The BICAMS Battery for Assessment of Lithuanian-Speaking Multiple Sclerosis Patients: Relationship with Age, Education, Disease Disability, and Duration

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Background: Assessment of cognitive impairment (CI) in multiple sclerosis (MS) patients is very useful, but it requires time-consuming expert evaluation with specialized materials. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was created as a brief and specific instrument for the evaluation of CI.
The aims of this study were to assess the cognitive status of MS patients by using the Lithuanian version of BICAMS, to evaluate the test-retest reliability of the Lithuanian version of BICAMS, and to measure the impact of CI on disability and duration of MS.

Material/Methods: We enrolled 50 MS patients and 20 cognitively normal control subjects, matched for age, gender, and level of education. Cognitive functions were assessed by the BICAMS tests, which include the Symbol Digit Modalities Test, the Brief Visuospatial Memory Test Revised, and the California Verbal Learning Test, 2nd edition.

Results: MS patients performed significantly worse than controls on the 3 neuropsychological tests of BICAMS ($p < 0.001$). Younger and intellectually employed persons performed significantly better on these tests than older persons, manual workers, or unemployed persons ($p < 0.05$). MS patients with higher disability scores tended to perform worse on the tests ($p < 0.05$), but we found no relationship between BICAMS test scores and the duration of the disease or relapse rate ($p > 0.05$). Test-retest reliability was excellent for all 3 subtests ($r > 0.8$, $p < 0.05$).

Conclusions: Our study shows that BICAMS is a valid and acceptable cognitive assessment tool that can be recommended for routine use in Lithuania for assessing patients with MS.

MeSH Keywords: Cognition Disorders • Multiple Sclerosis • Neurobehavioral Manifestations • Neuropsychological Tests

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Background

Multiple sclerosis (MS) is a progressive, chronic, demyelinating, neurodegenerative disease affecting the central nervous system (CNS). MS can cause a wide range of symptoms, including decline of cognitive abilities [1,2]. Cognitive impairment (CI) in MS patients substantially impacts the lives of the patients and their families [3]. Half to three-quarters of people with MS are unemployed within 10 years of diagnosis [4]. CI is the leading predictor of occupational disability, while physical disability, age, sex, and education account for less than 15% of the likelihood of being employed [5]. Therefore, the assessment and follow-up of cognitive status, as well as treatment (in case of deterioration), should be as much a priority as is the evaluation and treatment of physical disability [6–8].

Studies on the prevalence of CI in MS patients show that CI occurs in up to 70% of MS patients [3,9]. It involves all the subtypes of MS and often is found in early stages of MS, even in case of clinically and radiologically isolated syndromes. Often the degree of the impairment can be mild and patients may not be fully aware of it [10,11].

MS adversely affects various aspects of cognitive functioning. The cognitive domains affected first in MS seem to be information processing efficiency and speed, episodic memory, and higher executive functioning [3,12,13]. Areas of cognition that are not usually affected are "simple" attention (e.g., repeating digits) and essential verbal skills (e.g., word naming and comprehension). Although most studies indicate that general intelligence remains intact in patients with MS, other investigations have detected slight but significant decreases. Overt dementia is rare in MS, and the most common clinical presentation is specific and subtle cognitive deficits that can vary substantially among patients [3,13–16].

In recent decades the assessment of cognitive decline related to MS has received increasing attention. Many different neuropsychological batteries have been proposed. Among the most frequently used instruments is the Brief Repeatable Battery of Neuropsychological tests (BRB-N) [17]. Another popular assessment instrument is the Minimal Assessment of Cognitive Function in MS (MACFIMS) [18,19]. While both batteries are known to be highly specific for the evaluation of CI in MS patients, their implementation in everyday clinical practice remains limited due to their high time demand (BRB-N requires 45 minutes and MACFIMS requires approximately 90 minutes to perform) and the need for surveillance and interpretation by proficient neuropsychologists [17–20]. Due to these limitations, there have been considerable efforts made over the past decade to create a simpler but specialized neuropsychological instrument for the assessment of CI in MS patients; the result is the BICAMS battery. The BICAMS battery is very short and highly sensitive. It is easily

administered (the time needed for full assessment is 15 minutes). BICAMS does not require any special equipment or training and the battery may be conveniently used in everyday clinical practice. It is convenient for neurologists dealing with a small number of MS patients and MS practices with very few staff neurologists, without specialized neuropsychological training [21,22].

The objective of our study was to evaluate the cognitive status of MS patients by use of the Lithuanian translation of the BICAMS, to check the test-retest reliability of BICAMS, and to evaluate the relationship between the CI assessed with BICAMS, physical disability, MS duration, and relapse rate.

Material and Methods

Our clinical research study was initiated at the Neurology and Neurosurgery Clinic, Faculty of Medicine at Vilnius University, Vilnius University Hospital Santariskiu Clinics, Department of Neurology from 2014 to 2015. The study protocol was approved by the Lithuanian Bioethics Committee and written informed consent was obtained from each study participant.

Study population

A total of 70 subjects were enrolled in the study: 50 patients with MS treated at the Vilnius University Hospital Santariskiu Clinics, and 20 control group participants matched for age, gender, and years of education (Table 1). MS patients were recruited cross-sectionally and there was no pre-selection applied for CI.

Inclusion criteria for MS patients were:
- Willing and able to sign written informed consent;
- MS diagnosed based on the revised McDonald criteria (2010 Revisions);
- Subjects older than 18 years of age;
- Neurologically stable MS patients, with no evidence of relapse, and steroids- and/or plasmapheresis-free for at least 4 weeks preceding the enrollment;
- The patients are proficient in the Lithuanian language.

Exclusion criteria for MS patients were:
- Evidence of any neurological or psychiatric disorder other than MS, not limited to major head trauma, seizures, or systemic medical diseases, that are likely to affect cognitive functioning;
- History of learning disability;
- Any vision or hearing problems that could influence performance on the tests;
- Patients currently receiving or having taken any other cognition-enhancing medication (e.g., antidepressants, neuroleptics, and anticholinergic drugs) within the 6 months prior to enrollment;
- Current or past alcohol or drug abuse.

Table 1. Demographic characteristics in participant groups.

	MS patients	Control group	p
Number of subjects, N	50	20	–
Gender, Women/Men, N	16/34	5/15	0.774
Age (years), mean ±SD	38.8±10.2	36.7±16.4	0.606
Education (years), mean ±SD	15.9±2.8	17.5±3.5	0.100
Duration of the disease (years), mean ±SD	11.7±9.2	–	–
EDSS score, mean ±SD	3.3±1.3	–	–
The mean number of exacerbation per year, mean ±SD	1.8±2.0	–	–

The course of the disease, N (%):
  RRMS
  SPMS
  PPMS
  CIS
	
	44 (88.0%)
	3 (6.0%)
	1 (2.0%)
	2 (4.0%)
		
		–
		
			–

EDSS – *Expanded Disability Status Scale*; RRMS – relapsing remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis; PP – primary progressive multiple sclerosis; CIS – clinically isolated syndrome.

The CG included healthy persons with no history of any cognitive dysfunction, with sight and hearing sufficient for compliance with the study assessment and proficient in the Lithuanian language.

Within the patient group (n=50, 68.0% were women) average age was 38.8±10.2 years, with time from MS onset 11.7±9.2 years, EDSS (Expanded Disability Status Scale) score 3.3±1.3, and 15.9±2.8 years of completed education. Patients in the MS group had relapsing-remitting MS (RRMS, 88.0%), secondary-progressive MS (SPMS, 6.0%), primary-progressive MS (PPMS, 2.0%), and clinically isolated syndrome (CIS, 4.0%).

Patients were compared with 20 healthy participants in the control group (CG, 75.0%) with a mean age of 36.7±16.4 years and 17.5±3.5 years of education. CG participants were recruited from the relatives of, and persons accompanying, the patients attending the Neurology Department, with no history of cognitive dysfunction.

Neuropsychological tests and procedures

All subjects were examined by the same person and the tests were administered in the same sequence: the Symbol Digit Modalities Test (SDMT) [23]; the Brief Visuospatial Memory Test Revised (BVMT-R), first 3 recall trials [24]; and the California Verbal Learning Test, 2nd Edition (CVLT-II), first 5 trials [25].

SDMT is used for evaluation of information processing speed in MS patients. It presents a sequence of 9 symbols. Any 1 of these symbols is paired with a single digit in the upper part of the page.

The working area of the page contains the pseudo-randomized sequence of these symbols. Tested participants respond by saying the digit, which is paired with the appropriate symbol at the top of the page, as quickly as possible. The indicator of performance is the total number of correct pairings in 90 seconds [23].

BVMT-R is a test to evaluate visuospatial memory and learning. A group of 6 simple figures are shown to the participants for 10 seconds. After the presentation of the visual stimulus figures, participants try to draw the correct figures using a pencil on a sheet of paper. The test time is not limited. Each figure reproduced by a participant may be scored 0, 1, or 2 based on the scoring criteria for accuracy and location. The indicator of performance is total recall score in all 3 trials [24].

CVLT-II is a tool for measuring verbal memory and learning. The initial 5 trials were used to evaluate the ability of a participant to learn a 16-word list. The 16-word list is read aloud by the investigator. After the full list has been read, the participants are asked to repeat as many words as they can remember. The entire list of words is read aloud by the investigator during each trial. The indicator of performance is the total number of words recalled during all 5 learning trials [25].

This is the first study of the Lithuanian version of the BICAMS scale. BICAMS was translated and adapted into the Lithuanian language. The CVLT-II list of words was translated and retranslated from English to Lithuanian by a professional translator whose native language was Lithuanian. The words in English and Lithuanian lists were matched for frequency and semantic similarity.

Table 2. The mean scores of BICAMS comparing patients with MS and control group.

	MS patients	CG	p
SDMT, mean ±SD	42.7±13.9	57.7±11.5	<0.001
BVMT-R, mean ±SD	23.1±7.0	29.6±4.1	<0.001
CVLT-II, mean ±SD	55.9±10.0	65.7±5.9	<0.001

CG – control group; SDMT – Symbol Digit Modalities Test; BVMT-R – Brief Visuospatial Memory Test revised; CVLT-II – California Verbal Learning test, 2nd edition.

Table 3. The mean BICAMS scores in individual MS and CG subgroups.

		SDMT	BVMT-R	CVLT-II	p
MS	Men (N-16)	40.4±12.8	23.1±7.2	52.5±10.9	>0.05
	Women (N-34)	43.1±14.0	23.1±7.1	57.5±9.3	
CG	Men (N-5)	55.6±10.3	30.4±3.6	65.6±5.9	>0.05
	Women (N-15)	58.4±12.1	29.3±4.3	65.7±6.1	
MS	Intellectual work (N-27)	48.7±10.0	25.3±5.7	60.5±8.5	<0.05
	Physical work/unemployment (N-23)	35.0±13.4	20.4±7.6	50.5±9.1	
CG	Intellectual work (N-15)	60.7±11.8	31.1±2.8	68.1±3.0	<0.05
	Physical work/unemployment (N-5)	48.8±2.6	25.0±4.2	58.4±6.6	
MS	Higher education (N-28)	45.4±12.2	24.5±6.9	60.9±7.2	p (SDMT, BVMT-R) >0.05 p (CVLT-II)<0.05
	Less than higher education (N-22)	38.3±14.2	21.2±7.0	49.5±9.5	
CG	Higher education (N-15)	60.7±11.8	30.6±3.0	67.5±4.2	<0.05
	Less than higher education (N-5)	48.8±2.6	26.4±5.6	60.2±7.3	
MS	Age, up to 35 y. (N-23)	48.2±11.7	26,5±4,9	60.7±8.9	<0.05
	Age, above 36 y. (N-27)	37.3±13.1	20.1±7.4	51.8±9.2	
CG	Age, up to 35 y. (N-12)	64.8±9.0	32.1±2.0	68.7±3.0	<0.05
	Age, above 36 y (N-8)	47.1±4.1	25.8±3.4	61.2±6.5	
MS	EDSS (0-3.0) (N-28)	47.0±12.3	25.1±5.8	59.3±8.2	<0.05
	EDSS (3.5-5.0) (N-19)	39.3±11.0	20.9±8.0	52.5±10.6	p (SDMT,) <0.05 p (BVMT-R, CVLT-II) >0.05
	EDSS (5.0-10.0) (N-3)	18.0±7.6	17.3±3.8	45.7±10.8	

CG – control group; SDMT – Symbol Digit Modalities Test; BVMT-R – Brief Visuospatial Memory Test revised; CVLT-II – California Verbal Learning test, 2nd edition.

Statistical analysis

Comparisons between groups were performed using paired-sample t-tests and the Mann-Whitney U test for continuous variables where appropriate. The chi square test was used for categorical variables. Normal distribution of data was verified using the Shapiro-Wilk test. Multinomial logistic regression was performed to evaluate associations among the individual neuropsychological tests, education status, disability level, duration of the disease, and the relapse rate. Correlation of BICAMS test-retest scores was evaluated by Pearson correlation coefficient r.

Statistical analysis was done using SPSS 20.0 software. The statistical significance value was set at p<0.05.

Table 4. The impact of education and disease activity on the BICAMS results.

		SDMT	BVMT-R	CVLT-II	p
Education (years) (B)	MS	2.4	1.0	2.4	<0.05
	CG	2.0	0.9	1.2	
EDSS (B)		−5.9	−2.3	−3.7	<0.001
Duration of the disease (years) (B)		−0.3	−0.2	−0.2	>0.05
The total number of the relapses (B)		−1.1	−0.5	0.1	>0.05

B – the regression coefficient; CG – control group; SDMT – Symbol Digit Modalities Test; BVMT-R – Brief Visuospatial Memory Test revised; CVLT-II – California Verbal Learning test, 2nd edition; EDSS – *Expanded Disability Status Scale.*

Results

Mean scores of all 3 cognitive tests (SDMT, BVMT-R, and CVLT-II) were significantly higher in the CG than in MS patients. The most affected cognitive domain in MS patients was information-processing speed; the mean SDMT test score was 15 points higher in the CG than in MS patients. The least-affected cognitive domain was verbal learning and memory domain; the mean CVLT-II score was 9.8 points higher. The least-affected domain was visuospatial memory; the mean BVMT-R score was 6.5 points higher in healthy controls (Table 2).

Older (over 35 years old) and unemployed MS and CG subjects tended to perform worse on all tests than younger and intellectually employed persons (p<0.05). CG subjects with higher education performed better on all 3 tests (p<0.05) than subjects with lower education; however, MS patients with higher education performed better only on the CVLT-II test, and the results of SDMT and BMVT-R tests did not differ from the results of MS patients with less education (Table 3). We assessed the impact of age, education level, and employment status on the individual cognitive status by examining the regression model between the BICAMS battery and values mentioned above. The results of all 3 tests were influenced by the level of education in MS patients and in the CG. The impact was greater in MS patients; when the duration of education was increased by 1 year, the results of SDMT and CVLT-II tests were increased by 2.4 points and BVMT-R results were increased by 1.0 point (Table 4). There was no statistical difference between performance on any neuropsychological test and the gender of MS patients and the group of healthy control participants (Table 3).

We divided the MS patients into 3 groups based on the EDSS disability score: low-disability (EDSS score up to 3.0 points, N=28), moderate-disability (EDSS score 3.5–5.0 points, N=19), and high-disability (EDSS scores above 5.5 points, N=3) MS patients. Lower level of disability was associated with better
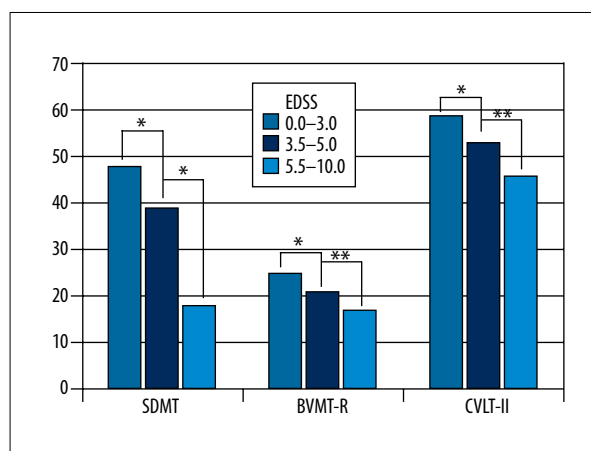

Figure 1. The association between disability severity and cognitive impairment. * p<0.05, ** p<0.05; SDMT – Symbol Digit Modalities Test; BVMT-R – Brief Visuospatial Memory Test revised; CVLT-II – California Verbal Learning test, second edition; EDSS – *Expanded Disability Status Scale.*

performance on all 3 tests. We found that the mean SDMT score decreased with increased disability (p <0.05). Mean scores of BVMT-R and CVLT-II tests were significantly lower in the moderate-disability group than in the low-disability group. Mean scores of BVMT-R and CVLT-II tests in the high-disability group were also lower than in the medium-disability group; however, the difference was not significant (p>0.05) (Figure 1). When the EDSS score was increased by 1 point, the results of the SDMT test decreased by 5.9 points, and the results of BVMT-R and CVLT-II decreased by 2.3 and 3.7 points. However, a clear relationship among severity of CI, MS duration, and relapse rate in MS patients was not found (Table 4).

Finally, Table 5 shows the correlations between the tests and the retests. Overall correlations were very strong: SDMT was 0.91, BVMT-R was 0.82, and CVLT-II was 0.81 (p=0.000).

Table 5. Test-retest reliability of the BICAMS tests.

	Test	Retest	r/p
SDMT	42.7±13.9	46.2±15.4	0.91/p<0.001
BVMT	23.1±7.0	24.1±7.2	0.82/p<0.001
CVLT-II	55.9±9.0	56.8±12.6	0.81/p<0.001

SDMT – Symbol Digit Modalities Test; BVMT-R – Brief Visuospatial Memory Test revised; CVLT-II – California Verbal Learning test, 2nd edition.

Discussion

It is obvious that the assessment of cognitive status and characterization of damaged domains are useful in every MS patient from the initial stages of the disease, and it is recognized that assessments and follow-ups should be as much as a priority as the evaluation of physical disability. However, the questions of how to observe the cognitive functions and which methods of observation to use in MS patients have remained unanswered. To diagnose cognitive decline and to perform follow-up in MS patients, it is important to select tests or batteries that are optimal, reliable, sensitive, simple, and convenient to use in everyday practice, which is why the BICAMS for assessing CI in MS patients has been suggested [21,22]. Translation and validation studies of the BICAMS battery are being performed in several countries and it undoubtedly has the potential to increase the accessibility of cognitive assessment in most small, non-specialized centers.

Here, we assessed the cognitive status of MS patients by use of the Lithuanian translation of the BICAMS and the impact of CI on the disability and duration of disease. We found significant differences (p<0.001) in all tests between the MS group and the CG group scores. We also found strong correlations (r>0.8, p<0.001) when assessing the test-retest reliability. With this method, we have shown that the Lithuanian version of the BICAMS battery is just as reliable as the original English version [21].

In this study, as expected, the level of disability, measured by the EDSS, was a significant predictor of the severity of CI; however, the duration of disease and the number of relapses did not independently predict performance on the cognitive tests. Several studies [26,27], which used more detailed assessments of cognitive functions and/or larger sample sizes were assessed, found a relationship between disease duration and severity of CI. In our study the smaller population and specific characteristics of the methodology may have influenced these results. However, it is likely that the longer disease duration is associated with the progression of disability.

This suggests that, in the context of growth in population size, disease duration and severity of disability most likely influence the severity of CI.

In comparing the results of this and other studies [26–28], we found that the mean scores of BVMT-R in MS patients and the CG and the mean score of SDMT in the CG in our study were similar, but the mean SDMT score in MS patients was 7–8 points lower than reported in other studies [28]. This difference could be influenced by the older age and/or longer duration of disease in our patients, as they were 4 years older. The mean duration of MS in our study was almost 4 years longer than in the other studies, but the differences in patient age and disease duration were different from those in our MS patients' CVLT-II results, which were 5 points higher than described in the other studies [28–30]. However, the results of our study and other studies suggest that Lithuanian MS patients have more damaged information-processing speed domain than persons of other nationalities, but verbal memory is more often preserved in our patients.

The Lithuanian version of BICAMS is a short, easily administered, and specific tool for clinical evaluation of CI in MS patients. Our findings suggest that the extent of MS disability is closely related to the severity of CI, as the progression of the disability has a negative impact on the cognitive state.

Conclusions

BICAMS is useful as a monitoring test for identifying MS patients with CI. The Lithuanian version of the BICAMS is as reliable as the original English version, and it will undoubtedly increase the accessibility for cognitive assessment in our small MS center.

Conflict of interest statement

No conflict of interest is declared.

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