Computerized Neuropsychological Test Battery CogniSoft for Assessment of Cognition in Patients with Multiple Sclerosis

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Abstract: *Cognitive dysfunction is a leading cause of disability in multiple sclerosis (MS) and is associated with unemployment, need of assistance with daily activities and poor quality of life. The introduction of neuropsychological testing and monitoring of cognitive status as part of the overall evaluation of MS patients in parallel with clinical and paraclinical parameters is highly recommended. Recent studies have demonstrated a better perception and preference for computerized cognitive tests than classic variants, with no significant difference in results. In accordance with global trends, a bilingual computer system CogniSoft for assessment and rehabilitation of cognitive status in persons with MS has been developed, including: 1) a set of diagnostic tests for evaluation of memory and executive functions based on the nature of Brief International Cognitive Assessment for MS (BICAMS); 2) a set of games for cognitive rehabilitation. Questionnaire for depression (Beck Depression Inventory – BDI-II) will be filled before conduction of the neuropsychological tests for differentiation of possible depression which could interfere with the results. The CogniSoft information system will incorporate two approaches for evaluation of neuropsychological results which will allow early detection of cognitive impairments in these patients, which will initiate timely cognitive rehabilitation.*

Keywords: *Computerized cognitive test, Multiple sclerosis, Cognitive impairment, Cognitive rehabilitation.*

Introduction

Multiple sclerosis (MS) is an autoimmune chronic inflammatory disease of the central nervous system with progressive course and social importance. It engages persons of working age and affects many neurological modalities, including high cortical functions. The physical and neuropsychological deficit could be manifested simultaneously or independently of each other [10].

Subsequent neurodegeneration and brain atrophy (both of the cerebrum and spinal cord)

further aggravate physical damage and impaired cognitive status in most patients. The course and progression of the disease are largely unpredictable, which is a great challenge for both patients and physicians, not only in terms of the therapeutic approach but also in the successful adaptation of patients to work and social environment [14].

The neuropsychological deficit in MS was found and described long ago by Charcot [8], who registered memory disorders, pathological laughter and crying, euphoria, mania, hallucinations and depression. It is surprising, however, that for many years these impairments have been neglected both in clinical practice and in research. Currently, they naturally attract the attention of more and more researchers, especially because according to literature data, cognitive impairment affects up to 70% of patients with MS [11, 15] and negatively affect all stages and all forms of the disease [23]. Cognitive dysfunction is a leading cause of disability in MS and is associated with unemployment [20], need of assistance with daily activities [21] and poor quality of life [32].

Most commonly deteriorated cognitive domain in MS population is speed of processing the information (20-50%) followed by violation of episodic memory (33-65%), and in lesser extent – attention (12-25%), executive functions (17-19%), visual perceptual functioning (up to 25%), while the language functions remain spared for a long time [10, 19, 23], without global cognitive decline [7].

Nowadays it is accepted that MS relapse could result only from decline in cognitive functioning that is associated with location of new MRI lesions in specific cortical and subcortical structures. The latter are the so-called isolated cognitive relapses that are associated with an increased risk of long-term deterioration of cognitive decline [26]. The rapid development of neuroimaging technologies provides reliable identification and tracking of such neuropathological findings. Psychometric procedures are being improved in parallel, making it possible to objectively evaluate cognitive abilities [3].

Although the cognitive impairment is an extremely important aspect of quality of life and an important determinant of employment, social functioning, and high social costs for these patients, it is not yet an emphasis in clinical practice and is difficult to detect during routine neurological examinations [23]. The detection of early changes in cognition requires a targeted neuropsychological study, which is unfortunately often overlooked in routine practice [22].

Neuropsychological status is currently being evaluated by a neurologist/neuropsychologist based on patients test results. The paper version of the tests is usually applied. This form of neuropsychological examination is time consuming, requires involvement of a qualified specialist during the study, making it difficult to archive and compare patient success rates. Until recently, testing of major neuropsychological domains takes about 90 minutes to administer extended neuropsychological tests designed for MS (Brief Repeatable Battery of Neuropsychological Tests [29] and Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) [5]). In 2012, Benedict and co-authors introduced the Brief International Cognitive Assessment for MS (BICAMS), which largely overcomes the restrictions mentioned above [4].

Worldwide, computer cognitive batteries are increasingly required to facilitate the integration of neuropsychological assessments into routine clinical practice in patients with MS and more accurately detect the presence of cognitive impairment [17]. Recent studies have demonstrated a better perception and preference for computerized cognitive tests than classic

variants [13], with no significant difference in results [24]. Their application avoids bias as a result of conducting the survey of various neurophysiologists, provides uniform administration and allows collection and statistical processing of large volumes of information [18]. This is extremely important because of the high inter-patient variability in cognitive test scores due to:

- variations in individual compensatory capacity (so-called cognitive reserve) [36];
- degree of physical disability as assessed by EDSS score [25];
- sex differences.

Analysis of results from large samples of MS patients show that gender is an important determinant of cognitive impairment, with men more likely to be impaired compared with women in verbal learning and memory tests [15]: (i) age characteristics [15, 33]; (ii) level of education [25, 33].

Materials and methods

In accordance with global trends, a bilingual computer system CogniSoft for assessment and rehabilitation of cognitive status in persons with MS has been developed, including:

- Questionnaire for depression (Beck Depression Inventory – BDI-II);
- A set of diagnostic tests for evaluation of memory and executive functions based on the nature of BICAMS;
- A set of games for cognitive rehabilitation.

The battery of tests for assessment the level of cognition consists of 3 tests, covering most vulnerabilnite neuropsychological domains in the disease – speed of information processing, episodic memory, visual perceptual performance, attention:

- *Diagnostic test, based on Symbol Digit Modalities Test* (*SDMT*);
- *Diagnostic test, based on Brief Visuospatial Memory Test* (*BVMT*);
- *Diagnostic test, based on California Verbal Learning Test* (*CVLT*);

The choice of the battery of diagnostic tests that evaluate cognitive status in patients with MS, is reasonable for the following reasons:

- High diagnostic value [16, 23].
- It is intended for international use. Minimizing cultural differences, it maximizes international use and cross-country comparability [16, 23, 35].
- Battery tests allow objective monitoring of cognition and evaluation of the effects of immunomodulating drugs and rehabilitation therapy.
- It is suitable for assessment of cognition in healthy subjects.
- The relatively short time span for its administration makes it convenient for physicians and patients and does not lead to cognitive fatigue that could affect the evaluation of results.
- Opportunity to conduct the tests at convenient time for the patient.
- Lack of need for assistance in most cases.

Symbol digit modalities test

SDMT was published in 1973 as a method for cognitive assessment in neurological diseases and was revised in 1982 [34]. SDMT is a well-known test that emerged in the world practice because of proven high susceptibility to cognitive impairment in MS and convenience of application – it only takes about 5 minutes for conduction and assessment. Its results correlate with the findings of magnetic resonance imaging (MRI) [27]. The lower SDMT test scores in MS correspond to the severity of diffuse abnormalities of the supratentorial pathways composed of white marrow, as well as atrophy of the right anterior cingulate gyrus, left postcentral gyrus, right temporal medial gyrus [30]. SDMT is used for measurement of attention and speed of information processing [28]. The test is independent of cultural differences as it involves only geometric figures and numbers and can be administered in any language.

Brief visuospatial memory test

BVMT is a short test for assessment of visual-spatial orientation and constructive praxis that also evaluates the episodic memory. Since its first edition, the test has been revised several times, with each new version showing increasing reliability and validity.

BVMT-R [2] can be used both as part of a large neuropsychological battery and as a screening tool for baseline cognitive level and for monitoring the changes in cognitive status over time. It is applicable in a wide age range (18-79 years). Because age has a significant impact on the results of this test, it is required to create norms in narrow age categories [33].

California verbal learning test

Rey Auditory Verbal Learning (RAVLT), developed by Andre Rey in 1964, is the basis of CVLT, created by Delis et al in 1987 [6]. CVLT is based on auditory perceived stimuli and is a reliable assessment tool for episodic verbal learning widely used in the worldwide neuropsychological practice. The test predicts the employment in long-term, it is effective in monitoring the advantages of treatment in MS and strongly correlates with MRI findings in regard to the lesion load and loss of volume of the gray matter [31]. Its validity in MS is supported by a large number of actual literary sources, which justifies its inclusion in the MACFIMS [5] and BICAMS [1]. CVLT allows further assessment of the individual strategies for learning as semantic, serial and subjective clustering in a requirement for learning [37]. It is designed for a wide age range, because similar to BVMT-R, the results of this test insignificantly vary with age [33].

Computer adaptation of neuropsychological tests

The proposed computer implementation provides easy technical performance of the tests from persons with MS. References to the scientific literature in the field suggest objectivity of results and insignificant difference in speeds compared to the classic paper version [9, 17].

Computer adaptation of diagnostic test, based on SDMT

The computer adaptation of this test "duplicates" the classic paper version with almost no change. Innovation includes advanced capabilities of measuring the coping regarding speed of response in each patient for each specific symbol. As a result of further measured parameters, cognitive changes can be more accurately captured and more detailed statistical processing performed. It will allow the statistics to be generated by symbols, i.e. for each symbol the percentage of correct matches, the wrong ones, the blank characters, and calculation of the mean, longest, and shortest time to fill in the corresponding digit for a given symbol (response time) to be determined.

Computer adaptation of diagnostic test, based on BVMT

The computerized implementation of the adapted version of BVMT enriches the database of characters used in the test. As a result, the habituation in subsequent BVMT studies is reduced and it can be used in rehabilitation procedures in the course of the disease. The BVMT computer adaptation allows execution time to be recorded; also recording the type of subject's error (geometric image recognition and incorrect spatial positioning), monitoring the effect of rehabilitation on the basis of the above mentioned indicators, comparison of difficulties in recognizing a specific symbol at baseline and in the course of rehabilitation and creating a base data with the number of errors for each symbol used, which can serve to correct and enrich the symbols used in the test.

Computer adaptation of diagnostic test, based on CVLT

This test is strongly dependent on nationality because of the use of verbal stimuli. The computerized implementation of the test will allow the preparation of a standard for the Bulgarian population, standardization of the conditions for conducting the test, unification of the test results in subsequent statistical processing and extension of the studied parameters – taking into account the execution time. Words with the highest and lowest reproduction frequency and belonging to a specific semantic category will be identified.

The results of the test will allow registration of the personal associative strategy during learning. For this purpose, a modified score for evaluation of the test result was developed – for each correctly recognized word the subject will receive 2 points, and for each wrongly recognized but belonging to the corresponding semantic categories word will receive 1 point. The maximum possible score will be 32.

Interpretation of neuropsychological test results

Up to date, only the presence of cognitive impairment in MS patients has been reported in the literature, based on comparison with healthy subjects with similar demographics, without interpreting the severity of cognitive impairment. The CogniSoft information system will incorporate 2 approaches for evaluating the neuropsychological results obtained, based on a norm built by control subjects.

Let B_L be the left boundary (minimum) of the 95% confidence interval (regardless of the type of distribution) of the results obtained from healthy controls when performing a neuropsychological test (or the total score from a non-psychologic battery test):

$$B_L = \bar{x} - 1.96 \times \frac{\sigma}{\sqrt{n}},$$

where $\bar{x}$ is the mean value;

σ – standard deviation;

n – sample size of the cohort (number of the observed cases).

Methods for determination of assessment in cognitive disorders

Variant 1

If the patient's result from specific neuropsychological test (or the total score received from the performance of a battery of neuropsychological tests) is within the range of:

- $(0; 0.25\times B_L)$ – the result is interpreted as a "very severe cognitive impairment";
- $(0.25\times B_L; 0.5\times B_L)$ – the result is interpreted as a "severe cognitive impairment";
- $(0.5\times B_L; 0.75\times B_L)$ – the result is interpreted as a "moderate cognitive impairment";
- $(0.75\times B_L; B_L)$ – the result is interpreted as a "mild cognitive impairment".

Variant 2
The following indicators are determined on the basis of literature data:

- L – the percentage of MS patients who have a mild cognitive impairment;
- M – the percentage of patients with MS who report a "moderate cognitive impairment";
- H – the percentage of patients with MS who report a "severe cognitive impairment";
- V – the percentage of MS patients who report a "very severe cognitive impairment".

If the patient's result from the specific neuropsychological test (or the total score he has achieved from performing a battery of neuropsychological tests) is within the range of:

- $\left(0; \frac{V}{100}\times B_L\right)$ – the result is interpreted as a "very severe cognitive impairment";
- $\left(\frac{V}{100}\times B_L; \frac{V+H}{100}\times B_L\right)$ – the result is interpreted as a "severe cognitive impairment";
- $\left(\frac{V+H}{100}\times B_L; \frac{V+H+M}{100}\times B_L\right)$ – the result is interpreted as a "moderate cognitive impairment";
- $\left(\frac{V+H+M}{100}\times B_L; B_L\right)$ – the result is interpreted as a "mild cognitive impairment".

Conclusion

The computerization of tests for assessment of cognitive status in patients with MS is a natural result of worldwide trend. Thus, it is possible to introduce neuropsychological testing as part of the overall evaluation of MS patients and to monitor cognitive status in parallel with clinical and paraclinical parameters. This approach will allow early detection of cognitive impairments in these patients, which will initiate timely cognitive rehabilitation.

The implementation of CogniSoft information system in clinical practice will allow to compare two approaches for interpretation of cognitive impairment severity, proposed by the authors of the article. On the basis of the neuropsychological findings, not only presence or absence of cognitive abnormality will be reported, but also the degree of cognitive impairment will be defined. The test results will serve the physician to make a specific decision to select rehabilitation program for the particular patient, which will take place within the rehabilitation module of the CogniSoft computer system.

The obtained norms (general – formed by all examined subjects; or norms by gender; by age; level of education, etc.), composed by own control persons' cohort, will make possible

comparison of results with norms, accepted from standard (paper version) tests. This will allow more in-depth analysis of the aspects of cognitive impairment.

In addition, the computer-based form of neuropsychological research saves time and financial resources and does not involve qualified specialists. It eliminates subjectivity in the administration and interpretation of results by different examiners, facilitates the collection and archiving of large volumes of data and their subsequent statistical processing, as well as the formation of reliable norms.

Bilingual model assumes implementation of the platform in English spoken countries, which will allow comparison of the results according to national peculiarities and will generally enrich the knowledge of MS.

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