JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/15182

Modern Approaches to Diagnosing Cognitive Impairments in Patients with Multiple Sclerosis

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Received: 2024-06-16.
Accepted: 2024-09-21.

J Clin Med Kaz 2024; 21(5): 40–45

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Abstract

Multiple sclerosis in patients can cause not only motor, sensory, cerebellar and autonomic dysfunctions, but also cognitive and psychoemotional disorders such as difficulty with learning and recalling information, problems focusing on tasks and maintaining attention, slowed ability to process information, depression, anxiety. Cognitive impairment can appear at any stage of the disease and can be observed in more than half of patients. Patients with multiple sclerosis may not fully recognize or underestimate their complaints of psycho-emotional disturbances, fatigue or pain. For this reason, doctors should rely on the results of neuropsychological tests. Like all symptoms of multiple sclerosis, cognitive impairment is highly variable and significantly affects patients' work habits, social interactions and quality of life. Therefore, the assessment of cognitive functions in patients with multiple sclerosis is of undoubted interest.

Keywords: multiple sclerosis, cognitive dysfunction, social cognition, neuropsychological tests.

Introduction

Multiple sclerosis (MS) is indeed a chronic disease characterized by demyelination of nerve fibers in the Central nervous system (CNS), which includes the brain and spinal cord [1]. Cognitive impairments is a common features of MS, although it can vary widely in severity and manifestation from person to person [1]. In addition, to date, multiple sclerosis is an incurable disease [2]. According to recent data, more than 2.3 million people worldwide have a history of the disease, and it is most commonly diagnosed between the ages of 20 and 50, with more cases in women [3]. In addition, people of Northern Europe and people of European descent have the highest risk of developing the disease [3]. In Central Asian countries, the overall prevalence is 10.1 per 100,000 population, with Caucasians having a much higher prevalence of 16.8 per 100,000 compared to Asians – 4.9 per 100,000 [4].

Absolutely, multiple sclerosis is a multifaceted disease that can affect various functions of the central nervous system (CNS), leading to a wide range of symptoms beyond the typical motor and sensory dysfunctions [5]. Here's a breakdown of some of the cognitive and psychoemotional impairments that can occur in individuals with MS: difficulty with learning and recalling information, problems focusing on tasks and maintaining attention, slowed ability to process information, depression, anxiety [5].

The understanding and recognition of cognitive impairments in multiple sclerosis (MS) have evolved significantly over time. Thus cognitive impairments in MS were first described by Charcot and his colleagues in the mid-1800s [6]. However, these cognitive symptoms were often overshadowed by the more prominent motor and sensory deficits associated with the disease. For much of the 20th century, cognitive aspects of MS received relatively little attention in clinical practice and research [6].

It wasn't until the late 20th century, particularly in the last decade of that century, that there was a resurgence

of interest in cognitive impairments in MS [6]. This renewed focus was driven by advancements in neuropsychological testing methodologies, which allowed for more specific and sensitive assessment of cognitive functions in individuals with MS [6].

Specific and sensitive batteries of neuropsychological tests have been developed to assess various cognitive domains affected by MS. These tests can identify qualitative (types of cognitive deficits) and quantitative (severity of deficits) characteristics of cognitive impairment in MS patients [6].

With the advent of advanced neuroimaging techniques such as MRI (Magnetic Resonance Imaging), researchers have been able to correlate cognitive impairments with the neurological manifestations of MS. MRI can reveal the presence and location of lesions in the brain and spinal cord, which can help explain specific cognitive deficits observed in patients [6]. While cognitive impairments in MS were initially overlooked, advances in neuropsychological testing and neuroimaging have allowed for a more nuanced understanding of these deficits. This has led to increased awareness, research, and clinical attention towards managing cognitive aspects of MS alongside its other neurological manifestations [6].

Cognitive impairment is indeed a common feature of multiple sclerosis (MS), and it can occur at any stage of the disease, from the early stages to more advanced phases. The prevalence rates of cognitive impairment in MS vary widely across studies but generally range from 42% to 70% [6, 7]. Cognitive symptoms in multiple sclerosis (MS) can often be subtle and less noticeable compared to more visible sensorimotor symptoms [6].

The assessment of cognitive impairment in patients with multiple sclerosis (MS) can be challenging due to several factors, including the underestimation or lack of awareness of symptoms by the patients themselves [6].While acknowledging the importance of patient-reported symptoms and experiences, objective cognitive tests play a crucial role in the accurate assessment and management of cognitive impairment in MS. They provide reliable data that can guide clinical decision-making and facilitate interventions aimed at improving cognitive function and quality of life for individuals living with MS [6]. Given the variability and impact of cognitive impairment in MS, it is essential for healthcare providers to assess cognitive function routinely and consider its implications for treatment planning and support. Addressing cognitive deficits early and comprehensively can help improve overall outcomes and enhance the quality of life for individuals living with MS [6].

The present review aims to study cognitive impairment in patients with multiple sclerosis. A systematic search of English-language studies was conducted in the Web of Science, Scopus and The Cochrane Library from January 2008 to June 2024, which resulted in 187 matches. After checking the titles and annotations, we identified 88 potentially acceptable articles, of which 35 were included in this review. Figure 1 shows a detailed algorithm for selecting studies for this literature review.

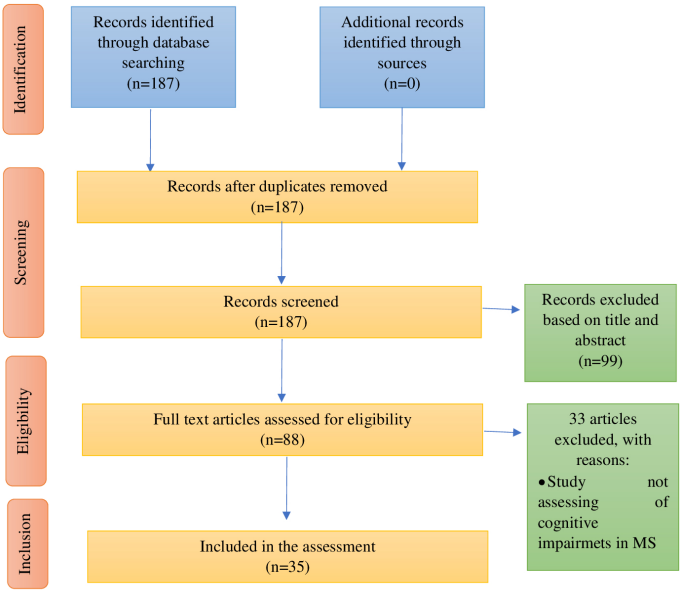

Figure 1 – Flow diagram of the of the literature search

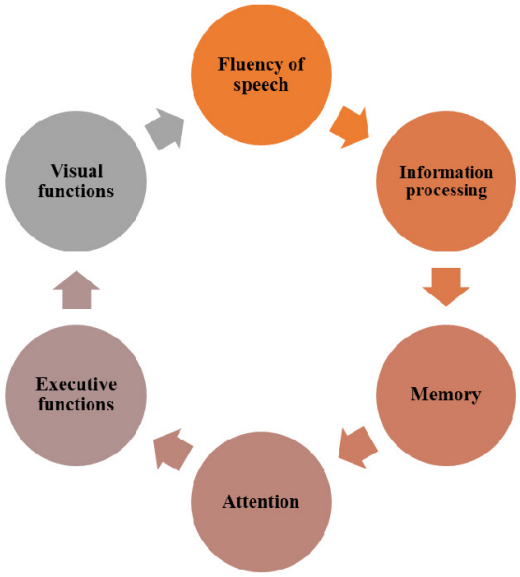

Figure 2 – The main cognitive functions impaired in patients with multiple sclerosis

Specific profile of cognitive impairment in patients with MS

In MS cognitive impairments can vary widely, but several domains are commonly affected. The most frequently observed cognitive impairments include: difficulties in processing information quickly and efficiently, memory deficits, visual-spatial skills (Figure 2). In patients with MS, attention processes are disrupted, in particular selective and sustained attention, although focused attention is preserved for a long time. Also, patients in this category have problems with information processing. Some of the first studies on MS showed that MS patients take much longer to analyze information than healthy patients. One of the first signs of cognitive impairment is manifested by a change in the speed of information processing. An important observed cognitive impairment in patients with MS is memory impairment. Thus, problems with long-term memory are most common. Although visual-spatial impairments have received less attention, there are reports that a quarter of MS patients suffer from them. These changes are manifested in patients by deficits in pattern integration and dislocation and an inability to follow an object. In recent years, there has been increasing recognition and study of cognitive impairments beyond the traditional domains in MS, including social cognition, decision-making, and moral judgment [6].

The pathophysiology of cognitive deficit development in multiple sclerosis is a complex multifactorial process and is

associated with lesions of the basal ganglia, thalamus, cerebellum and brainstem. In addition, white matter lesions and atrophy are known to contribute significantly to cognitive dysfunction in MS patients. However, the exact mechanisms leading to cognitive impairment in MS are not fully understood. Although it is known that in MS there are foci of inflammatory demyelination and neuronal damage in both white and gray matter associated with infiltration of activated lymphocytes. Over time, the incidence of external focal inflammation decreases and begins to be dominated by progressive axonal and neuronal loss, as well as diffuse glial dysfunction and lymphocyte organization in ectopic follicle-like structures. On the other hand, there is evidence that cognitive impairment may be associated with both structural damage and functional abnormalities of neuronal networks in the brain [5, 6].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), provides a structured framework for diagnosing cognitive disorders and categorizes cognitive impairment across several domains: ability to sustain attention and process information quickly, encoding, storage, and retrieval of information, speech, cognitive flexibility, perceptual-motor/visual-spatial abilities social cognition [8]. Cognitive impairment of various etiologies is categorized in this guideline into "severe" and "mild" severity, with cognitive disorders in MS categorized in the "mild cognitive impairment" subsection [8].

Despite the fact that the results of various neuropsychological tests should be 1–2 points below the normative values in "mild" MS, neither the currently available international literature nor the DSM-5-TR Guidelines specify in their recommendations any standardized, internationally recognized neuropsychological tests, as well as their thresholds for measuring cognitive impairment, which are necessary for accurate and timely determination of cognitive disorders in multiple sclerosis [8].

Neuropsychological batteries for assessing cognitive impairment in patients with multiple sclerosis

There is a diverse array of neuropsychological tests utilized to assess cognitive impairment in patients with MS.

The Mini-Mental State Examination (MMSE) is a widely used screening tool to assess cognitive impairment in clinical and research settings. The MMSE is a valuable screening tool for assessing cognitive impairment, but for more comprehensive assessment of visual-spatial abilities, specific neuropsychological tests such as the Rey Complex Figure Test or other tests that involve more detailed visuospatial tasks may be utilized. These tests provide a more nuanced evaluation of visual-spatial abilities and their potential impairments in conditions like multiple sclerosis [9, 10]. However, the MMSE and the three-word memory test are currently considered insensitive for assessing cognitive impairment in multiple sclerosis because they do not take into account the specific neuropsychological profile of patients in this group [8].

Luria-Nebraska Neuropsychological Battery scale has 14 domains and assesses praxis, expressive and expressive speech, memory, visual-spatial gnosis, numeracy, intelligence [11]. This battery is highly informative, but has a number of limitations in the form of lack of standardization and difficulties in quantifying the results, contradictory data regarding the reliability of the test [8].

Paced Auditory Serial Addition Task (PASAT) provides valuable information about a person's cognitive abilities, particularly in tasks requiring rapid processing of auditory information, sustained attention, and manipulation of information in working memory. Its use helps clinicians and researchers assess cognitive function objectively and monitor changes over time in individuals with various neurological conditions, including MS. During the PASAT participants are indeed asked to listen to a series of single-digit numbers presented audibly at fixed intervals. To get the correct answer, patients must verbally respond before the next number appears [12]. The PASAT is recognized for several advantages that contribute to its reliability and suitability for clinical practice and research in assessing cognitive function. However, its use requires a trained professional, a device to play back the recording, and the test may be negatively perceived by the patient due to its complexity and the possibility of a learning effect cannot be ruled out [8].

The Symbol Digit Modalities Test (SDMT) provides valuable insights into processing speed, attention, and visual scanning abilities, making it a valuable tool in assessing cognitive impairment and monitoring cognitive function in clinical practice and research settings. Its standardized administration and reliable scoring enhance its utility for evaluating cognitive status across various populations [13, 14]. The SDMT test demonstrates high sensitivity and specificity not only in detecting cognitive impairment, but also demonstrates its dynamics over time or in response to treatment [13]. While the SDMT offers significant advantages in terms of reproducibility and correlation with MRI findings, its limited trainability should be considered when interpreting longitudinal changes in cognitive performance. Overall, it remains a valuable and widely used tool in the assessment of cognitive function, particularly in clinical neurology and research settings [8].

The Stroop Test is a classic neuropsychological test known for its ability to assess cognitive processes such as response inhibition, cognitive flexibility, and selective attention. The Stroop Color-Word Interference Test is a robust tool for assessing executive functions and cognitive flexibility through its structured administration of color naming, word reading, and interference conditions. Its ability to quantify interference effects provides valuable insights into cognitive processing abilities in both clinical and research settings [15, 16].

The two-minute Processing Speed Test (PST) screening test is designed to optimize the assessment of cognitive function in patients with MS. The advantage of this test is that the patient completes it independently using a tablet, and the high stability of the results, correlation with neuroimaging data [17–19].

The presence of cognitive disorders in patients with MS is possible by interviewing them using the Montreal Cognitive Assessment (MoCA), in which a score between 26 and 30 is considered normal (30 points is the maximum possible score) [20]. In patients with MS the Montreal Cognitive Assessment (MoCA) scale is often used to assess cognitive function and detect generalized cognitive impairment have highlighted the Montreal Cognitive Assessment (MoCA) scale's effectiveness in detecting cognitive impairment across various populations, including those with neurological conditions like MS [21]. However, it has been reported that lower scores than the initial threshold level are useful for optimal screening because they reduce false positives, increase the speed and accuracy of diagnosis of cognitive disorders. Adjusting the threshold value to 27 points on the MoCA scale in MS patients without subjective cognitive complaints appears to strike a better balance between sensitivity and specificity. This approach aims to optimize the

identification of cognitive impairment while minimizing the risk of overdiagnosis, thereby enhancing the clinical utility of the MoCA in MS management. As always, individualized assessment and interpretation of cognitive test results remain essential in clinical practice to ensure comprehensive care for MS patients [21]. Researchers have indeed highlighted the ongoing need for more robust studies to determine the optimal threshold on the Montreal Cognitive Assessment (MoCA) scale specifically for detecting cognitive impairment in patients with MS [21].

Modern specific tests for the assessment of cognitive impairment in patients with MS

Three groups of validated tests are widely accepted for the assessment of cognitive impairment:

BRB-N (Brief repeatable battery of neuropsychological tests in multiple sclerosis), MACFIMS (Minimal assessment of cognitive functioning in multiple sclerosis) and BICAMS (Brief international cognitive assessment for MS) [8, 22–25].

The Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (BRB-N) is a comprehensive assessment tool designed to evaluate various cognitive domains commonly affected in multiple sclerosis (MS). While the BRB-N is a robust tool for assessing cognitive impairment in MS, its practical limitations, including time intensity and expertise required, necessitate careful consideration in its use within clinical practice settings. Addressing these challenges could enhance its utility in providing comprehensive cognitive evaluations for MS patients [8, 22].

MACFIMS (Minimal assessment of cognitive functioning in multiple sclerosis) is validated 90-minute battery that includes 7 tests assessing working memory, attention, visual-spatial gnosis, executive functions, visual and auditory memory. The tests used in this methodology have high reliability, but their widespread implementation is limited by the length of time it takes to administer them [23].

BICAMS (Brief International Cognitive Assessment for MS) – in 2012, a new battery of tests was proposed for routine use in clinical practice and research. The battery evaluates the speed characteristics of cognitive activity, auditory-verbal and visual memory. The testing time is no more than 15 minutes. This method allows predicting the daily activity of patients can be used as monitoring of cognitive functioning in patients receiving multiple sclerosis medications (PITRS) [24, 25]. This battery has recently been validated in the iBICAMS version for the iPad [26]. A recent study including 139 patients with MS showed that the electronic version of the iBICAMS neuropsychological test has high specificity, allows for clear and instantaneous integration of test results, automatic calculation, and digital data storage, which greatly facilitates the work of the researcher. However, the study had some limitations: highly disabled patients who could not perform the BVMT-R using the electronic tablet pen were not included [26]. Given the inherent advantages of automatic scoring, digital data storage, and standardized time, iBICAMS may become a standard in clinical practice [26].

The Multiple Screener represents an adaptation and refinement of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a well-established tool for assessing cognitive function in MS.The Multiple Screener represents a promising advancement in the assessment of cognitive impairment in MS, offering practical advantages such as ease of administration, automated scoring, and consideration of psychological factors. Its implementation has the potential to enhance clinical management and research efforts aimed at improving outcomes for individuals living with MS-related cognitive challenges [27].

Assessing cognitive function in MS patients using smartphone learning games. The dreaMS smartphone application represents an innovative approach to monitoring multiple sclerosis (MS) activity and assessing cognitive function through the integration of cognitive games. The dreaMS smartphone application represents a promising tool for assessing cognitive function in MS patients through adaptive cognitive games. Its potential to complement traditional neuropsychological assessments and facilitate remote monitoring underscores its role in advancing personalized care and research in MS management. Continued research and development efforts will further refine its utility and impact in clinical practice [28].

The Virtual Brain (TVB) is an advanced open-source brain simulation platform designed to create personalized brain models using data on structural and functional connectivity. TVB represents a powerful tool in neuroscientific research, particularly in elucidating the complexities of cognitive impairment in MS through its modeling of brain connectivity. By linking structural and functional connectivity alterations to cognitive deficits, TVB contributes to a deeper understanding of MS pathology and opens avenues for personalized approaches to diagnosis and treatment [29]. However, despite advances in MRI technology and our understanding of brain connectivity in MS, the relationship between structural and functional connectivity and how these interact with disability and cognitive impairment remains a complex area of study.

Cognitive phenotypes in patients with MS

In the context of multiple sclerosis (MS), cognitive impairment can manifest across a spectrum of severity and complexity. Researchers and clinicians often classify these cognitive presentations into different phenotypes based on the extent and domains of cognitive deficits observed [30]. The characterization of cognitive phenotypes in multiple sclerosis (MS) involves considering various demographic, clinical, and MRI features that may indicate different neural substrates of dysfunction at different stages of the disease [30]. Defined as a decrease of 1.5 standard deviations (SD) below the normative mean of the tests used. Significant Impairment: Defined as a decrease of 2 standard deviations or more below the normative mean. This level of impairment suggests more pronounced cognitive deficits that can significantly affect daily activities and quality of life. This level of impairment is considered mild and may indicate subtle cognitive changes that do not significantly impact daily functioning. Thus patients are categorized into cognitive phenotypes according to the severity of impairment (mild or significant) depending on the number of domains affected (one or more) [30].

Prognostic value of serum biomarkers for early disease progression in MS

Neurofilaments are indeed emerging as promising biomarkers in the field of MS and other neurological conditions. Neurofilaments are structural proteins found in neurons, and their levels in the cerebrospinal fluid (CSF) or blood can serve as biomarkers for neuronal damage or inflammation in diseases

like MS. Effective therapy in MS aims to reduce the frequency and severity of relapses and to slow down the progression of the disease [31].

The idea of using genetic biomarkers associated with gray matter lesions to predict cognitive impairments in multiple sclerosis (MS) is an intriguing area of research. Gray matter lesions in MS are known to contribute to cognitive impairments. Identifying specific genes linked to these lesions can potentially provide insights into the underlying mechanisms of cognitive decline in MS. TLR9, CCL5, CXCL8, and PDGFRB are mentioned as genes that have been identified as potential biomarkers for cognitive impairments in MS. Each of these genes may play a role in inflammation, neuroprotection, or repair mechanisms within the CNS [32].

Neuroimaging methods in the diagnosis of cognitive impairments in patients with MS

Routine MRI measures of brain volume did not show a significant correlation with cognitive impairment in the recent study, ongoing research continues to explore more nuanced imaging biomarkers and their associations with cognitive outcomes in MS. Integrating advanced imaging techniques and comprehensive cognitive assessments may enhance our understanding and clinical management of cognitive impairments in MS patients. Studies have consistently shown that higher T2 lesion loads are associated with greater physical disability in MS patients. This is because lesions in areas crucial for motor function can disrupt neural pathways, leading to motor impairments and disability [33].

Another study, which associates basal ganglia functional connectivity with both subjective and objective fatigue in MS, represents an important advancement in understanding the underlying mechanisms of fatigue in this disease. In addition, local basal ganglia functional connectivity during fatigue-inducing tasks may serve as a neurophysiological biomarker of cognitive impairment [34].

Meanwhile, atrophy of the cerebral white matter, corpus callosum, shell, and pallidum also showed significant correlation with the z-score of CogEval in secondary progressive multiple sclerosis (SPMS). Thus, the shell may be an important area of atrophy contributing to the impaired rate of cognitive impairment in MS, especially in the late stages of the disease after progression to SPMS [35].

Electroencephalography (EEG) has been used to investigate cognitive function and brain activity in patients with multiple sclerosis (MS), revealing various patterns that indicate dysfunction within the CNS. EEG is a valuable tool for investigating the neurophysiological changes associated with cognitive dysfunction in MS. The identified patterns of dysfunction, such as alpha rhythm alterations and paroxysmal activity, contribute to our understanding of how MS affects brain function and may inform future diagnostic and therapeutic strategies [36].

Conclusion

Thus, cognitive impairment is a common and impactful symptom in patients with multiple sclerosis. Detecting cognitive deficits in patients with multiple sclerosis as early as possible is critical for several reasons, particularly because cognitive impairments can significantly impact daily functioning and quality of life, even in the absence of noticeable motor impairment. However, the validation and active integration of neuropsychological techniques into clinical practice for assessing cognitive deficits in multiple sclerosis remain important and ongoing areas of focus. While the development of a universal cognitive assessment test for MS presents challenges, its potential benefits in guiding treatment decisions, monitoring disease progression, and enhancing clinical care underscore the importance of ongoing research and innovation in neuropsychology and MS management.

Author Contributions: Conceptualization, T. P., N. Z.; methodology, T. P., N. Z.; validation, A. Ye.; formal analysis, G. T., A. Ye.; investigation, T. P., G. T.; resources, T. P., A. Ye.; data curation, S. Ye.; writing – original draft preparation, G. M., T. P., N. Z.; writing – review and editing, T. P., N. Z., G. M.; visualization, S. Ye., T. P., N. Z.; supervision, T. P., A. Ye.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: None.

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