

REVIEW

Cognitive Impairment in Multiple Sclerosis

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Multiple sclerosis (MS) is a socially significant immune-mediated disease, characterized by demyelination, axonal transection and oligodendropathy in the central nervous system. Inflammatory demyelination and neurodegeneration lead to brain atrophy and cognitive deficit in up to 75% of the patients. Cognitive dysfunctions impact significantly patients' quality of life, independently from the course and phase of the disease.

The relationship between pathological brain findings and cognitive impairment is a subject of intensive research.

Summarizing recent data about prevalence, clinical specificity and treatment of cognitive disorders in MS, this review aims to motivate the necessity of early diagnosis and complex therapeutic approach to these disturbances in order to reduce the social burden of the disease.

INTRODUCTION

Multiple sclerosis (MS) is a socially significant disease with unclear multifactorial etiology. One or more environmental factors unlock the disease in genetically predisposed individuals. Immune-mediated processes in the peripheral blood and in the central nervous system (CNS) produce disseminated foci of inflammatory demyelination mainly in white matter, but recent studies found pathomorphological disorders also in gray matter of the thalamus, hippocampus, cerebral cortex. The immune-mediated destruction of myelin is accompanied by chronic progressive degeneration within the CNS - the cause of tissue damage and brain atrophy in the later stages of disease evolution.¹ Pathomorphological changes are expressed clinically with various combinations of neurological symptoms - motor, sensory, visual, bowel/bladder dysfunctions, and a significant proportion of patients have cognitive impairments. Although neuropsychological manifestations of MS have been

described decades ago by Jean-Martin Charcot, they have recently been a subject of scientific interest because of their high incidence, occurrence in the early stages of the disease and great importance for professional realization, personal relationships and quality of life of MS patients.

CHARACTERISTICS OF MS-RELATED COGNITIVE DEFICIT

A review of the literature shows variation in the prevalence rate of cognitive disorders - from 40% to 65%-75%.^{2-6,9} Differences in the study design, characteristics of the sample, neuropsychological tests used for diagnosis, heterogeneity in the type and severity of the disease are some of the factors determining these discrepancies.¹⁰ A cross-sectional multicenter survey of Cáceres et al. (2011) has shown a prevalence rate of 43.2% for cognitive impairments among patients with MS in Argentina, and similar research of Papathanasiou et al. (2014)

in the Greek MS population has registered cognitive deficits in 53.75%.^{4,5} A study in Bulgaria by Genov, (2003) has found cognitive disturbances in 74.7% of the observed contingent distributed according to the severity of cognitive dysfunction as follows: mild - 26.7%, moderate - 25.3%, severe - 12.7%.⁶

The prevalence of cognitive disorders in MS varies with the type and stage of the disease – it is the highest for the secondary progressive MS and even can get as high as 80% as reported by Papathanasiou et al. (2014).^{5,9} It has been stated that 7% to 29% of the patients with primary progressive MS develop cognitive deficit.¹⁰ Cognitive dysfunction has been also found in the early stages of the disease (duration of less than 5 years). According to various authors, the frequency is in the range of 20 to 45% and is observed even in patients with a clinically isolated syndrome.^{7,11-13} According to the study by Achiron and Barak (2003), 95% of the studied patients with possible MS had an abnormal score in at least one neuropsychological test.¹⁴

Cognitive dysfunctions in MS patients have been found to be correlated with a number of other factors besides the type and duration of the disease. Studies have shown that race, and possibly other genetic factors influence the clinical presentation of the disease, including the effect on the cognitive functions. Weinstock-Guttman et al. (2003) have found that cognitive deficit had earlier onset in African Americans with MS than in Caucasian patients.¹⁵ Similar data were reported in children with MS.¹⁶ On the other hand, the patients' age and the age at disease onset are factors determining the variability of cognitive impairment.¹⁷ Gender differences have been established in the severity of clinical signs and the course of the MS. In men, the course of the disease is more severe, with more rapid progression of disability than in women. Similarly, the prevalence and severity of cognitive impairment are more pronounced in male patients.⁷

Intelligence and education, as factors determining the cognitive reserve, also affect the appearance of cognitive deficit. A five-year longitudinal study has found significant cognitive decline in patients with low baseline cognitive reserve, unlike those with higher intelligence and education, in whom no cognitive deficits were detected up to the end of the observational period.¹⁸

The first Bulgarian longitudinal study of cognitive functioning in MS conducted by Genov K., (2015) has found an association between different cognitive domains and age, disease duration, EDSS,

overall intelligence. Similar to previous reports of other researchers Bulgarian patients with primary progressive and secondary progressive MS have shown more severe cognitive decline. An important finding of the same study is the predictive value of lower results on neuropsychological tests in early relapsing-remitting MS for progression of the neurological deficit assessed by EDSS.¹⁹

Presence of depression, chronic fatigue and the overall physical disability affect the cognitive abilities of MS patients, but a tight causal relationship between the severity of neurological and cognitive deficit has not been proven.^{19,20}

Recently, the correlation between the localization and intensity of pathomorphological changes and the severity of cognitive deficit has been extensively studied. Modern MRI techniques demonstrate high sensitivity in visualizing pathomorphological damage that is credible perspective for research in this aspect.^{17,21} Patients with impaired cognition have been found to have a significantly higher total T1 and T2 lesion load compared to cognitively preserved subjects. A number of observations have reported correlation between cognitive disorders and localization of the lesions in the white or gray matter, but the link with the total lesion load in the white brain matter is more pronounced in comparison with the lesion volume in gray cortical/subcortical structures.^{22,23} The dependence of poor results in neuropsychological tests with frequent location of MS lesions in forceps major and splenium corporis callosi established by Rossi et al. (2012) supports the hypothesis of functional disconnection between key areas in cortical gray matter as a primary mechanism underlying the cognitive deficit in MS.²³ A study combining two different MRI techniques has shown that both intracortical lesions and mixed lesions play a more significant role than juxtacortical lesions and measures of atrophy in cognitive impairment.²⁴

The total brain atrophy and atrophy of cerebral cortex and subcortical gray nuclei like the thalamus, putamen, hippocampus, amygdala, nucleus accumbens, are proven to be associated with cognitive impairment in MS.^{17,23}

Over recent years many studies started measuring abnormalities in normally appearing grey matter by using various quantitative MRI techniques and their correlations with cognitive functions in MS. Cortical magnetization transfer (MT) ratio has been the only MRI parameter associated with impaired mental processing speed in patient with clinically

isolated syndrome.²⁵ A 13-year follow-up study have established grey matter MT-ratio as the only MRI predictor of global cognitive impairment, supporting the notion that grey matter plays a major role in the long-term development of cognitive decline.²⁶

Studies have found an association between changes in certain areas of gray matter and deficit in a specific cognitive domain.¹⁷ A significant association between memory, deep gray matter structures, and cortical thinning of the frontal and temporal gyrus was demonstrated by Pellicano et al. (2013).²⁷

Cognitive disorders in MS show heterogeneity in their type and severity, but are similar to those of subcortical dementias. Despite considerable individual variations, the most frequently affected domains are attention, executive functions, information processing, visuo-spatial perception and memory and working memory.^{2,3}

MS patients perform attention-demanding tasks slower, with more inaccuracies and omissions.²⁰ They have difficulty in sustaining attention for a long period of time as well as in divided attention, but a so-called simple attention (i.e., repetition of numbers) is usually unaffected.^{3,28} The ability for dividing and switching attention between different tasks is predominantly affected and shows decreased cognitive plasticity in MS.¹⁹

Memory deficit is presented primarily by impaired learning of new information, and in lesser extent by difficulty in recall and recognition. MS patients with cognitive deficit need more repetitions to learn the predetermined amount of information. Unlike Alzheimer dementia, accelerated forgetfulness and loss of memories of people and events from the past is not typical for MS-driven cognitive decline. According to some researchers, the disturbed encoding is a consequence of low information processing speed and impaired executive functions. Attention deficit, with difficulty in ignoring irrelevant stimuli, also contributes to impaired learning.^{3,29}

Efficiency of information processing depends on the ability of the brain to retain and manipulate it for a short period of time as well as the speed with which this process is carried out. The reduced information processing speed is one of the most common cognitive impairments in MS and predicts long-time development of cognitive decline. Studies have established a positive correlation between the slow information processing speed and the memory deficit.^{30,31} The disturbances in working memory and information processing speed are interrelated - the

deficit in both spheres becomes more pronounced with increased requirements for working memory. The slowed information processing speed also affects the performance of the attention-demanding tasks.³²

Executive functions, including abstract and conceptual thinking, verbal fluency, ability to plan and organize, are affected in cognitively impaired MS patients. According to Drew et al. (2008) 17% of patients have difficulties in multiple executive skills.³³ Verbal fluency tests, assessing the spontaneous production of words at search-restricting conditions (a certain initial letter or from one semantic category), show deficits in phonetic and semantic fluency, frequent perseverative errors and are a sensitive method for detecting cognitive impairment in MS.

The deficit of visuoperceptual functions is typical for MS cognitive impairment. These functions include not only the recognition of visual stimuli, but also the ability for accurate determination of their characteristics. Despite the limited number of studies on the incidence of these disorders in MS, it is assumed that about one quarter of the patients have deficits in the visuo-spatial domain. Disturbances in visuoperceptual functions have been detected not only in MS patients diagnosed with cognitive decline, but also in those determined as cognitively preserved. Abnormalities in the afferent visual pathway (optic neuritis) and the primary visual cortex in the occipital lobe may further aggravate the visuoperceptual defect.^{20,34}

Usually, storage of learned information, semantic knowledge and intelligence are not impaired, but in 10 to 15% of MS patients multiple cognitive domains are affected leading to the so called MS-associated dementia.¹⁸

DIAGNOSTIC POSSIBILITIES

The diagnosis of cognitive dysfunction in patients with MS and determination of its type and severity is crucial for establishing a proper and comprehensive treatment, rehabilitation and social adaptation of those individuals. The assessment of various indicators - continuing employment, independence in daily activities, educational level provides primary information about the presence of cognitive impairment. For this purpose different questionnaires directed towards the patients or their relatives have been developed. They allow screening of the cases that require further cognitive assessment. For a more precise examination of cognitive functions specific neuropsychological tests are used. They enable the

detection, identification of the type and severity of cognitive impairment, and allow long-term follow-up. The neuropsychological examination can vary from a short screening test to a detailed evaluation of overall cognitive functioning of a patient. Neuropsychological testing in routine clinical practice occupies an intermediate position, focusing on evaluation of MS-related cognitive dysfunctions.

In 2001, an expert group of neurologists and neurophysiologists developed and introduced a battery of psychometric tests to study cognitive functions in MS that is highly consistent with the specifics of the pathological process of the disease. The battery known as MACFIMS (Minimal Assessment of Cognitive Function in MS) includes 7 tests that assess the information processing speed, working memory, the ability to learn and recall new information, visuospatial perception and higher executive functions.³⁵ The battery, including Trail Making Test (TMT), Stroop Colour-Word Tests (SCWT), Verbal Fluency Test (VFT), Digit Span Forward (DSF), Paced Auditory Serial Additional Test (PASAT) Symbol Digit Modality Test (SDMT) and Raven Progressive Matrices is very sensitive for early diagnosis of cognitive deficit as well as for a longitudinal follow-up.¹⁹ However, a disadvantage of such batteries is the long time for examination, which makes them unpopular in the daily clinical practice and increases the chance for higher cognitive fatigability of these patients to influence the final results. The screening batteries used for the detection of patients at risk with respect to cognitive dysfunction, who need more thorough neuropsychological study and treatment, require considerably shorter time and are more easily applicable in everyday clinical practice. There are different variants of such tests: Brief Repeatable Battery of Neuropsychological Test (BRBNT), Repeatable Battery for Assessment of Neuropsychological Status (RBANS), Screening Examination for Cognitive Impairment (SEFCI), Neuropsychological Screening Battery for MS Status (NPSBMS), Brief International Cognitive Assessment for MS (BICAMS).³⁶⁻³⁹ They include tests focusing on learning and information processing speed.

Parmenter et al. (2007) established the good predictive value of SDMT administered alone. The test assesses primarily visuospatial cognitive domain and working memory. The study has shown that the effectiveness of SDMT as a screening tool is approximately equal to that of MACFIMS, as a

score of 55 or less adequately categorizes 72% of patients with cognitive deficit.⁴⁰ The test has shown particular sensitivity to the cognitive changes in MS, as well as reliability in quantitative tracking of changes for an extended period of time.^{11,41} This data, along with the short time of administration, makes this test a preferred tool both in clinical trials and routine clinical practice.⁴² The significant value of this test in cognitive assessment and monitoring of MS patients has been confirmed by the longitudinal study of Genov (2015).¹⁹

SOCIAL ASPECTS OF COGNITIVE IMPAIRMENT

Cognitive impairment in MS patients is closely related to their overall functional status. The presence of cognitive deficit hampers normal daily activities such as shopping, household activities, use of public transportation, driving, and has a significant effect on professional employment and payment, and on interpersonal relationships and social adaptation of these individuals. Such problems are caused most often by the cognitive deficit in learning new information and the executive dysfunction, but the reduced information processing speed is also known to affect considerably the ability of these patients for adequate functioning in everyday life.⁴³ The deficit in verbal memory, executive functioning and information processing speed has predictive value with respect to professional status even taking into account other related factors such as gender, age, education, course of the disease and the like. Studies show that 40 to 80% of MS patients are unemployed and cognitive disorders are an important factor in the high rate of unemployment among people with this disease.⁴⁴ The negative effect of cognitive deficits on the listed areas of daily activity results in reduction of overall quality of life of patients with MS.⁴⁵ Physical disability is a determining factor in the performance of daily activities, but cannot account for all the difficulties that these patients experience in solving tasks requiring significant cognitive capacity.

THERAPEUTIC STRATEGIES

Therapeutic approaches to cognitive impairment in MS are two main types - pharmacological and non-pharmacological. The pharmacological approach involves pathogenetically effective drugs that are capable in various degrees to suppress the immune-mediated demyelination and neurodegeneration in the CNS, and thus reduce the severity

of clinical signs and progression of the disease. Clinical studies with acetylcholinesterase inhibitors (donepezil) provide promising results in some aspects of cognitive dysfunction, particularly in the memory disturbances of MS patients.⁴⁶ Cognitive rehabilitation is a non-pharmacological approach that includes various compensatory strategies to improve day-to-day functional capacity of the patients and therapeutic activities aimed at restoration of the affected cognitive functions. Regardless of the contradictory results about the benefits of these methods, some experts recommend their use according to the individual characteristics and needs of each patient.⁴⁷

In conclusion, cognitive impairment can appear at any stage of the disease in up to 75% of patients with MS and significantly affects daily, professional and social functioning. The cognitive dysfunction is relatively independent from the physical disability, but the severity of both physical and cognitive deficit increases with disease progression. This fact requires precise assessment and monitoring of cognitive impairment in order to implement adequate therapeutic methods and to reduce the adverse effect on the quality of life of MS patients.

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Когнитивные нарушения при множественном склерозе

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Множественный склероз (МС) - социально значимое иммунообусловленное заболевание, характеризующееся демиелинизацией, аксональным перерывом и олигодендропатией в центральной нервной системе. Воспалительная демиелинизация и нейродегенерация влекут за собой атрофию мозга и когнитивный дефицит почти у 75% пациентов. Когнитивные дисфункции оказывают серьезное влияние на качество жизни пациентов, независимо от хода и фазы заболевания.

Связь между патологическими находками в мозге и когнитивным нарушением является объектом интенсивного исследования.

В качестве обобщения последних данных о распространении, клинической специфичности и лечении когнитивных расстройств, настоящая статья ставит перед собой целью мотивировать необходимость в ранней диагностике и комплексном терапевтическом подходе к этим нарушениям, с целью снижения степени социальной тяжести заболевания.