

Masaaki Niino<sup>a</sup>, Shoko Fukumoto<sup>b</sup>, Tatsusada Okuno<sup>c</sup>, Nobuo Sanjo<sup>d</sup>, Hikoaki Fukaura<sup>e</sup>, Masahiro Mori<sup>f</sup>, Takashi Ohashi<sup>g</sup>, Hideyuki Takeuchi<sup>h</sup>, Yuko Shimizu<sup>i</sup>, Juichi Fujimori<sup>j</sup>, Izumi Kawachi<sup>k</sup>, Jun-ichi Kira<sup>b</sup>, Eri Takahashi<sup>a</sup>, Yusei Miyazaki<sup>a</sup>, Nobuhiro Mifune<sup>l</sup>

a. Department of Clinical Research, National Hospital Organization Hokkaido Medical Center, Sapporo, Japan  
 b. Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan  
 c. Department of Neurology, Osaka University Graduate School of Medicine, Suita, Japan  
 d. Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Tokyo, Japan  
 e. Department of Neurology, Saitama Medical Center, Saitama Medical University, Saitama, Japan  
 f. Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan  
 g. Department of Neurology, Tokyo Women's Medical University Yachiyo Medical Center, Chiba, Japan  
 h. Department of Neurology and Stroke Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan  
 i. Department of Neurology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan  
 j. Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan  
 k. Department of Neurology, Brain Research Institute, Niigata University Medical Education Center, Niigata University School of Medicine  
 l. School of Economics and Management, Kochi University of Technology, Kochi, Japan

## Abstract

**Background:** This study aimed to evaluate the association between cognitive impairment and health-related quality of life (HRQOL), fatigue, and depression in Japanese patients with multiple sclerosis (MS).

**Methods:** The Brief International Cognitive Assessment for MS (BICAMS) was performed in 184 Japanese patients with MS. The Functional Assessment of MS (FAMS), Fatigue Severity Scale (FSS), and Beck Depression Inventory-Second Edition (BDI-II) were used to evaluate HRQOL, fatigue, and depression, respectively.

**Results:** Multiple linear regression analysis demonstrated positive correlations of the Symbol Digit Modalities Test (SDMT) with the scores on the FAMS subscales of mobility, symptoms, emotional well-being, and additional concerns and with the total FAMS score even after controlling for the Expanded Disability Status Scale score, age at examination, and duration of education. The SDMT score in the BICAMS battery had negative correlations with the BDI-II score, as revealed by multiple linear regression analysis. None of the three tests in the BICAMS had any correlation with the FSS score.

**Conclusion:** The SDMT has a significant relationship with HRQOL and depression in Japanese patients with MS.

## Background and Objectives

The objective of the present study was to examine the impact of cognitive impairment on QOL, fatigue, and depression measures in Japanese patients with MS.

## Methods

The present study was conducted between December 2019 and May 2021 and included 184 Japanese patients with MS (Table 1) from 11 sites in Japan (Kyushu University, Osaka University, Tokyo Medical and Dental University, Saitama Medical University, Chiba University, Tokyo Women's Medical University Yachiyo Medical Center, Yokohama City University, Tokyo Women's Medical University, Tohoku Medical and Pharmaceutical University, Niigata University, and Hokkaido Medical Center). The study comprised patients diagnosed with clinically isolated syndrome or MS according to the 2017 revised McDonald criteria (Thompson et al., 2018) and those with MS who experienced relapse within one month before the examination were excluded from the study.

### Battery for neuropsychological evaluation, fatigue, and depression

- Assessment of cognition  
 The Japanese version of the Brief International Cognitive Assessment for MS (BICAMS) was used to evaluate cognitive function. The BICAMS comprises a battery of three individual tests: Symbol Digit Modalities Test (SDMT) to assess cognitive processing speed, first five recall trials of the second edition of the California Verbal Learning Test (CVLT2) to assess auditory/verbal learning and memory, and first three recall trials of the revised Brief Visuospatial Memory Test (BVMTR) to assess visual or spatial memory.

- Assessment of QOL  
 The FAMS, a MS-specific measure for QOL, was used in the present study. The FAMS comprises seven subscales (mobility, symptoms, emotional well-being, general contentment, thinking/fatigue, family/social well-being, and additional concerns), with a total of 58 items. Each item is scored on a 5-point scale (ranging from "not at all" to "very much") to produce a score between 0 and 4 for each item.

- Assessment of fatigue  
 Fatigue in patients with MS was previously examined using the Fatigue Severity Scale (FSS), a 9-item scale which measures the severity of fatigue and its correlation with the activities and lifestyle of patients with a variety of disorders. The FSS, originally devised for patients with MS or systemic lupus erythematosus, has been designed to differentiate fatigue from clinical depression, since they share some of the symptoms.

- Assessment of depression  
 The Beck Depression Inventory-Second Edition (BDI-II), which comprises 21 items rated on a scale from 0 to 3, is a valid and reliable measure of depression.

**Statistical analysis**  
 Statistical analyses were performed using the SAS 9.4 (SAS Institute, Cary, NC, USA). First, means, SDs, and zero-order correlations were calculated for each variable using raw data from each BICAMS test (SDMT, CVLT2, and BVMTR), each subscale (mobility, symptoms, emotional well-being, general contentment, thinking/fatigue, family/social well-being, and additional concerns), and total FAMS, FSS, and BDI-II scores. Next, multiple linear regression analyses were performed using each subscale score and the total FAMS, FSS, and BDI-II scores as dependent variables and scores of individual BICAMS tests and EDSS, age at examination, and duration of education as independent variables. EDSS score, age at examination, and duration of education were also used as control variables. P values of <0.05 were considered to indicate statistical significance.

## Demographic and clinical profiles for patients with MS

N (female/male)	184 (135/49)
Age at examination (years) (range)	41.5 ± 10.5 (17–74)
Education* (years) (range)	14.2 ± 1.8 (9–19)
Age at onset (years) (range)	30.6 ± 10.1 (12–63)
Disease duration (years) (range)	10.9 ± 7.8 (0.5–41)
EDSS (range)	2.5 ± 2.0 (0–7.5)
MSSS (range)	3.22 ± 2.63 (0.04–9.74)
<b>Clinical course</b>	
Primary progressive	5
Clinically isolated syndrome	1
Relapsing–remitting	147
Secondary progressive	31
<b>Disease-modifying drug at examination</b>	
Interferon	19
Glatiramer acetate	14
Dimethyl fumarate	51
Fingolimod	57
Natalizumab	16
Ofatumumab	1
Rituximab	1
Prednisolone	2

## Results

Table 2. BICAMS, FSS, and BDI-II scores in 184 patients with MS

BICAMS	
SDMT	53.0 ± 15.5 (5–88)
CVLT2	49.8 ± 13.3 (16–76)
BVMTR	25.6 ± 7.7 (1–36)
FAMS	
Mobility	18.4 ± 7.1 (0–28)
Symptoms	20.2 ± 5.8 (3–28)
Emotional well-being	19.6 ± 6.7 (1–28)
General contentment	16.0 ± 5.9 (4–28)
Thinking/fatigue	21.0 ± 8.8 (0–36)
Family/Social well-being	17.5 ± 5.9 (2–28)
Total FAMS score	112.8 ± 31.1 (36–174)
Additional concerns	38.4 ± 7.9 (18–54)
FSS	37.6 ± 13.5 (9–63)
BDI-II	15.4 ± 10.6 (0–48)

Table 3. Multiple linear regression analysis of the relationship of BICAMS with total and subscale scores of FAMS

FAMS	Parameter	Partial regression coefficient	Standard error	Standardized partial regression coefficient	t value	P value
Mobility	SDMT	0.08	0.04	0.17	2.05	<0.05
	CVLT2	0.02	0.04	0.03	0.38	n.s
	BVMTR	-0.10	0.08	-0.11	-1.37	n.s
Symptoms	SDMT	0.09	0.04	0.24	2.20	<0.05
	CVLT2	-0.06	0.04	-0.14	-1.41	n.s
	BVMTR	-0.07	0.08	-0.09	-0.84	n.s
Emotional well-being	SDMT	0.13	0.05	0.31	2.83	<0.01
	CVLT2	-0.04	0.05	-0.09	-0.88	n.s
	BVMTR	-0.01	0.10	-0.01	-0.08	n.s
General contentment	SDMT	0.02	0.04	0.04	0.38	n.s
	CVLT2	0.00	0.05	0.00	0.00	n.s
	BVMTR	0.10	0.09	0.13	1.13	n.s
Thinking/fatigue	SDMT	0.09	0.06	0.17	1.60	n.s
	CVLT2	-0.12	0.06	-0.18	-1.87	n.s
	BVMTR	0.10	0.12	0.09	0.82	n.s
Family/social well-being	SDMT	0.02	0.04	0.06	0.53	n.s
	CVLT2	0.01	0.05	0.02	0.15	n.s
	BVMTR	0.01	0.09	0.01	0.09	n.s
Total	SDMT	0.43	0.20	0.22	2.14	<0.05
	CVLT2	-0.20	0.22	-0.09	-0.93	n.s
	BVMTR	0.02	0.41	0.01	0.06	n.s
Additional concerns	SDMT	0.13	0.05	0.26	2.45	<0.05
	CVLT2	-0.07	0.06	-0.12	-1.16	n.s
	BVMTR	-0.04	0.11	-0.03	0.32	n.s

Table 4. Multiple linear regression analysis of the relationship of BICAMS with FSS and BDI-II scores

	Parameter	Partial regression coefficient	Standard error	Standardized partial regression coefficient	t value	P value
FSS	SDMT	-0.04	0.10	-0.04	-0.37	n.s.
	CVLT2	0.14	0.11	0.14	1.35	n.s
	BVMTR	-0.04	0.20	-0.02	-0.20	n.s
BDI-II	SDMT	-0.28	0.07	-0.41	-3.85	<0.001
	CVLT2	0.16	0.08	0.20	1.98	<0.05
	BVMTR	-0.01	0.15	-0.00	-0.04	n.s

## Conclusion

The SDMT has a significant relationship with HRQOL and depression in Japanese patients with MS.