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Review Article

Cognitive Decline and Treatment Strategies in Multiple Sclerosis Patients

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ABSTRACT

Multiple Sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS), mainly appeared in young adults, characterized by neuroinflammation, demyelination, neurodegeneration and remyelination and with a variety of CNS-related symptoms. The prevalence of cognitive decline in MS patients has been reported to range widely, from 13% to 72%, occurring in all stages of the disease, and can lead to mental disability, social impairment, and an impoverished quality of life. The pathogenetic mechanism of the cognitive decline in MS has yet to be revealed, and, thus, we are still unable to predict which patients are more likely to manifest such a decline and at what stage of the disease. Clinical factors, including the type and the course of the disease, but also fatigue and emotional disturbances, can impact the degree of MS-related cognitive impairment. It has been reported that almost 40% of the MS patients demonstrate a significant deficit in recognizing and recalling verbal and visual memories, either at the onset of the disease or at its later stages, whereas short-term memory remains almost intact. Many patients also demonstrate deficits in complex attention, a slower efficiency in information processing, a declined ability of problem-solving, planning, and prioritization tasks or even visual agnosia and aphasia. Most of the MS-specific disease-modifying treatments seem to reduce the rate of MS attacks and slower the progression; however, their impact on cognitive impairment remains unclear. We propose that cognitive function evaluations should be incorporated in the regular assessment and monitoring of MS patients since they seem to be well correlated with the progression of the disease. Even if the effect of the neuropsychological batteries used for diagnostic and therapeutic purposes still remains very much limited, especially due to the validation and standardization issues, specific cognitive functions treatment strategies should be implemented in the therapeutic scheme of MS patients.

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Introduction

Multiple Sclerosis (MS) is an autoimmune demyelinating and neurodegenerative disease of the Central Nervous System (CNS), mainly appeared in young adults, usually being diagnosed in their 3rd or 4th decade of their life and lasting for the rest of their life. MS is more frequent in females (two to three times more frequent than in males) and it can be presented with a variety of CNS-related symptoms since it can potentially affect almost every region within the CNS [1]. MS is characterized by autoimmune processes, neuroinflammation, demyelination, neurodegeneration and remyelination, demonstrating in relapses and remissions, and its (primary or secondary) progress remains

unpredictable. The literature reviews emphasize the fact that several pathophysiological processes, such as the disruption of the blood-brain barrier (BBB), neuroinflammation, demyelination, axonal loss, gliosis and remyelination, all contribute to the complex manifestation and progression of the disease [2].

It has been reported that up to 42% of the MS patients demonstrate a significant deficit in recognizing and recalling verbal and visual memories [3, 4]. There is also a significant decline in retrieving information from long-term memory either at the onset of the disease or during its later stages, whereas short-term memory remains almost intact [5, 6]. Many patients also demonstrate deficits in complex attention and

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slower efficiency in information processing. Many researchers believe the latter to be due to poor working memory, which has been linked to general dysfunction of cognitive processes, while others support that is due to purely motor deficits [7, 8]. Other studies have shown a disability in problem-solving, planning, and prioritization of tasks [9, 10]. Such problems seem to affect up to 19% of MS patients and they are most likely related to damage to the prefrontal circuits [11, 12]. Visual-spatial and speech impairment have been studied to a lesser extent due to sensory, motor and visual deficits, which are commonly manifested in MS patients and are highly dependent on the disease-related progression [2]. Some studies concluded that severe visual agnosia and aphasia could be linked to MS, not an unexpected finding since the patients show impaired language performance and, thus, they are more prone to naming and reading test mistakes when compared to healthy controls [4, 8, 13, 14].

Many studies do not demonstrate any significant correlation between cognitive impairment and physical disability or the progression and duration of MS [15]. Some authors claim these impairments to be more common in the progressive type of MS, rather than its relapsing [16]. Comi *et al.* suggest that cognitive impairment may become most evident as the disease transits from the relapsing/remitting type of MS to secondary progressive MS [17]. Many studies indicated that MS has been correlated with mild to moderate cognitive decline, while dementia (manifesting as apraxias, aphasia, amnesia and agnosias) is rare [18-20].

However, cognitive decline can even be identified in patients without any physical disability or are at the initial stages of the disease, such as patients with the clinically isolated syndrome (CIS). The aforementioned evidence offers an explanation as to why we still have not found the neuroanatomical basis and the pathogenetic mechanisms of the cognitive decline, and, thus we are still unable to predict the patients who are more likely to manifest such decline and at what stage of the disease [17, 21-23].

Treatment Strategies

I Pharmacological Interventions

i MS-Specific Disease-Modifying Treatments

MS-specific disease-modifying treatments such as the injectables (interferon beta, glatiramer acetate), oral agents (teriflunomide, dimethyl fumarate, fingolimod, cladribine), and monoclonal antibodies (alemtuzumab, natalizumab, ocrelizumab) have shown significant benefits in reducing the annualized relapse rate and MRI activity (new T2 or gadolinium-enhancing lesions), with a more discrete efficacy over reducing disability progression and the brain atrophy rate [24]. However, their specific effect on cognitive decline is not clear enough, mainly because most phase-III clinical trials treat cognitive impairment as a secondary or tertiary outcome parameter. Comparative efficacy on cognitive outcomes across trials demonstrates great difficulties because of the different neuropsychological batteries used, the varied methods for evaluation and statistical analysis, and the differences between MS populations included in the trials. Intramuscular interferon beta 1a versus placebo included a neuropsychological evaluation as a secondary outcome parameter and indicated a 52.7% improvement compared to the

29% of the placebo group, including processing speed and episodic memory outcomes [25].

A Brief Comprehensive Neuropsychological (NP) Battery was administered, grouped into domains of information processing and learning/memory (set A), visuospatial abilities and problem-solving (set B), and verbal abilities and attention span (set C). IFNbeta-1a had a significant beneficial effect on the set A composite, with a favorable trend evident on set B. Secondary outcome analyses showed significant between-group differences in slopes for Brief NP Battery performance and time to sustained deterioration in a Paced Auditory Serial Addition Test processing rate, favoring the IFNbeta-1a group. These results support and confirm previous observations of significant beneficial effects of IFNbeta-1a for relapsing MS [25].

In two Italian Cognitive Impairment in Multiple Sclerosis (COGIMUS) studies, subcutaneous (sc) interferon beta 1a protected RRMS patients from general cognitive decline when reevaluated after 3 and 5 years of therapy [26, 27]. In these studies, cognitive impairment was assessed using the Rao's Brief Repeatable Battery (BRB) and the Stroop Colour-Word Task (Stroop Test), which have been validated for use in patients with MS and for which Italian normative values are available. Cognitive impairment was defined as 1 standard deviation (SD) below the mean local population normative values in both cognitive tests. The results reported add to the evidence suggesting that sc IFN β -1a may have dose-dependent cognitive benefits in patients with RRMS [26]. In the second study, the researchers demonstrated that these benefits persist over at least 5 years of treatment and may be more pronounced in women than in men, although it is possible that the gender difference reflects the inherently poorer prognosis in men [27].

Regarding subcutaneous (sc) interferon beta 1 β , Pliskin *et al.* reported only improvement of delayed visual reproduction performance [28]. There was a significant improvement in the Wechsler Memory Scale Visual Reproduction-Delayed Recall scores between years 2 and 4 of the trial in MS subjects receiving high-dose IFN-beta-1b. Motor performance, MRI lesion area, and depression rating scores did not correlate with this finding. The Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study showed that in patients with CIS interferon beta 1 β had beneficial effects on working memory, and the effects remained over 8 years [29]. The neuropsychological evaluation included the MS Functional Composite (MSFC), conversion to Secondary Progressive MS, and patient-reported quality of life (QoL) as measured by the Functional Assessment of MS (FAMS), the FAMS-Trial Outcome Index (FAMS-TOI) and the EuroQoL 5-Dimensional questionnaire (EQ-5D).

Glatiramer Acetate subcutaneous (sc) trials, while included extensive neuropsychological evaluation, did not show significant differences versus placebo [30]. A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial studying the effects of glatiramer therapy on MS was conducted at 11 centers in the United States. Two hundred fifty-one patients with relapsing-remitting MS were randomly assigned to receive once-daily subcutaneous injections of glatiramer acetate 20 mg, or matching placebo and were followed up systematically for 2 years. That was the first large-scale study to determine whether a treatment used to alter the course of MS also affects cognition. Although clear

evidence of improvement in other measures of disease activity, such as relapse rate and physical disability, no effect of glatiramer treatment on the course of cognitive impairment in relapsing-remitting MS was found. Physical and cognitive decline are not strongly associated with each other in MS patients, and outcome measures for these parameters have different degrees of sensitivity for impairment and therapeutic effects. Thus, it is possible that the use of glatiramer truly had an effect on physical but not on cognitive functions, yet the data do not support definitive conclusions [30].

Once-daily oral fingolimod has shown beneficial effects on cognitive function in multiple sclerosis (MS). Recently a multicenter study, examiner-blinded, controlled, prospective design with neurological evaluations and cognitive tests performed at baseline and every six months for 2 years, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery was admitted that includes Symbol Digit Modality Test (SDMT), the Brief Visuospatial Memory Test-Revised (BVMT-R) and the California Verbal Learning Test-2 (CVLT-2). A significant improvement in the cognitive function since the sixth month of initiation of fingolimod in patients with RRMS was revealed. The researchers highlight that the observed cognitive improvement in RRMS patients is clearly due to fingolimod treatment [31].

Teriflunomide, an oral first-line treatment for RRMS patients, significantly reduced Brain Volume Loss (BVL) vs placebo in a blinded post hoc SIENA (Structural Image Evaluation using Normalization of Atrophy) reanalysis of the TEMSO MRI dataset. The effect of teriflunomide on cognition was confirmed by a change from baseline in Paced Auditory Serial Addition Test (PASAT-3) scores in the TEMSO core (N=1,086) and extension (N=740) studies. Additional analyses confirmed the correlation between core study BVL and change in PASAT-3 scores in the extension study by categorizing percentage BVL changes from baseline to Year 2 (assessed by SIENA). Teriflunomide significantly improved PASAT-3 performance vs placebo over 96 weeks in the TEMSO core study. This result was maintained over the extension, suggesting that long-term teriflunomide treatment preserves cognition, with the greatest result observed in MS patients showed the most reduced BVL. This study indicates that the rate of BVL in the initial stages of the disease predicts longer-term cognitive function [32].

Delayed-release oral dimethyl fumarate (DMF) 240mg, twice daily, has demonstrated efficacy regarding the benefit-risk profile in RRMS patients. To evaluate the effectiveness of DMF in RRMS patients treated in real-world clinical practice over two years, focusing on cognition, as well as other functional functions, a multicenter (24 Italian sites), single-arm, open-label study, enrolled 232 patients, with 156 of them completed the study. All patients were evaluated at baseline and every 12 months thereafter using the Rao's Brief Repeatable Battery (BRB), Stroop test and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Cognitive impairment (CI) was defined as a failure in ≥ 2 out of 10 batteries among the BRB and Stroop test. The cognitive data coming from 167 patients over 2 years demonstrated that 83 (49.7%) did not develop CI. However, 49/167 (29%) patients in the intent-to-treat population exhibited CI at baseline. 34 of these patients had cognitive data available at Year 2: among these, 19 (55.9%) did not experience

deteriorating CI over two years compared to baseline. This data indicates that DMF can delay cognitive decline in RRMS patients [33].

Natalizumab, the first humanized monoclonal antibody recommended for RRMS patients, infused intravenously every four weeks, was one of the first to show benefit on cognition in the short term (two years) through a randomized, placebo-controlled trial called AFFIRM. It demonstrated a sustained, significant improvement from baseline in Paced Auditory Serial Addition Test (PASAT) scores. Additional pivotal studies showed that Natalizumab could reduce by 43% the risk of progressive impairment in working memory compared with placebo [34]. In a long-term observational study by Jacques *et al.*, natalizumab was reported to preserve cognition over 7 years of continuous therapy using a computerized test and the Symbol Digit Modalities Test (SDMT). No patient demonstrated evidence of sustained cognitive deterioration over a 24-month period [35]. Recently, an open-label, prospective, single-center, observational study demonstrates the long-term (two to seven years) efficacy of natalizumab on cognitive functions in RRMS patients using Cogstate battery and SDMT. The SDMT and a Cogstate battery were performed every four weeks just prior to Natalizumab infusion for a period of 24 months.

The Beck Depression Inventory (BDI) was administered at baseline and every four months thereafter. Patient data were excluded if the BDI score was greater than nineteen. The number of patients with no evidence of cognitive decline was calculated at twelve months (interim analysis) and twenty-four months. A clinically significant decline was defined as a decline in the performance of ≥ 1.96 SD on one or more tests or ≥ 1 SD on two or more tests that are sustained for at least three months. Results from the Cogstate battery were consistent with results from the SDMT, providing evidence of the validity of using the SDMT in estimating overall cognition in RRMS patients and demonstrating that natalizumab preserves the ability to learn and maintain cognition over the long term, even in patients with pre-existing cognitive deficits [35].

Alemtuzumab is an infusion monoclonal antibody that depletes T and B-cells targeting CD52 and recently recommended for active and very-active RRMS patients. In a study including twenty-one patients during a 15-month follow-up period, it showed stable cognitive function using an extensive neuropsychological battery that covered the domains of verbal learning, verbal and visual memory, attentional span, processing speed, visuoconstruction, and executive functions [36]. Additionally, a measure of premorbid intelligence and questionnaires for depression and fatigue were included. Alemtuzumab stabilized disease progression and improved overall cognition, specifically processing speed within the observational period of 15 months. In this study, although the number of MS patients is very low, cognitive improvement seems to be partly independent of the physical one. More research is needed to investigate whether cognitive impairment in active MS is a potentially relevant but independent marker of disease activity [36].

Ocrelizumab, the first anti-B cell treatment in MS, has shown improvement in Functional Composite score (a composite measure of walking speed, upper-limb movements, and cognitive function assessed by PASAT) compared with subcutaneous interferon beta 1a, in the two identical phase 3 trials Opera I & II, randomly assigned 821 and 835 patients with RRMS to receive intravenous ocrelizumab at a dose of 600

mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 44 µg three times weekly for 96 weeks [37].

ii Cognitive Impairment-Specific Treatment

The use of cholinesterase inhibitors (ChEIs) in MS patients remains controversial. The initial studies in a small number of patients with MS reported contradictory results. Krupp in 2004 reported the positive impact of donepezil in verbal learning and memory in 69 patients, while the same investigator reported no significant effect in 2011, which included 120 MS patients [38, 39]. It is also important to mention the side effects of long-term treatments with ChEIs. Regarding memantine, contradictory findings were reported in a small number of studies prevailing negative outcomes for this drug [40]. Amphetamines significantly improved visuospatial memory and verbal memory, but their long-term usage is not recommended [41]. The exact mechanisms of action and how these drugs affect the brain remain unknown.

Fampridine, a voltage-dependent potassium channel blocker, is indicated for the improvement of walking in adult patients with multiple sclerosis with moderate to severe walking disability (EDSS 4-7). Two recent studies demonstrate the positive impact of fampridine on the motor and cognitive functions, mood and quality of life among multiple sclerosis patients improving cognitive fatigue, alertness, psychomotor speed, and verbal fluency [42, 43]. Further evidence is needed to assess the effect of fampridine, administered according to standard clinical practice, on cognition, fatigue and quality of life in patients with MS.

Amphetamines and modafinil alter the concentration of catecholamines and upregulate activity in attention and executive control networks in the brain. These changes are hypothesized to allow individuals to perform better on cognitive tasks, particularly those requiring good focus and problem solving but there is not enough data indicating benefit in MS patients, while no benefit on learning was found using modafinil and there are enough side-effects of the long term usage [44].

II Non-Pharmacological Interventions

i Neuropsychological Rehabilitation, Cognitive Stimulation and Training

Recently, neuropsychological rehabilitation has been established as a useful therapeutic tool for improving the cognitive function in MS patients. Multidisciplinary and cognitive-behavioural interventions, computer-assisted training and combinations of the above interventions have been indicating consistently better results, especially when tailored individually for each of the MS patients [45, 46]. Evidence-based data has recently become stronger in regard to which interventions may benefit MS patients. In a recent review and meta-analysis including literature from 2007 to 2016, only one intervention received support for a practice standard in verbal learning and memory (modified Story Memory Technique-mSMT), two computer programs received support as a practice guideline for attention and multicognitive domains (Attention Process Training-APT and RehaCom), and several studies provided support for the practice option in attention, learning, and memory [47-50].

ii Physical Exercise

Numerous publications have shown the positive impact of physical exercise on different clinical parameters in MS patients, but evidence remains to be demonstrated, as clinical trials have shown equivocal results [51, 52]. A systematic review by Sandroff *et al.* indicated that a few studies did not show a significant positive result of physical exercise on cognitive impairment [53]. Another systematic review of the impact of yoga also failed to show a positive effect on cognitive decline [54]. This may be the result of insufficiently designed research, and the fact that cognitive impairment is viewed as a secondary outcome. The impact of physical exercise on cognitive decline in MS is gaining hype among cognitive researchers, as one effective intervention both in preventing and improving cognitive decline, although clear results, as well as doses and regimens (e.g., aerobic versus weight training), have not specified yet [55].

Conclusion

One of the biggest challenges treating MS is the effective stratification facing an uncertain prognosis. A major objective at the time of the diagnosis is to arrest the disease at the inflammatory stage, with the hope that this will delay disease progression and minimize future disability. Thus, we need sensitive, specific, and inexpensive biomarkers that can detect disease activity and serve as surrogate markers for assessing therapeutic efficacy. Predictive biomarkers of therapeutic response are needed to be identified and validated in order to guide optimal treatment strategies in MS patients. Furthermore, cognitive decline, such as memory and executive functions impairment, could be present in all stages of the disease even in the very early stages and is considered to be one of the initial manifestations of MS [56-59].

Mini-Mental State Examination (Folstein, 1975), which was used for dementia, is not sensitive to MS cognitive disorders. The three most frequently used neurocognitive batteries in MS are:

- i. The Brief Repeatable Battery of Neuropsychological tests (BRB-N), also known as Rao's battery
- ii. The minimal assessment of cognitive function in MS (MACFIMS) introduced by Benedict *et al.*
- iii. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. BICAMS should not be used within one month after the relapse or within one month of steroid therapy, and the recommended order of administration is first the Symbol Digit Modalities Test (SDMT), then the California Verbal Learning Test (CVLT-II T1-5), and then the Brief Visuospatial Memory Test Revised (BVRT-R T1-3). In most MS patients, annual or bi-annual BICAMS evaluations would be recommended. All of the batteries have similarities and differences, but they all are sensitive, specific, reasonably brief and cover the most frequently affected cognitive domains.

In conclusion, cognitive disorders have an integral effect on the quality of life of MS patients. The evaluation of cognitive status should be considered when making therapeutic decisions, especially for patients who already have cognitive impairment. Cognitive function assessment should become an essential part of the routine clinical examination and follow-up for MS patients because it has been shown to be an important variable of disease prognosis. Recently found proteins that could serve

as biomarkers for the cognitive impairment among MS patients are neurofilaments (NfLs) [60]. Specific and reliable tools should be used for the diagnosis of cognitive decline in MS, and the correlation with clinical parameters, neuroimaging findings and biological markers would help the neuroscientists to find effective treatment strategies improving cognitive impairment and patients' quality of life.

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