

Association of cognitive impairment and quality of life in patients with multiple sclerosis: A cross-sectional study

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Keywords

Cognitive Dysfunction; Quality of Life; Multiple Sclerosis; Cross-Sectional Studies; Depression

Abstract

Background: Cognitive impairments in patients with multiple sclerosis (MS) are suggested as a prognostic factor for disease development, and consequently higher disability and more deficits in daily and social activities. In this regard, we aimed to investigate the association between quality of life (QOL) and cognitive function in patients with MS.

Methods: We conducted a cross-sectional study on patients with relapsing-remitting MS (RRMS). General characteristic variables were carried out, and then all patients underwent assessments such as Multiple Sclerosis Quality of Life-54 (MSQOL-54), Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), Expanded Disability Status Scale (EDSS), Beck Depression Inventory-II (BDI-II), and North American Adult Reading Test (NAART).

Results: In the present study, a total of 92 patients, including 76 women with a mean disease duration of 6.82 ± 4.80 years were involved. Results of simple Pearson correlation revealed a significant positive relation between California Verbal Learning Test (CVLT) total learning with MSQOL mental health ($r = 0.267$, $P = 0.017$) and physical health ($r = 0.299$, $P = 0.007$). After adjusting for potential confounders, there was a negative correlation between MSQOL mental health with Delis-Kaplan Executive Function System (D-KEFS) ($r = -0.303$, $P = 0.015$) and Judgment of Line Orientation (JLO) ($r = -0.310$, $P = 0.013$). Besides, MSQOL physical health was negatively associated with Brief Visuospatial Memory Test-Revised (BVM-T-R) in the adjusted model ($r = -0.270$, $P = 0.031$).

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Conclusion: There is a statistically significant association between specific aspects of cognitive decline and QOL. Therefore, more attention should be paid to cognitive impairment in patients with MS as based on our findings, it is significantly associated with QOL.

Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system, which mostly affects younger adults, and causes disability.¹ Patients with MS suffer from physical disability, while 40%-60% of them also show cognitive impairment.² According to evidence, cognitive decline occurs in all MS phenotypes, and prevalence differs based on criteria and population of study.³ There are also findings revealing that patients with secondary progressive MS (SPMS) appear to have more cognitive decline compared to the patients with clinically isolated syndrome, relapsing-remitting MS (RRMS), and primary progressive MS (PPMS).⁴ It is stated that cognitive impairment in the early stages of disease predicts the earlier conversion of RRMS to SPMS, and subsequently disability progression.⁵ Furthermore, the relation between cognitive decline and MS in the early stages is not well established, while an accurate diagnosis of cognitive impairment in early MS may be used as a determinant for disease progression.⁶ In light of this, Cortese et al. findings revealed that intelligence quotient (IQ) scores were lower in those who developed MS later compared to controls.⁷ Harel et al. study demonstrated that 23.7% of patients treated with disease-modifying drugs had low cognitive performance and 42.7% had moderate performance after a mean disease duration of 19.6 years.⁸ Multiple factors can affect cognitive function in MS. History of smoking, level of disability, and verbal intellectual ability may influence cognition, while physical exercise and a healthy diet have a positive effect.⁹ Moreover, recent studies indicate that white matter lesions and also cortical and subcortical gray matter atrophy may contribute to cognitive impairment in MS.¹⁰

A 10-year follow-up shows that physical disability, progressive disease course, and age predict cognitive decline, and on the other hand, cognitive decline causes limitation in a person's work and social activities independently.¹¹ Fatigue, depression, mood disorder, anxiety, behavioral changes, and personality may influence the quality of life (QOL) in patients with MS.¹²

QOL in the past referred to economic variables but nowadays, QOL is categorized as the objective and subjective QOL. Objective QOL mainly represents economic aspects, while subjective QOL indicates life satisfaction and happiness.¹³ Moreover, there are two types of subjective QOL including generic and disease-specific. Generic measures can be applied to a variety of diseases, while specific determinations are used for a particular patient and give a more accurate vision.¹⁴ Recently, Multiple Sclerosis Quality of Life-54 (MSQOL-54) emerged as a disease-specific instrument to assess the QOL in the MS population.¹⁵

Cognitive impairments in patients with MS are suggested as a prognostic factor for disease development, and consequently, higher disability and more deficits in daily and social activities.¹⁶ This study aimed to investigate the correlation between QOL and cognitive function in patients with MS. This is the first study that describes the relation between MSQOL-54 and cognition in the MS population.

Materials and Methods

Participants: We conducted a cross-sectional study on patients diagnosed with RRMS who were referred to the MS clinic of Sina Hospital, Tehran, Iran, from July 2018 to May 2019. In this study, one hundred patients were selected using a non-probability convenient sampling. Exclusion criteria were a history of any substance or drug use that could affect cognitive performance, alcohol use, any major psychiatric disease and physical disorder other than MS, and relapse or corticosteroid therapy within the three months. After exclusion, 92 patients remained in the study. All participants were informed of the design and purposes of the study, then they were asked to provide written informed consent.

Assessments: General characteristic variables were carried out by a general questionnaire including the level of education, disease duration, family history of MS, presentation sign of the disease, number of attacks, type of medication, and marital status.

Physical disability was assessed by Expanded Disability Status Scale (EDSS), which is measured by a neurologist and ranges from 0 to 10 in 0.5 increments.¹⁷ The score of 0 represents no disability, while the score of 10 represents death due to MS and extreme disability.

Patients' moods were assessed by the Beck Depression Inventory-II (BDI-II) which includes

21 items with multiple choice and a total of 63 scores, while higher scores indicate the severity of depressive symptoms.¹⁸

North American Adult Reading Test (NAART) is a proven valid test for assessing verbal intellectual ability in a variety of neurological disorders. NAART test consists of 61 words that are scored based on their pronunciation,¹⁹ and there was a correlation between NAART and IQ index.²⁰

QOL evaluation was done using MSQOL-54, which measures the generic and disease-specific aspects of QOL. Results are divided into mental health (MSQOL-MH) and physical health (MSQOL-PH).¹⁵

Cognitive function was evaluated utilizing Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), which was translated to Persian,²¹ in a quiet room with enough light. MACFIMS is one of the most commonly used neuropsychological batteries that is the collection of previously published tests:

Paced Auditory Serial Addition Test (PASAT) has clinical utility for cognitive impairment in multiple neurological diseases. Previously, it was assumed that PASAT measured the speed of information processing, but currently, it is described as a measure for various cognitive domains such as processing speed, attention, and calculation ability.²²

Symbol Digit Modalities Test (SDMT) assesses divided attention, visual scanning, tracking, and motor speed. In this examination, the patient has 90 seconds to pair numbers with geometric symbols.²³

California Verbal Learning Test - second edition (CVLT-II), as an instrument represents verbal learning and memory. The psychologist reads 16 nouns loudly, and the patient is asked to recall as many words as they can at the end of each five trials.²⁴

Brief Visuospatial Memory Test-Revised (BVMT-R) was used for visuospatial learning and memory assessment. It provides three learning trials, a 25-minute delayed recall trial, and a delayed yes/no recognition task.²⁵

The Controlled Oral Word Association Test (COWAT) is a test of verbal fluency in which the examinee is given one minute to name as many possible words beginning with one of three letters (C, F, and L).²⁶

Judgment of Line Orientation (JLO) Test is a widely used examination for visuospatial judgment. Individuals are asked to indicate which two lines are matched with an identical pair

immersed within an 11 semicircular array.²⁷

Delis-Kaplan Executive Function System (D-KEFS) contains nine tests that provide a precise assessment of executive function including flexibility of thinking, inhibition, problem-solving, planning, impulse control, concept formation, abstract thinking, and creativity.²⁸

Variable definition: MACFIMS results are presented as 14 variables consisting of PASAT total correct, PASAT percent correct, SDMT, BVMT (T1 + T2 + T3), BVMT delay, BVMT copy, BVMT index, BVMT bias, COWAT, D-KEFS (total point), D-KEFS (total group), JLO, CVLT total learning, and CVLT long delay free recall.

The education level of patients was reported in four categories as diploma, upper diploma, bachelor, and master degrees. Participants had at least one family member in the first, second, and third-degree or other relatives with MS described as a familial MS. Moreover, BDI-II outcomes were available in two forms: quantity and quality.

Statistical analysis was performed using SPSS software (version 14, SPSS Inc., Chicago, IL, USA). First, we adopted simple Pearson correlation models to investigate the possible correlation of each cognitive variable with patient demographics, EDSS, BDI-II quantity, BDI-II quality, NAART, MSQOL-PH, and MSQOL-MH separately. Next, we used a partial correlation model controlled for age, level of education, duration of disease, number of attacks, marital status, EDSS, NAART, and BDI-II quantity and quality to evaluate the correlation of cognitive scores with MSQOL-PH and MSQOL-MH. All results were regarded as significant at $P < 0.05$.

Results

In the present study, a total of 92 patients, 16 men and 76 women with a mean disease duration of 6.82 ± 4.80 years were involved. The mean age was 33.42 ± 7.59 years. Eighteen patients had a positive family history of MS. The mean EDSS score of the patients was 1.98 ± 0.91 , while the mean NAART score was 42.05 ± 3.98 . Demographic features are detailed in table 1.

Results of bivariate correlation between characteristic variables and cognitive scores revealed a significant correlation between age, level of education, duration of disease, number of attacks, marriage condition, EDSS, NAART, and BDI-II quantity and quality with cognitive scores including PASAT, SDMT, BVMT, BVMT index, BVMT delay, BVMT bias, JLO, CVLT long delay

free recall, CVLT total learning, and D-KEFS. According to these results, we adopted age, level of education, duration of disease, number of attacks, marital status, EDSS, NAART, and BDI-II quantity and quality as cofounders in all further models in the association between cognitive scores and QOL.

Table 1. Demographic and clinical features

Characteristic	Value
Age (year)	33.42 ± 7.59
Female sex	76 (86.2)
Duration (year)	6.82 ± 4.80
Education	
Diploma	27 (29.3)
Upper diploma	7 (7.6)
Bachelor's degree	47 (51.1)
Master's degree	9 (9.8)
Type of medications	
Low dose	31 (33.7)
High dose	49 (53.3)
Cytotoxic	3 (3.3)
Other	3 (3.3)
Cytotoxic + high dose	2 (2.2)
Nothing	1 (1.1)
Family history	18 (19.6)
Marriage status	
Single	38 (43.2)
Married	50 (56.8)
NAART	42.05 ± 3.98
EDSS	1.98 ± 0.91
BDI-II quantity	16.69 ± 11.15
BDI-II quality	2.51 ± 1.45

Data are presented as mean ± standard deviation (SD) or number and percentage

EDSS: Expanded Disability Status Scale; NAART: North American Adult Reading Test; BDI-II: Beck Depression Inventory - second edition

Next, we investigated the association of cognitive scores with MSQOL-MH and MSQOL-PH. For this purpose, first, we implemented a simple Pearson correlation between cognitive scores and QOL variables including MSQOL-MH

and MSQOL-PH, and then entered the cofounders mentioned previously into the model.

Our results revealed that higher CVLT total learning correlated with higher MSQOL-MH and MSQOL-PH (Figure 1). After controlling for cofounders, this correlation did not persist (Tables 2 and 3). In the adjusted model, MSQOL-MH was negatively associated with D-KEFS and JLO (Table 2, Figure 1).

Besides, higher MSQOL-PH was associated with lower BVMT delay in the corrected model (Table 4, Figure 1).

Table 2. Results of cognitive tests

Cognitive index	Mean ± SD
PASAT (total correct)	44.64 ± 11.28
PASAT (percent correct)	74.41 ± 18.81
SDMT	46.59 ± 13.22
COWAT	27.47 ± 9.40
D-KEFS (total point)	32.93 ± 10.77
D-KEFS (total group)	9.13 ± 3.05
BVMT (T1 + T2 + T3)	25.42 ± 7.14
BVMT delay	9.37 ± 2.52
BVMT copy	11.46 ± 0.74
BVMT index	5.60 ± 0.89
BVMT bias	0.45 ± 0.12
JLO	21.10 ± 5.23
CVLT (total learning)	49.70 ± 10.22
CVLT (long delay free recall)	11.54 ± 3.52

PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; COWAT: Controlled Oral Word Association Test; D-KEFS: Delis-Kaplan Executive Function System; BVMT: Brief Visuospatial Memory Test; JLO: Judgment of Line Orientation; CVLT: California Verbal Learning Test; SD: Standard deviation

Discussion

In our study, we investigated the correlation between cognitive function and QOL in 92 patients with MS. We found that MSQOL-MH was associated with D-KEFS and JLO. Higher levels of MSQOL-PH were also associated with lower BVMT delay.

Table 3. Significant results of Pearson correlation analyses between Multiple Sclerosis Quality of Life (MSQOL) mental health and cognitive scores

Cognitive index	Correlation coefficient	Adjusted for cofounders
CVLT (total learning)	0.267*	-0.039
D-KEFS (total group)	-0.077	-0.303*
JLO	-0.059	-0.310*

Confounders include age, education, duration of disease, number of attacks, marriage condition, Expanded Disability Status Scale (EDSS), North American Adult Reading Test (NAART), Beck Depression Inventory - second edition (BDI-II)

*P < 0.05

CVLT: California Verbal Learning Test; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation

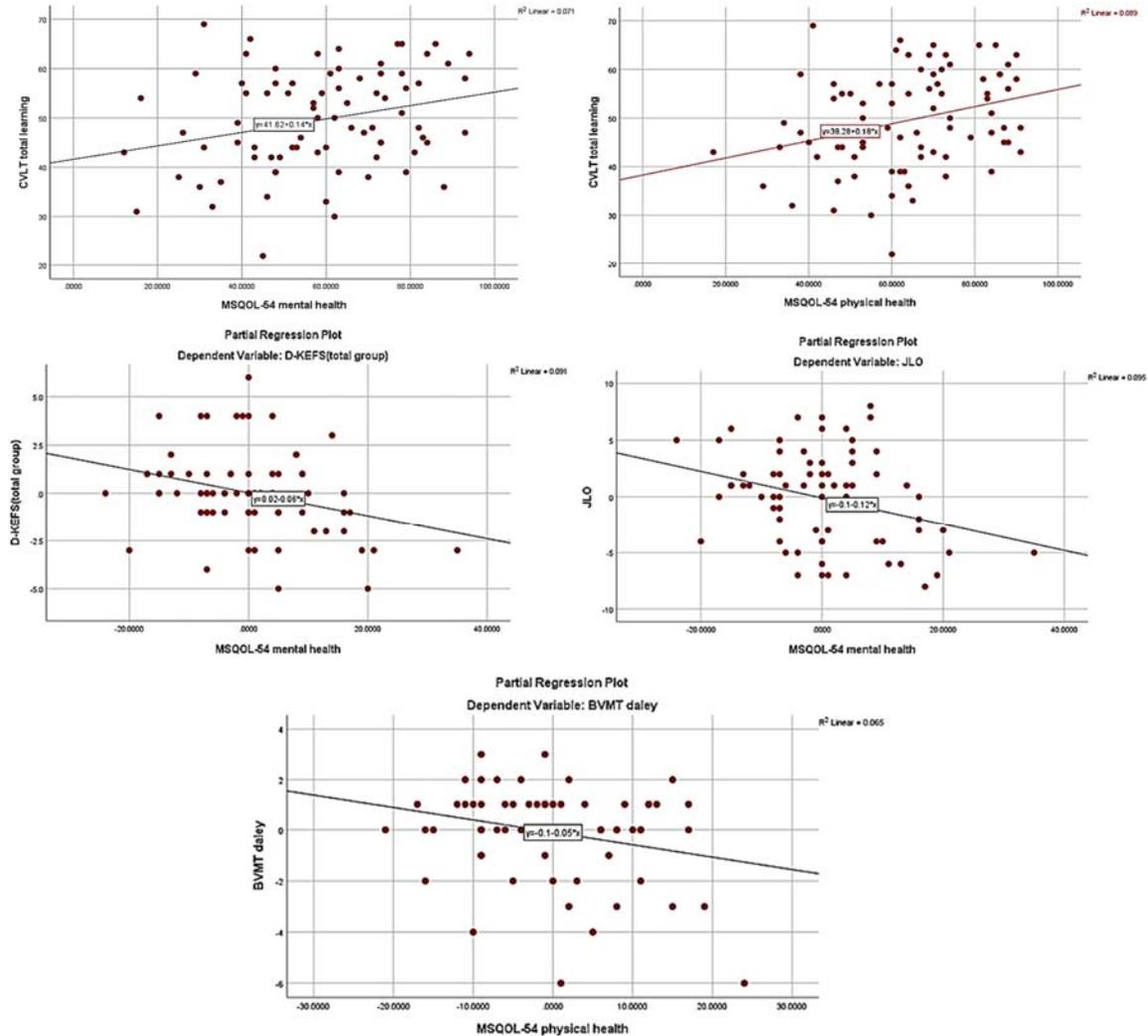


Figure 1. Significant results of correlation between cognitive function and Multiple Sclerosis Quality of Life (MSQOL) scores
 CVLT: California Verbal Learning Test; D-KEFS: Delis-Kaplan Executive Function System; JLO: Judgment of Line Orientation;
 BVMT: Brief Visuospatial Memory Test; MSQOL-54: Multiple Sclerosis Quality of Life-54

The decline in cognitive function is common among patients with MS, interfering with memory, information processing, attention, and executive functioning.²⁹

In the previous study by Campbell et al., the

incidence of cognitive impairment in patients with MS was about 65%³⁰ and the same result was mentioned in a similar study.³¹ Mild cognitive impairment was identified in up to 49% of patients with early MS.³²

Table 4. Significant results of Pearson correlation analyses between Multiple Sclerosis Quality of Life (MSQOL) physical health and cognitive scores

Cognitive index	Correlation coefficient	Adjusted for confounders
CVLT (total learning)	0.299**	-0.063
BVMT delay	0.006	-0.267*

Confounders include age, education, duration of disease, number of attacks, marriage condition, Expanded Disability Status Scale (EDSS), North American Adult Reading Test (NAART), Beck Depression Inventory - second edition (BDI-II)

*P < 0.05; **P < 0.01

CVLT: California Verbal Learning Test; BVMT: Brief Visuospatial Memory Test

Our results indicate that cognitive impairment is associated with lower MSQOL in patients with MS, probably resulting in increased rates of unemployment in these patients and other aspects of their lives. This is in line with a recent research investigating the association between cognitive impairment and QOL in patients with MS using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).³⁰ A retrospective multi-center study was performed on patients with early onset of MS disease and it revealed the importance of cognitive impairment as a predictor factor of disability progression in early-onset MS.³³ Some studies also found a correlation between self-reported cognitive impairment and impaired QOL³⁴ and another study suggested that perceived cognitive impairment specifically impairment of planning affected QOL.³⁵

In order to examine the neuropsychological status of the patients, we performed the MACFIMS test. In the case of MS disease, MACFIMS is among the batteries that have been used extensively and is proven that can assist neurologists and neuropsychologists to evaluate disease-related cognitive impairments³⁶ and is a valid approach to assessing patients with MS from a neuropsychological aspect.³⁷

As mentioned above, MSQOL-MH was negatively correlated with D-KEFS and JLO. D-KEFS can identify patients with MS with depression and higher physical disability³⁸ and is widely used to evaluate higher cognitive functions. We demonstrated that compromised executive function in patients with MS was correlated with QOL. This is somehow unexpected due to the findings of Denney et al., mentioning that the measures of executive functioning did not differ between patients with MS and the control group,³⁹ and in contrast with our result, Grech et al. found that there was no significant correlation between executive dysfunction and further changes in QOL and level of depression in patients with MS.⁴⁰ Although consistent with our results, previous studies reported an association between deficits in executive function and physical health QOL.⁴¹ It is

hypothesized that this failure in replicating the same results is due to the different methodology.⁴⁰

We found a correlation between QOL and CVLT, but after controlling the bivariate correlation for cofounders such as EDSS, NAART, and age, we observed no significant correlation, which represents no association between the decline of verbal learning and memory with any subtype of MSQOL. The same result was revealed by Glanz et al., who reported the negative association between verbal and spatial memory capacity and one's life satisfaction.³² Meanwhile, our results revealed a significant correlation between BMVT and MSQOL-PH. BMVT is proven to be a reliable instrument to evaluate visuospatial learning in patients with MS.⁴² Deficits of visuospatial learning and memory are common in patients with MS and correlate to atrophy in the hippocampus region.⁴³

We found that there was a statistically significant association between specific aspects of cognitive decline and QOL from the perspective of both mental and physical health. Therefore, more attention should be paid to cognitive impairment in patients with MS as based on our findings, it is significantly associated with QOL.

Conclusion

MS is a life-long disease which is more prevalent among young population and affects their QOL. The present study suggests significant association between decline in specific aspects of cognition and low QOL. Thus, it seems that more attention should be paid to cognitive assessment and rehabilitation in patients with MS to improve their QOL.

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran (IR.TUMS.NI.REC.1400.039).

Conflict of Interests

The authors declare no conflict of interest in this study.

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