skills, and executive function, affects a considerable portion of people with multiple sclerosis. Although the precise pathogenic pathways are still unclear, they may be linked to immunological alterations, pathological alterations in white matter, and specific gray matter structures. These modifications significantly impact synapse transmission and plasticity[18].

Assessing disease disability among cases indicated a mild level of disability with an average EDSS score of 1.65. This may be due to variable disease duration with mean duration of 9.37±5.83 years.

Event-related potentials (ERPs) have been used to evaluate cognitive performance in multiple sclerosis (MS), where the integrity of the auditory pathway is dramatically altered by sclerotic plaques. Numerous studies employ the *P*300 to assess how well information is processed centrally by the auditory system over the course of the disease[19] *P*300 latency and amplitude in this study were noticeably affected than controls. According to De Gennaro *et al*., MS patients' *P*300 amplitude was non-significantly lower than that of the control group. This might be because normal persons' *P*300 amplitudes vary widely, ranging from boundaries as extreme as 5 to 20 μV[20].

According to the current study, *P*300 in MS differed significantly from that in the control group. Cortical lesions or a gap between the cortical and subcortical regions may be the cause of cognitive dysfunction and the resulting reduced *P*300 response in MS patients. Numerous cognitive domains would be impacted by this gap, leading

to a range of neuropsychological deficiencies[21]. A reliable indicator of information processing speed is latency. An extended period of information processing is indicated by a prolonged *P*300 latency. On the other hand, lower *P*300 amplitude suggests a delay in information processing or a disturbance in some areas' (such the thalamus or frontal and parietal cortex) function. However, decreased *P*300 amplitude or prolonged *P*300 latency, or both must be present in order to diagnose cognitive impairment[22].

According to Fuhr and Kappos[23] *P*300 latency is more sensitive to minor early alterations in cognitive processing impairments in MS patients and offers a general, straightforward, and objective indicator of cognitive dysfunction. Pokryszko-Dragan *et al*.[24] and Kaddoori[25] both found a statistically significant delayed *P*300 latency in the MS group compared to the controls. *P*300 mostly originates in the frontal and parietal lobes, and any pathology that affects these regions in MS patients would subsequently influence *P*300 characteristics. Therefore, cognitive problems may be uniquely associated with aberrant *P*300 recording in MS patients[26].

The limbic system is affected by demyelination with the greatest impact on cognitive processes (like memory), illustrating the relationship between these neuroanatomical regions and information processing speed. For this reason, the *P*300 is a useful assessment tool in cognitive dysfunctions, and because of its practicality and repeatability, it may also be an index of this impairment[27] Consistent with previous research, our results demonstrate a robust correlation between cognitive impairment and physical status as assessed by the EDSS. Ateş and colleagues are stated the significant correlation between *P*300 and EDSS and disease duration[27]. Additionally, Triantafyllou and associates[28] found a substantial correlation with EDSS, but not with the disease duration. A substantial association was shown by Rasoulifard *et al.*[29] between *P*300 latency and EDSS, disease duration but not the amplitude.

Information processing speed and attention, which are essential for cognitive function, can be reflected in *P*300 latency and amplitude. Additional evidence regarding the use of *P*300 to assess CI in MS is provided by correlations between *P*300 and neuropsychological tests. Therefore, neurophysiological testing is crucial for examining cognitive impairment and thought to be a helpful addition to standard clinical screening[30].

MMSE and SDMT, which demonstrated a significant decrease in MS patients' overall scores, can be used to subjectively assess cognitive skills. Similar findings were also observed by Johnen *et al*., who noted the prevalence of attention deficits, abstract thinking disorders, memory deficiencies, poor language skills, impaired executive functions, and decreased processing speed[30].

When the MMSE and SDMT were administered to both groups in the current study, the MS group performed worse on cognitive tests than the controls, particularly in patients with longer disease duration and greater EDSS scores. This was also reported by Zeng and colleagues, who administered the MMSE to MS and controls. They discovered that the MS group's MMSE scores significantly decreased when compared to the controls, and that CI was higher with older age, more depressive symptoms, or greater EDSS scores. This result was also in line with Potagas and associates[31, 32].

In fact, there have been conflicting findings on the connection between MS-related neurologic disability and CI. Variability in the disease's progression and lesion location may be the cause of the contradictory findings. According to studies, MS patients with higher lesion burdens exhibit noticeably more CI than those with lower lesion burdens. Therefore, in future research, it will be helpful to examine white matter lesion loading and brain atrophy[33, 34].

Although *P*300 parameters were clearly shown to be significantly affected among patients, Waliszewska-Prosól *et al*. found that all patients obtained normal results in SDMT evaluation, indicating that they were not significantly cognitively impaired based on neuropsychological testing[35]. This contrasted with the current study's findings, which showed that the SDMT was much lower than that of the control group.

There were significant correlations between disease duration and prolonged *P*300 latency, lower *P*300 amplitude, and low MMSE, SDMT scores, all of which reflect changes in the central nervous system over time, CI was significantly correlated with disease duration in the current study. This finding was in line with Kaddoori[25] Evaluations of the patients' short-term verbal memory, abstract reasoning, and linguistic skills revealed a decline in their cognitive capacities with time[36, 37]. Other research, however, shows little to no association between disease duration and CI[38].

According to Bartosz *et al.*[39], MS patients had lower SDMT scores than controls. The authors conducted a series of neuropsychological tests to evaluate information processing speed, verbal fluency, and memory. The results of this study were in line with the findings of SDMT, which was found to be the most sensitive tool in the diagnosing CI among applied neuropsychological tests[40]. Data about differences in SDMT performance between controls and MS patients is ambiguous, which contradicts the current study even though the majority of studies consistently confirmed that MS patients performed worse on the SDMT than healthy controls[40].

Numerous studies have documented correlations between alterations in brain MRI and SDMT-measured information processing speed. Both; brain atrophy, quantity and location of demyelinating lesions were found to be associated with SDMT scores[40]. Lesion burden in the cerebrum, as opposed to the brainstem or cerebellum, was shown to be associated with lower SDMT scores; this finding may be explained by the oral version of SDMT's features, which significantly include the sense of sight and visuospatial memory[41].

Indeed, 40–70% of MS patients suffer with CI, which is now recognized as a primary deficit that can appear at any stage of the disease, including onset, and in all subtypes. Verbal fluency and executive functions are the second most affected cognitive domains after information processing speed, attention and memory, but MS impacts many more. As the disease progresses, cognitive decline gets worse[42].

To the best of our knowledge, all the tests used in the current study showed high sensitivity and specificity in diagnosing CI among MS patients.

CONCLUSION

Our study revealed the deteriorating effect of MS on cognition. MS patients were found to have cognitive impairment based on MMSE, SDMT and *P*300 test. MS duration and severity are inevitable risk factors that could be associated with decline in cognition. Cognitive decline risk in MS could occur earlier in age and become more severe with higher EDSS scores.

RECOMMENDATIONS

It is crucial to assess cognitive functions in MS. We recommend early implementation of MMSE and *P*300; which are simple tools; to be done for MS patients earlier in age. Early identification of cognitive affection may help to prevent more cognitive deterioration. This can be done by leisure activities such as computer games, crosswords and sudoku.

AUTHORS' CONTRIBUTIONS

First author contributed with sharing in writing the paper and submission and correspondence. All authors contributed with application of the idea, steps of the methods and supervising the study work, contributed with data collection and writing the paper. All authors have read and approved the manuscript.

CONFLICT INTERESTS

There are no conflicts of interest.

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