European Review for Medical and Pharmacological Sciences 2021; 25: 2021-2030

The relationship between vitamin D levels and cognitive impairment in patients with multiple sclerosis

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Abstract. – OBJECTIVE: Neurocognitive impairment is one of the most common manifestations of multiple sclerosis (MS). However, the pathophysiology of this issue is still poorly understood. The objective of this study is to investigate the relationship between vitamin D levels and cognitive function in patients with MS as assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB).

PATIENTS AND METHODS: This was a cross-sectional, case-control study; the subjects were 39 Saudi patients diagnosed with MS. For all participants, demographic information, including age, sex, and educational level, was collected. Participants were also evaluated using the disease steps scale and the PHQ-9 scale. Their vitamin D levels were assessed, and the participants completed a computerized cognitive assessment using the CANTAB.

RESULTS: From the total sample of 39 patients with MS, 31 (79.5%) were female. Physical disability due to MS was insignificant in 25 (64.1%) of the subjects and significant in 14 (35.9%). Seventeen (43.6%) of the participants had normal vitamin D levels; 22 (56.4%) had low vitamin D levels. The MS patients had lower MOT mean errors than the control group, and this difference was statistically significant ($t = -4.313$, $p < 0.01$). Moreover, the scores of the two groups for all subcategories of the memory domain were different at statistically significant levels. Furthermore, the control group had higher PAL total errors (adjusted), PAL total errors (6 shapes, adjusted), and PRM percent correct than the MS patients ($p < 0.01$). The control group also achieved lower scores on SWM between errors and SWM strategy than the MS patients ($p < 0.01$). The MOT mean error was found to correlate with the disease steps score ($r = 0.394$, $p < 0.05$) and with significant physical disability ($r = 0.457$, $p < 0.01$). In the memory domain, PAL total errors (adjusted) correlated with age ($r = 0.381$, $p < 0.05$), SWM between errors correlated with age at onset of disease ($r = 0.345$, $p < 0.05$), and vitamin D level ($r = 0.335$, $p < 0.05$) and SWM strategy correlated with the number of relapses in the past 12 months ($r = -0.355$, $p < 0.05$).

CONCLUSIONS: Cognitive performance was impaired in patients with MS. Vitamin D deficiency, a potentially modifiable risk factor, independently predicted cognitive impairment in MS patients.

Key Words:
MS, Cognition, Cognitive impairment, Vitamin D.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disorder characterized by demyelinating and gliosis, which can occur in any part of the central nervous system. It affects around 100 to 200 of every 100,000 people in North America and Europe and is more common among females[1]. Due to its unique, non-selective nature, MS can present with any features of central lesion. The most common symptoms are motor weakness, sensation abnormalities, visual disturbance, balance problems, Lhermitte's sign, vertigo, bladder control problems, pain, and changes in cognitive functions[2].

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Based on the presentation, MS can be classified into four different subtypes. When the patient presents with the first clinical attack, it is described as a clinically isolated syndrome. This has recently been included as a subtype, although it does not fulfill the criteria regarding dissemination over time. The second and most common subtype is relapsing-remitting MS (RRMS), which is characterized by episodes of neurological deficits followed by either complete or partial recovery. A number of patients with RRMS progress into the secondary progressive (SPMS) subtype, in which acute episodes are less frequent but patients experience continuous deterioration in neurological function. The third subtype is primary progressive MS (PPMS), in which patients experience steady deterioration in neurological function without any acute attacks at all[1-3].

Around 40-65% of MS patients have some degree of cognitive deficit associated with the disease4-6. The incidence of cognitive problems in this population represents a significant problem for both patients and healthcare providers. Various types of cognitive problems have been recorded, including issues with memory, attention, information processing speed, executive function, mental flexibility, and visuoconstruction ability[4,6]. The most commonly noted cognitive deficits are in the areas of information processing speed[7-11] and working memory[12-14].

Many studies[15,16] have suggested that vitamin D plays a role in MS, and a vitamin D deficit is considered one of the risk factors of the disease. Observational studies have showed that MS patients have significantly lower levels of vitamin D than healthy controls and that higher vitamin D levels can decrease the risk of MS[17,18]. In early clinical trials, vitamin D replacement therapies have showed promising results as complementary treatments to enhance cognitive function in patients with MS and other neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease[19,20]. Studies[21,22] in Saudi Arabia have suggested that 28 to 80% adults have a vitamin D deficiency.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a nonverbal, valid, reliable neuropsychological battery used to test different cognitive domains: visuospatial memory, attention, and working memory and planning[23,24]. It has marked sensitivity and specificity in identifying memory deficits in elderly subjects[25,26]. As it is taken using a simple touchscreen, the CANTAB requires no computer experience, giving no advantage to those familiar with advanced technology[27]. The CANTAB has proven valid in several countries with different cultures, making it a good choice for assessing pathological changes in cognition in patients with MS[24,28-30].

The aim of this study is to investigate the relationship between vitamin D levels and cognitive function in patients with MS as assessed by the CANTAB.

Patient and Methods

Study Design

This study is a quantitative, observational, cross-sectional study conducted in inpatient and outpatient clinics at the King Saud University Medical City (KSUMC). We recruited 39 patients with MS using convenience sampling.

The participants include patients with MS who live in Saudi Arabia and have visited the KSUMC. Participants' ages ranged from 16 to 60, and all participants received a vitamin D level assessment within three months of the cognitive assessment. Patients who had experienced a relapse in the previous three months and those who had neurological diseases that are known to affect cognition were excluded from the study. The Institutional Review Board King Saud University approved the study protocol. All methods were performed in accordance with the relevant guidelines.

Data Collection Methods

Five types of data were collected: demographic information, a disease steps scale rating, a PHQ-9 scale rating, vitamin D level, and a computerized cognitive assessment. The investigators met the neurology patients during admission to clinics and day care units. During the initial interviews, the participants were asked to fill out a validated Arabic-language PHQ-9 scale to assess depression. Next, participants provided demographic information and a disease steps score *via* a pre-structured questionnaire. Finally, each participant's cognitive function was assessed using the CANTAB. Vitamin D levels within three months of the interview were obtained from the participants' electronic medical records.

Cambridge Neuropsychological Test Automated Battery Tests

Motor Screening Task (MOT)

The MOT is a general measure of whether sensorimotor or comprehension difficulties limit the collection of valid data from a subject. In the task,

participants must touch a flashing cross that appears in different locations on a computer screen. The test's outcome measures are response speed and accuracy.

Pattern Recognition Memory (PRM)

The PRM is a test of visual pattern recognition and memory that uses a two-choice forced discrimination paradigm. During this test, a series of visual patterns appear in the center of the computer screen one at a time. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, participants must choose between a pattern they have already seen and a novel pattern. During this phase, the patterns are presented in the reverse order to the original order of presentation. The test is then repeated with new patterns. The second recognition phase can be administered immediately or after a delay. The test's outcome measures are latency (response speed) and the number and percentage of correct trials.

Spatial Working Memory (SWM)

SWM requires the retention and manipulation of visuospatial information. This self-ordered test measures executive function: the outcome measures are strategy use and errors. Firstly, during the test a number of colored squares (boxes) are shown on the screen. Participants touch the boxes and use a process of elimination to find one blue "token" in several boxes; these tokens are moved to an empty column on the right-hand side of the screen. The number of boxes gradually increases until the participant must search through eight boxes. The colors and positions of the boxes change in each trial to discourage the use of fixed search strategies. The test's outcome measures are errors (touching boxes that have been found to be empty and revisiting boxes from which the token has been collected), strategy, and latency.

Paired Associates Learning (PAL)

PAL assesses visual and episodic memory and new learning. It is an essential tool for accurately assessing individuals with possible dementia, mild cognitive impairment, Alzheimer's disease, and age-related memory loss. In this test, boxes are displayed on the screen and opened in a random order. Some of the boxes contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. If the participant makes an error, that pattern is presented again to remind the participant of its location. The difficulty level increases as the test progresses. In the clinical mode, the number of patterns increases from one to eight, which challenges even very able participants. This test has multiple outcome measures: errors, the number of trials required to correctly locate the pattern(s), memory, and stages completed.

Statistical Analysis

Data analyses were conducted using the statistical package SPSS for Windows, version 24 (IBM, Armonk, NY, USA). The $p<0.05$ value was considered to be statistically significant.

Results

Demographics and Vitamin D Levels

Of the 39 MS patients who participated in this study, 8 (20.5%) were male and 31 (79.5%) were female. Eighteen (46.2% of the participants) were under 30 years old, 8 (20.5%) were 30 to 39 years old, and 13 (33.3%) were over 39 years old. Two (5%) participants had less than a high school education, 12 (30.8%) had a high school education, 24 (61.5%) had a bachelor's degree, and only 1 (2.6%) had a higher degree. Twenty-five (64.1%) participants experienced MS onset before the age of 30, 9 (23.1%) patients experienced MS onset between age 30 and 39, and 5 (12.8%) experienced MS onset after the age of 39. Fourteen (35.9%) participants had experienced relapses in the previous 12 months; 25 (64.1%) had not experienced relapses. Of those who had experienced relapses, 12 (30.8%) participants had experienced one relapse in the previous 12 months and 2 (5.1%) had experienced two relapses in the previous 12 months. Four (10.3%) patients had never experienced a relapse requiring steroids, 12 (30.8%) had experienced a relapse requiring steroids less than one year before the study, 12 (30.8%) had experienced such a relapse in the previous one to three years, and 11 (28.2%) patients had not experienced such a relapse in more than three years. Participants' current treatment protocols were also included in the data. Nine (23.1%) patients were taking Interferon beta-1a, 2 (5.1%) were taking Interferon beta-1b, 5 (12.8%) were taking Fingolimod, 11 (28.2%) were taking Natalizumab, 4 (10.3%) were taking other treatments, and 8 (20.5%) were not taking any DMT. In addition, 7 (17.9%) participants had changed their treatment in the previous 24 months, and 32 (82.1%) had not. Twenty-five (64.1%) participants had insig-

Table I. Frequency distribution of demographic and clinical characteristics (N=39).

	Frequency	Percent
Gender		
Male	8	20.5%
Female	31	79.5%
Age		
<30 years	18	46.2%
30-39 years	8	20.5%
>39 years	13	33.3%
Level of education		
Less than high school	2	5%
High school	12	30.8%
Bachelor's degree	24	61.5%
Higher education (E.g. Master's degree, PhD)	1	2.6%
Age at onset		
<30 years	25	64.1%
30-39 years	9	23.1%
>39 years	5	12.8%
Number of relapses in the past 12 months		
None	25	64.1%
1	12	30.8%
2	2	5.1%
Period since last relapse		
Never had a relapse requiring steroids	4	10.3%
< 1 year	12	30.8%
1 - 3 years	12	30.8%
> 3 years	11	28.2%
Current treatment		
Interferon beta-1a	9	23.1%
Interferon beta-1b	2	5.1%
Fingolimod	5	12.8%
Natalizumab	11	28.2%
Others	4	10.3%
Not on any DMT	8	20.5%
Changing the treatment in the last 24 months		
No	32	82.1%
Yes	7	17.9%
Physical disability		
Insignificant	25	64.1%
Significant	14	35.9%
Disease step score		
Normal	17	43.6%
Mild disability	8	20.5%
Moderate disability	5	12.8%
Early cane	3	7.7%
Late cane	3	7.7%
Confined to wheelchair	3	7.7%
Vitamin D level		
Normal	17	43.6%
Low	22	56.4%

nificant physical disabilities due to MS, and 14 (35.9%) had significant physical disabilities.

Responses to the disease step scale were categorized into seven categories based on the patient's level of functional disability: normal, mild disability, moderate disability, early cane, late cane, bilateral support, confined to a wheelchair, and unclassifiable. Seventeen (43.6%) of the participants had normal scores on the disease step scale, 8 (20.5%) had mild disabilities, 5 (12.8%) had moderate disabilities, 3 (7.7%) scored early cane, 3 (7.7%) scored late cane, and 3 (7.7%) were confined to a wheelchair. Participants' vitamin D levels were measured as well; 17 (43.6%) of the MS patients had normal vitamin D levels, and 22 (56.4%) had low vitamin D levels (Table I and Table II).

Controls' and MS Patients' CANTAB Scores

On the CANTAB, the MOT mean latency and the MOT median latency for the attention and psychomotor speed did not differ significantly between the MS group and the control group ($t = 0.791$, $p > 0.05$; $t = 1.236$, $p > 0.05$, respectively). However, the MS group scored lower than the control group for the MOT mean error of the same domain ($t = -4.313$, $p < 0.01$). Moreover, the scores of the two groups differed significantly for all the subcategories of the memory domain. Furthermore, the control group scored higher than the MS group on PAL total errors (adjusted) ($t = -4.279$, $p < 0.01$), PAL total errors (6 shapes, adjusted) ($t = -3.975$, $p < 0.01$), and PRM percent correct ($t = -2.969$, $p < 0.01$). The control group scored lower than the MS group on SWM between errors and SWM strategy ($t = 2.725$, $p < 0.01$; $t = 4.194$, $p < 0.01$, respectively) (Table III).

Correlation Between CANTAB Subcategories in MS Patients and Other Demographic/Clinical Variables

The Pearson correlation analysis showed that not all the CANTAB subcategories correlated significantly with a demographic or clinical variable. As shown in Table IV, none of the CANTAB subcategories correlate with age, gender, level of education, age at onset, disease duration, time since last relapse, current treatment, change to treatment in the last 24 months, or depression ($p > 0.05$). Moreover, PAL total errors (6 shapes, adjusted) and PRM percent correct (memory domain) did not correlate with any of the variables ($p > 0.05$). However, in the attention and psychomotor speed domain, MOT mean latency and MOT median latency correlated with the number of relapses in the past 12 months ($r = -0.342$, $p < 0.05$; $r = -0.362$, $p < 0.05$), with the presence of relapses in the pre-

Table II. Descriptive statistics of major study variables.

Variable		Mean	SD
Vitamin D level categories	Normal	82.899	9.882
	Low	47.241	16.378
Vitamin D level value		62.784	22.588
Depression score		6	4.679

vious 12 months (r = -0.324, $p < 0.05$; r = -0.357, $p < 0.05$), and with physical disability (r = 0.426, $p < 0.01$; r = 0.421, $p < 0.01$). In addition, MOT mean error correlated with the disease steps score (r = 0.394, $p < 0.05$) and with physical disability (r = 0.457, $p < 0.01$). In the memory domain, PAL total errors (adjusted) correlated with age (r = 0.381, $p < 0.05$), and SWM between errors correlated with age at onset (r = 0.345, $p < 0.05$) and with vitamin D levels (r = 0.335, $p < 0.05$). SWM strategy correlated with number of relapses in the previous 12 months (r = -0.355, $p < 0.05$).

Correlation Between the Vitamin D Levels of MS Patients and Other Demographic/Clinical Variables

The Pearson correlation analysis indicated that vitamin D levels had no significant relationships with other demographic or clinical variables ($p > 0.05$) (Table V).

Correlation Between the Depression Scores of MS Patients and Other Demographic/Clinical Variables

There was no statistically significant correlation between the depression scores of MS patients and most of the demographic/clinical variables. However, MS patients' depression scores did correlate significantly with physical disability (r = 0.324, $p < 0.05$) and the disease steps score (r = 0.341, $p < 0.05$) (Table IV).

Discussion

Cognitive impairment is one of the most common manifestations of MS[6,7,11,28]. Recently, the

Table III. Comparison between Control group and MS patients according to CANTAB subcategories.

CANTAB			Mean	SD	Std. Error Mean	*t*
Attention and Psychomotor Speed	MOT Mean latency	MS patients	1257.56	576.42	92.30150	.791
		Control	1159.343	518.772	83.07014	
	MOT Median latency	MS patients	1168.923	600.724	96.19289	1.236
		Control	1014.987	494.288	79.14949	
	MOT Mean error	MS patients	9.212	3.576	.57272	-4.313**
		Control	12.224	2.494	.39936	
Memory	PAL Total errors (adjusted)	MS patients	31.026	31.519	5.04708	-4.279**
		Control	72.205	51.167	8.19328	
	PAL Total errors (6 shapes, adjusted)	MS patients	7.615	9.642	1.54405	-3.975**
		Control	17.846	12.859	2.05903	
	PRM Percent correct	MS patients	72.329	12.260	1.96311	-2.969**
		Control	81.106	13.802	2.21015	
	SWM Between errors	MS patients	47.717	21.945	3.51399	2.725**
		Control	34.051	22.352	3.57925	
	SWM Strategy	MS patients	36.512	7.247	1.16045	4.194**
		Control	26.359	13.267	2.12449	

** $p < 0.01$.

Table IV. Correlation between CANTAB categories and demographic/clinical variables.

CANTAB/other variables	Attention & Psychomotor Speed			Memory				
	MOT Mean latency	MOT Median latency	MOT Mean error	PAL Total errors (adjusted)	PAL Total errors (6 shapes, adjusted)	PRM Percent correct	SWM Between errors	SWM Strategy
Age	-.149	-.213	.081	.381*	.133	-.022	.308	.148
Age categories	-.173	-.245	-.013	.303	.034	.108	.288	.088
Gender	.232	.285	-.064	-.064	.054	-.150	.065	.097
Level of education	-.204	-.185	.003	.061	.113	-.221	-.230	-.151
Age at onset	-.037	-.114	-.023	.291	.134	.063	.345*	.146
Age at onset categories	-.081	-.168	-.018	.233	.043	.064	.272	.097
Disease duration	-.228	-.224	.195	.258	.036	-.148	.026	.045
Number of relapses in the past 12 months	-.342*	-.362*	-.212	.112	.304	.139	-.209	-.355*
Presence of relapses in the past 12 months	-.324*	-.357*	-.255	.015	.154	.128	-.148	-.218
Period since last relapse	-.131	.104	.081	.224	-.053	-.093	.011	.226
Current treatment	.132	.209	.152	-.042	.026	.101	.162	.254
Changing the treatment in the last 24 months	.072	-.091	-.089	-.297	-.110	.012	-.127	-.065
Depression score	-.223	-.208	-.246	-.250	-.307	.115	-.009	-.082
Disease steps score	.285	.252	.394*	-.065	-.133	-.173	-.027	-.008
Physical disability	.426**	.421**	.457**	-.047	-.071	-.221	.052	.036
Vitamin D level categories	.148	.207	.075	.049	-.003	.073	.335*	.244

** $p< 0.01$. * $p< 0.05$.

use of computerized neuropsychological testing, such as the CANTAB, has revealed that MS patients perform poorer on such tests than healthy controls[28,30]. Our study was designed to compare the cognitive abilities of MS patients to those of healthy controls using the CANTAB. Our findings confirm that MS patients perform more slowly on cognitive tasks than healthy controls. However, the conventional outcome measures of the CANTAB do not distinguish between non-specific reductions in performance efficiency and more specific abnormalities in higher cognitive functions, such as difficulties with working memory and executive tasks.

Cognition is the sum of intellectual functions that result in thought. It includes receiving external stimuli, processing information, learning, storing information, and expressing ideas. A disturbance to even one of these functions can disrupt normal thought production and present as cognitive dysfunction, which is perhaps most easily observed on sensitive, timed measures of performance[7,9,11] and has been reported in 20 to 80% of patients with MS[3,5]. This wide variation might be due to multiple factors, including the heterogeneity of patients and the use of different assessment methods. Our study focused primarily on the detailed evaluation of cognitive patterns among patients with MS.

In the current study, we found that patients with MS performed significantly worse than healthy controls on executive function and memory tasks as assessed by the PAL and SWM tests, respectively. These results are similar to those of previous studies[10,28]. The most prevalent pattern of cognitive impairment in patients with MS is the

"subcortical" type, which frequently affects executive function, information processing speed, and verbal fluency[11]. These cognitive dysfunctions could be due to disruptions of the white matter neural circuits that connect subcortical structures and the prefrontal cortex. We also found that the MS group performed significantly worse than the healthy controls on total recall and learning (assessed by PAL). However, this is not common with the subcortical type of cognitive dysfunction. We also observed that the MS subjects experienced greater difficulty with information acquisition than with retrieval[31]. However, in the assessment of higher cognitive functions, this difference does not distinguish between reduced sensorimotor efficiency and impaired mental processing.

The MOT and SWM are sensitive to processing speed and attention, which can be impaired in MS patients; previous studies[8,9] have shown significant SDMT changes over five to ten years, particularly in progressive MS subtypes. Not surprisingly, given their short disease duration, the MS participants in this study had normal scores on the PAL and SWM. This is unsurprising since processing speed predicts performance on visuospatial learning and memory tests[11]. The CANTAB has been used in previous cross-sectional and longitudinal studies to evaluate cognitive performance in MS patients[28,30].

In our study, patients with MS and healthy controls did not score differently on the depression scale, as assessed by the BDI. Moreover, there was no statistically significant correlation between depression scores and the other psychometric tests.

Since delayed recall is a more demanding process, this could indicate that the effect of 25(OH) D plays an important role in long-term, demanding memory-related tasks. Interestingly, hippocampal neurons (necessary for delayed retrieval processes) express vitamin D receptors[17]. EDSS score were significantly higher and physical activity was significantly lower in the low vitamin D group than in subjects with normal vitamin D levels. The EDSS emphasizes mobility and walking, so MS patients with high disease severity as measured by the EDSS are less likely to leave their homes and get exposure to the sun. Moreover, low vitamin D levels correlate with greater disability and higher relapse rates in patients with MS[15].

The reported effects of vitamin D on cognitive function have primarily been demonstrated in animal studies[19,20]. Some studies[15,16] suggest that

Table V. Correlation between Vitamin D levels, Depression score and other demographic/clinical variables.

	Vitamin D level value	Vitamin D level categories	Depression score
Age	-.190	.027	.055
Age categories	-.194	-.011	.113
Gender	-.114	.190	-.124
Level of education	.071	.038	.142
Age at onset	-.279	.102	.059
Age at onset categories	-.165	.020	.101
Disease duration	.095	-.117	.008
Number of relapses in the past 12 months	.037	-.178	.047
Presence of relapses in the past 12 months	-.026	-.097	.023
Period since last relapse categories	.088	-.049	.148
Current treatment	-.192	.204	-.178
Changing the treatment in the last 24 months	.059	.142	.159
Physical disability	.174	.011	.324*
Disease steps score	.209	-.147	.341*
Depression score	-.043	.011	1

* $p < 0.05$.

low levels of serum 25(OH) D are associated with poor cognitive function, while others report no such association[18,19].

In our study, patients with MS had significantly lower vitamin D levels than the healthy controls. Previous research[31] suggests that vitamin D plays a substantial role in the activation of innate immunity, which subsequently results in the regulation of acquired immunity. A relationship between vitamin D deficiency and some autoimmune diseases, including MS, rheumatoid arthritis, and insulin-dependent diabetes mellitus, has been documented.

There are several possible explanations for the association between vitamin D levels and proper executive function. As mentioned previously, vitamin D (in addition to its receptors and 1, α-hydroxylase) enhances neuroprotection through its effects on proinflammatory cytokines, which contribute to cognitive decline and dementia[18,20]. Moreover, vitamin D appears to regulate intraneuronal calcium homeostasis *via* voltage-gated calcium channels. As an antioxidant, vitamin D may provide neuroprotection from glutamate toxicity[21]. It is perhaps to be expected that MS patients would perform better on the CANTAB than patients with stable demyelinating disease. However, the relative frequency of abnormalities that do not primarily affect the central nervous system in patients with MS raises concerns about the presumed etiology of deficits detected by the CANTAB.

A single pattern of MS-associated cognitive dysfunction has not been identified, but common abnormalities include overall cognitive slowing, decreased attention, and impaired working memory and executive dysfunction (e.g., difficulties with multitasking, organization, and planning). Since most MS patients with cognitive impairment have relatively mild deficits, the careful selection and assessment of cognitive performance in control groups is of critical importance to define expected levels of function in healthy individuals and in those with chronic diseases other than MS.

Limitations

The current study has several limitations. First, the study sample was not matched for potential confounders of education and ethnicity. Second, no formal neuropsychological assessments or neuroimaging methods were used to look for clinical behavioral and neuroanatomical correlates of the abnormalities identified by the CANTAB. More stringent specifications would lead to a smaller sample size, but inclusion of both variables in the multiple regression models for all analyses would partially compensate for this. Third, traditional neuropsychological testing was not performed to look for clinical behavioral correlates of the abnormalities found by the CANTAB. The small number of participants and the lack of correlation between vitamin D levels and immunosuppressant therapies and their impact on cognitive performance are important limitations of this study. Finally, the patients and controls did not undergo repeat CANTAB testing to determine if the detected differences would remain stable over time.

Although the CANTAB does not measure complex aspects of memory, language, or visuospatial functions, factor analyses have demonstrated that the CANTAB and traditional neuropsychological tests measure similar underlying cognitive domains, including processing speed, working memory, and resistance to interference[28,30].

Conclusions

To our knowledge, this is the first study to assess the relationship between vitamin D levels and multiple sclerosis using automated neuropsychiatric testing in our population. Further studies could assess the effect of vitamin D supplementation on cognitive functions using automated neuropsychiatric testing. What is the role of the CANTAB in assessing cognitive complaints in MS patients? The CANTAB cannot be used to measure impairment in specific cognitive domains, and it is not designed to substitute for formal neuropsychological assessments. Future studies must determine its role in screening for cognitive impairment in MS patients. Its value in the evaluation of changes in MS patients' cognitive performance over time may lie in its sensitivity, which was evident in ours and previous studies, but this will require longitudinal assessment, ideally with concurrent neuropsychological and neuroimaging investigations. However, our findings suggest that improving cognition early in the course of the disease with a simple intervention, such as vitamin D_3 supplementation could make a significant difference in the quality of life of patients with MS.

Acknowledgements
The authors thank the volunteers who participated in the study.

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FA, MA and SB conceived and designed the study. MA, AA, MA, LA conducted data gathering. FA, MA and SB performed statistical analyses. FA, MA, AA, MA, LA and SB wrote the article.

Funding Information

Dr. Fawaz was supported through the Deanship of Scientific Research at King 194 Saud University for funding this work through research group No (RG- 1438-089).

Conflict of Interest

The Authors declare that they have no conflict of interests.

Data Availability

All data are available with reasonable request to corresponding author.

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