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Clinical predictors to cognitive impairment in multiple sclerosis patients



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Abstract

Background: Cognitive dysfunction is increasingly recognized in multiple sclerosis, even in the early phase of the disease. Multiple sclerosis patients with even mild cognitive deficits may experience greater difficulties in social contact and daily activities, irrespective of physical handicap. This study aimed to estimate clinical predictors of cognitive dysfunction in a sample of Egyptian people with MS.

Results: Significant worse performance in assessed cognitive scales was observed in people with MS as compared to controls. This was related to low educational level, long disease duration, initial cerebellar and motor attacks, progressive course, frequent relapses, and immunosuppressive medications. Cognitive assessment scales were significantly negatively correlated with disability measured by Expanded Disability Status Scale (EDSS) scores.

Conclusion: Predictors of cognitive impairment in people with MS were low educational level, longer disease duration, type of initial attack, frequent relapses, progressive form, higher clinical disability, and immunosuppressive treatment.

Keywords: Multiple sclerosis, Clinical predictors, Cognitive impairment

Introduction

Cognitive dysfunction is reported in 45 to 70% of people with multiple sclerosis (MS) [1]. Attention, recent memory, verbal fluency, and information-processing speed are the frequently impaired cognitive domains. Executive dysfunction is less frequently reported [2]. MS-related cognitive decline may be related to MS subtype, disease duration, gender, race, and cognitive reserve [3]. People with progressive MS have more frequent and severe cognitive dysfunction than relapsing MS. Moreover, people with MS who have high levels of cognitive reserve are unlikely to practice cognitive dysfunction [4, 5].

Previous studies have discussed that immunomodulatory drugs have a beneficial effect on MS cognitive functions. These drugs may decrease the progression of brain atrophy [6].

This study was designed to investigate clinical parameters that may contribute to cognitive impairment in people with MS.

Methods

This is a case control study done on forty-five people with MS and forty-five healthy subjects matched for age, sex, and educational level. Patients were recruited from the Neurology Department and an outpatient clinic. An informed consent was obtained from all participants prior to inclusion in the study. The study was approved by the ethical committee of the Neurology Department (blinded for peer review).

This study included clinically definite MS patients according to the revised McDonald criteria 2017 [7]. Their age ranged from 20 to 45 years, educated with at least primary level of education to be operative in performing the cognitive scales with Mini Mental State Examination (MMSE) score ≥ 26 and Hamilton depression scale score

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(HDS) ≤ 6. Control subjects were selected to be age, sex, and educationally matched

This study excluded patients who are in relapse and receiving pulse steroids; patients with severe motor disability; patients with severe visual impairment; patients with diseases that may affect cognitive functions such as hypertension, diabetes mellitus, connective tissue disorders, thyroid disorders, renal or hepatic impairment, and major psychiatric illness; and patients on tranquilizers or antidepressants.

Patients were submitted to the following: Through neurological examination, assessment of clinical disability using Expanded Disability Status Scale (EDSS) [8], and cognitive assessment using Arabic version of Addenbrooke's Cognitive Examination (ACE-III), we used the validated Egyptian–Arabic ACE-III to evaluate orientation, attention, memory, language, verbal fluency, and visuospatial abilities [9]; paced auditory serial addition test (PASAT 3) to evaluate working memory and information-processing speed [10]; and trail making test (part B) to evaluate executive functions [11].

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done for quantitative parametric data as the range as well as mean ± SD (standard deviation) using independent *t* test, paired *t* test, and ANOVA test, then post-hoc test was used for pair-wise comparisons. While for qualitative data as number and percentage, inferential analyses were done using chi-square test and Fisher's exact test. Correlations were done using Pearson correlation. *P* values less than 0.05 were considered statistically significant.

Results

MS patients in our study were 23 males (51.1%) and 22 females (48.9%). Their age ranged from 25 to 40 years with a mean age of 32.9 ± 4.1 years. The control subjects included were 27 males (60%) and 18 females (40%), and their age ranged from 25 to 45 years with a mean age 34.6 ± 5.9 years. Seventeen patients (37.8%) received primary level of education, nineteen patients (42.2%) received secondary level of education, and nine patients (20%) received university education. Disease duration ranged from 2 to 10 years with a mean of 5.1 ± 1.8 years. EDSS score ranged from 2 to 6.5 with mean 4.3 ± 1.3. Clinical characteristics of people with MS are illustrated in Table 1.

As compared to controls, people with MS experienced significant worse performance in all cognitive assessment measures (*P* ≤ 0.05) Table 2.

Table 1 Clinical characteristics of MS patients

	Patients	
	Frequency (N = 45)	Percentage
Type of MS		
RRMS	30	66.7
SPMS	15	33.3
Type of first attack		
Motor	22	48.9
Cerebellar	13	28.9
Visual	7	15.6
Sensory	3	6.7
Attack/year		
One	9	20.0
Two	23	51.1
Three	13	28.9
Treatment		
Interferon B1b	13	28.9
Monthly cyclophosphamide + methylprednisolone	11	24.4
Fingolimod	8	17.8
Interferon Beta 1a	7	15.6
Azathioprine	5	11.1
Cyclophosphamide	1	2.2

RRMS relapsing-remitting multiple sclerosis, SPMS secondary progressive multiple sclerosis, N number

Regarding the scores of the cognitive scales, there was no significant difference between male and female patients.

Concerning the scores of ACE language and PASAT 3, there was a statistically significant difference between population subgroups distributed according to the level of education (*P* = 0.014 and 0.046) Table 3. Post-hoc

Table 2 Comparison of mean scores of cognitive assessment scales between MS patients and healthy controls

Mean ± SD	Patients (N = 45)	Controls (N = 45)	<i>P</i> value
ACE attention	16.7 ± 1.2	18.0 ± 0.0	< 0.001**
ACE memory	19.6 ± 2.3	24.5 ± 0.3	< 0.001**
ACE language	22.0 ± 2.3	25.2 ± 1.3	< 0.001**
ACE fluency	10.3 ± 1.7	12.6 ± 1.1	< 0.001**
ACE visuospatial	15.2 ± 1.1	16.0 ± 0.0	0.011*
ACE total	83.0 ± 5.7	95.5 ± 0.4	< 0.001**
PASAT 3	21.9 ± 9.0	44.8 ± 7.8	< 0.001**
Trail making type B	191.3 ± 73.1	77.5 ± 6.0	< 0.001**

*Significant

**Highly significant

ACE Addenbrooke's cognitive examination III, PASAT3 Paced auditory serial addition test, N number, SD standard deviation
P value is significant if ≤ 0.050

Table 3 Comparison of mean cognitive scale scores between MS patients with different levels of education

	Level of education			P value
	1ry	2ry	University	
ACE attention				
Mean ± SD	16.3 ± 1.6	16.7 ± 1.1	17.0 ± 1.4	0.499
ACE memory				
Mean ± SD	19.1 ± 2.0	20.1 ± 2.6	20.8 ± 1.8	0.148
ACE language				
Mean ± SD	20.8 ± 2.0	22.5 ± 2.4	23.3 ± 1.5	0.014*
ACE fluency				
Mean ± SD	10.1 ± 1.6	10.2 ± 1.8	10.0 ± 1.9	0.959
ACE visuospatial				
Mean ± SD	15.3 ± 1.0	15.5 ± 1.3	15.3 ± 1.0	0.434
ACE total				
Mean ± SD	81.6 ± 4.9	85.1 ± 6.1	86.3 ± 6.3	0.316
PASAT 3				
Mean ± SD	17.4 ± 9.9	21.6 ± 7.5	26.5 ± 7.9	0.046*
Trail making type B				
Mean ± SD	203.5 ± 78.2	187.0 ± 73.5	170.0 ± 63.7	0.554

*Statistically significant

**Highly significant

ACE Addenbrooke's cognitive examination III, PASAT 3 Paced auditory serial addition test, 1ry primary, 2ry secondary, SD standard deviation
P value is significant if ≤ 0.050

analysis revealed that patients with primary level of education had significant lower scores of ACE language compared to those with secondary and university education ($P = 0.023$ and 0.007 respectively). Patients with primary level of education had also significant lower scores of PASAT 3 compared to those with university education ($P = 0.019$).

People with RRMS (relapsing-remitting multiple sclerosis) showed significant better scores than those with SPMS (secondary progressive multiple sclerosis) regarding total ACE score ($P \leq 0.001$), ACE scores of attention ($P = 0.011$), memory and language ($P \leq 0.001$), PASAT 3 ($P = 0.032$), and trail making B ($P = 0.035$) (Table 4).

Patients with cerebellar and sensory attacks showed significant worse performance in ACE attention than those with motor and visual attacks ($P = 0.013$). Patients with cerebellar attacks showed the worst performance in ACE language ($P = 0.036$) (Table 5).

Patients who are on immunomodulatory drugs showed significant better cognitive performance than those on immunosuppressive medications in (ACE attention, ACE memory, ACE language, total ACE, and PASAT3) (0.009 , < 0.001 , < 0.001 , < 0.001 , and 0.011 , respectively) (Table 6).

There was a significant negative correlation between age and total score of ACE ($P = 0.046$, $r = - 0.299$).

Table 4 Comparison between patients distributed according to MS course regarding mean cognitive scales scores

	Type of MS		i value
	RRMS	SPMS	
ACE attention			
Mean ± SD	17.0 ± 1.2	15.9 ± 1.4	0.011*
ACE memory			
Mean ± SD	20.7 ± 2.1	18.0 ± 1.3	< 0.001**
ACE language			
Mean ± SD	23.1 ± 1.7	19.9 ± 1.6	< 0.001**
ACE fluency			
Mean ± SD	10.1 ± 1.6	10.2 ± 1.9	0.879
ACE visuospatial			
Mean ± SD	15.5 ± 1.0	15.2 ± 1.3	0.463
ACE total			
Mean ± SD	86.4 ± 5.7	79.1 ± 2.0	< 0.001**
PASAT 3			
Mean ± SD	23.0 ± 8.7	16.6 ± 8.2	0.032*
Trail making type B			
Mean ± SD	173.3 ± 66.0	224.0 ± 77.2	0.035*

*Statistically significant

**Highly significant

ACE Addenbrooke's cognitive examination III, PASAT3 Paced auditory serial addition test, RRMS relapsing-remitting multiple sclerosis, SPMS secondary progressive multiple sclerosis, SD standard deviation
P value is significant if ≤ 0.050.

Moreover, a significant negative correlation was found between EDSS and scores of cognitive scales ($P \leq 0.05$) except ACE visuospatial and trail making B tests. Also, there was a significant negative correlation between frequency of attacks/year and scores of ACE attention, memory, and language and total score ($P < 0.05$). Furthermore, duration of illness was negatively correlated with scores of ACE memory, language, and total score ($P < 0.05$) (Table 7).

Discussion

Cognitive domains which were observed to be affected in our patients were attention, memory, language, visuospatial, information-processing speed, and executive functions. This proposed that MS can affect both cortical and subcortical cognitive functions. This was in agreement with numerous previous studies which described cognitive dysfunction in people with MS [12–15]. MS-related cognitive dysfunction results from domain-specific disconnection phenomena. Reduced functional connectivity between cortico-cortical and cortico-subcortical cognitive processing regions results in impairment to specific cognitive domains [16]. Cortical lesions may also responsible for cognitive deficits in people with MS [17].

Table 5 Comparison of mean scores of cognitive scales between MS patients with different types of first attack

	Type of 1st attack				P value
	Motor	Cerebellar	Visual	Sensory	
ACE attention					
Mean ± SD	16.8 ± 1.2	15.7 ± 1.4	17.7 ± 0.8	16.7 ± 1.2	0.013*
ACE memory					
Mean ± SD	19.9 ± 2.5	19.2 ± 1.9	20.1 ± 2.9	21.3 ± 1.2	0.469
ACE language					
Mean ± SD	21.8 ± 2.1	21.1 ± 2.4	23.7 ± 1.4	24.0 ± 2.0	0.036*
ACE fluency					
Mean ± SD	9.8 ± 1.7	10.3 ± 1.8	10.6 ± 1.5	10.7 ± 2.3	0.664
ACE visuospatial					
Mean ± SD	15.1 ± 1.3	15.7 ± 0.8	15.7 ± 0.8	15.3 ± 1.2	0.433
ACE total					
Mean ± SD	83.3 ± 6.2	82.0 ± 4.8	87.9 ± 4.7	88.0 ± 6.9	0.069
PASAT 3					
Mean ± SD	19.6 ± 8.2	21.9 ± 10.3	21.6 ± 10.9	24.3 ± 5.1	0.667
Trail making type B					
Mean ± SD	191.4 ± 75.9	214.6 ± 81.7	140.0 ± 36.1	193.3 ± 23.1	0.240

*Statistically significant

ACE Addenbrooke's cognitive examination III, PASAT 3 Paced auditory serial addition test, SD standard deviation

P value is significant if ≤ 0.050

Table 6 Comparison of laboratory parameters and cognitive scale scores between MS patients distributed according to treatment type

	Treatment type		P value
	Immuno-modulator	Immunosuppressive	
ACE attention			
Mean ± SD	17.0 ± 1.2	15.9 ± 1.3	0.009*
ACE memory			
Mean ± SD	20.9 ± 2.2	18.1 ± 1.3	< 0.001*
ACE language			
Mean ± SD	23.3 ± 1.7	20.0 ± 1.6	< 0.001*
ACE fluency			
Mean ± SD	10.3 ± 1.6	9.9 ± 1.9	0.521
ACE visuospatial			
Mean ± SD	15.4 ± 1.1	15.3 ± 1.2	0.727
ACE total			
Mean ± SD	86.8 ± 5.7	79.3 ± 2.0	< 0.001*
PASAT 3			
Mean ± SD	23.6 ± 8.6	16.4 ± 7.7	0.011*
Trail making type B			
Mean ± SD	176.4 ± 67.1	212.9 ± 79.0	0.127

*Statistically significant

ACE Addenbrooke's cognitive examination III, PASAT 3 Paced auditory serial addition test, SD standard deviation

P value is significant if ≤ 0.050

Intelligence and education are responsible for the formation of cognitive reserve level which can affect the brain's resilience in the presence of insult [18]. In the current study, people with MS who have higher levels of education showed significant better performance in only ACE language and information-processing speed compared to those having lower educational level. This was in accordance with Benedict and his colleagues who found that MS patients with a low cognitive reserve at baseline suffered a noteworthy cognitive decline [5]. However, Russo and colleagues [19] found no significant differences in the educational level between patients whose cognition was unimpaired, mildly impaired, and severely impaired.

The current work revealed that people with MS who had high EDSS showed more impairment in attention, memory, language, fluency, information-processing speed, and to a lesser extent task switching for executive functions. Amato and colleagues found that MS patients with cognitive dysfunction had higher EDSS score than those without. Also, they found that EDSS score correlate weakly with impaired cognitive functions. Moreover, they revealed that cognitive functions correlates with physical disability and may predict disability levels [20].

People with MS who experienced frequent relapses had significant impairment in attention, memory, and

Table 7 Correlation between clinical parameters and scores of cognitive scales in MS patients

	Age		EDSS		Attacks/year		Duration of illness	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
ACE attention	-0.08	0.59	-0.45	0.002*	-0.38	0.009*	-0.236	0.119
ACE memory	-0.23	0.12	-0.64	< 0.001*	-0.46	0.001*	-0.58	< 0.001**
ACE language	-0.23	0.11	-0.81	< 0.001*	-0.49	0.001*	-0.47	0.001*
ACE fluency	-0.22	0.14	-0.33	0.027*	-0.08	0.600	-0.22	0.135
ACE visuospatial	-0.06	0.66	-0.27	0.065	0.00	0.988	-0.16	0.270
ACE total	-0.299	0.046	-0.843	< 0.001*	-0.500	< 0.001*	-0.55	< 0.001**
PASAT 3	-0.207	0.173	-0.373	0.012*	-0.268	0.075	-0.21	0.165
Trail making type B	-0.041	0.787	0.293	0.051	0.111	0.467	0.237	0.116

*Statistically significant

**Highly significant

ACE Addenbrooke's cognitive examination III, PASAT 3 Paced auditory serial addition test, EDSS Expanded Disability Status Scale

P value is significant if ≤ 0.050

language. Duration of illness also affected the cognitive performance especially in memory and language as concluded in this work.

The current study showed that MS course has a significant impact on cognitive abilities. People with SPMS experienced significant worse performance in tasks of attention, memory, language, information-processing speed, and executive functions compared to those with RRMS. This agreed with Borghi and colleagues, who concluded that people with progressive MS showed a marked cognitive deficit as compared to those with RRMS and healthy controls [21].

Type of first attack may correlate to cognitive functions in MS. In this study, patients with cerebellar followed by sensory attacks showed the worst performance in attention tasks compared to patients with motor and visual attacks. Patients with cerebellar followed by motor attacks showed the worst performance in language tasks compared to patients with visual and sensory attacks; these findings may direct attention to the role of cerebellum in cognition.

Treatment type may contribute to impairment of cognitive functions in people with MS. We found that attention, memory, language, and information-processing speed were significantly better in patients receiving immunomodulatory drugs compared to those on immunosuppressive medications. This agreed with Fischer and colleagues, who reported that interferon Beta 1a had a significant favorable effect on attention, memory, visuospatial abilities, information processing, and problem solving [22]. Available immune-modulatory treatments for multiple sclerosis rapidly inhibit the inflammation and reduce the progression of brain atrophy, and they may also have neuro-protective properties [6].

Conclusion

It could be concluded that cognitive impairment in MS patients affects both cortical and subcortical domains. Low educational level, longer disease duration, type of initial attacks, frequent relapses, progressive course, higher disability, and immunosuppressive medications are correlated with cognitive impairment in people with MS.

Abbreviations

MS: Multiple sclerosis; ACE-III: Addenbrooke's Cognitive Examination III; PASAT 3: Paced auditory serial addition test 3; EDSS: Expanded Disability Status Scale; MMSE: Mini Mental State Examination; HDS: Hamilton depression scale score; SPSS: Statistical Package for Social Sciences; SD: Standard deviation

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Authors' contributions

HE contributed in the data acquisition, data interpretation, and manuscript writing and reviewing. EMF took part in the research idea, data acquisition, data analysis, and interpretation. NME and AMA participated in the data acquisition, data analysis, and interpretation. RSI helped in the manuscript writing and reviewing. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the current Cairo University regulations and Egyptian legislation but are available from the corresponding author on reasonable request and after institutional approval.

Ethics approval and consent to participate

An informed written consent was taken from each patient. All data obtained from every patient were confidential and were not used outside the study. The patients have the rights to withdraw from the study at any time without giving any reason. All the costs of the investigations were afforded by the researcher.

Our study was approved by the ethical committee of the Department of Neurology, Faculty of Medicine, Cairo University on 15/6/2018 (ethical reference number is not available).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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