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Cognitive impairment in multiple sclerosis

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Background Cognitive impairment is increasingly being recognized as a common and disabling symptom of multiple sclerosis (MS) that contributes to poor quality of life in affected patients. Despite the high prevalence of cognitive impairment in MS, cognitive function is not assessed routinely in clinical practice or in clinical trials. The perception that cognitive assessments are costly, time-consuming, complicated, and difficult to administer and interpret has contributed, at least in part, to the failure to incorporate cognitive testing into standard clinical evaluation of patients with MS. Detailed studies of cognitive impairment in MS are rare and guidelines for the assessment of cognitive function in MS are lacking.

Treatment How to manage cognitive decline in MS also requires further study. Licensed disease-modifying drug (DMD) treatments for MS reduce brain lesion development, and associations between brain lesions and cognitive performance have been reported, providing a rationale for DMD treatment of MS-associated cognitive impairment. There is some evidence for cognitive benefits of DMDs, but as few pivotal DMD trials included cognitive assessments, the effects of these agents on cognition are not fully understood and more studies are needed.

Conclusions It is only through further studies that it will be possible to identify patients with, or at risk of, cognitive impairment and to provide appropriate therapy to limit the effects of this potentially devastating symptom. *Multiple Sclerosis* 2009; **15:** 2–8. http://msj.sagepub.com

Key words: cognitive function; cognitive testing; disease-modifying therapy; multiple sclerosis; quality of life

Introduction

It is well recognized that neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, result in cognitive decline, but only over the last two decades has cognitive impairment been recognized as an important feature of multiple sclerosis (MS) that affects up to 65% of patients [1]. Furthermore, cognitive impairment can occur from the early stages of MS [2,3] and in clinically isolated syndrome (CIS) [4]. Remission of cognitive symptoms is uncommon [1], and cognitive decline may indicate progressive disease despite stable physical symptoms [5,6].

Impaired cognitive function may reflect damage to brain regions that do not affect physical functioning and, therefore, may not be detected during routine neurological assessment. Traditionally, cognitive function has not been included in standard clinical assessments, and cognitive tests are widely perceived to be complicated, time-consuming, and expensive to perform. In addition, few cognitive tests have been validated in MS populations. Consequently, cognitive impairment is probably underdiagnosed in MS.

There is increasing recognition that impaired cognitive function contributes to the profound effect that MS has on patients' everyday functioning, including the ability to work, drive, and maintain and enjoy social relationships [5,7,8], leading to a reduced quality of life (QoL). It is essential, therefore, that cognitive function is considered when assessing the impact of MS on patients' QoL. Furthermore, early detection of cognitive impairment is essential to enable therapeutic intervention to alleviate symptoms or prevent further cognitive decline, although how best to manage MS-related cognitive impairment is currently unclear. There have been few studies investigating the effects of pharmacological therapies on cognitive outcomes in MS and robust data demonstrating cognitive benefits from approved MS therapies are

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currently lacking. Cognitive impairment may also reduce patients' ability to understand and adhere to treatment regimens [1,9].

There is a clear need for continued investigation into cognitive impairment in MS to develop prevention, management, and treatment strategies. This review will focus on the early detection of cognitive impairment in MS and discuss pharmacological treatment options for patients with or at risk of developing cognitive impairment.

Cognitive impairment – a significant feature of MS

Cognitive impairment may affect patients with any MS disease form or any disease stage [1]. Although the symptoms and severity of cognitive impairment can vary widely between individuals, learning, memory, attention, processing speed, visuospatial abilities, and executive functions are affected most frequently in MS, whereas dementia and language deficits are uncommon [9,10].

Little is known about the natural history of cognitive impairment in MS. Large studies of cognitive decline in MS are scarce, and the interpretation of available data is complicated by inter-patient heterogeneity in the disease course and the potential influence of disease subtype and duration on cognition. Furthermore, differences between published studies, for example, disease characteristics, treatment, and duration of follow up, complicate data interpretation. As a result, current data are conflicting [5,6,11,12], and there is no clear consensus regarding the relationship between cognitive function and disease duration, stage, type, or disability level. Despite these issues, cognitive impairment is believed to increase with worsening physical disability [6], duration of disease [5,12], and with the onset of a progressive disease course [1,10,12].

Further, large, well-designed, longitudinal studies are clearly needed to improve our understanding of cognitive decline in MS. Recently, two large, international, observational longitudinal studies have completed enrolment: the CogniMS [13] and CogniCIS [14] studies, which are assessing cognitive function and decline over 2 years in patients with early MS and CIS, respectively. Both studies also aim to assess geographical differences in the pattern of cognitive impairment in patients with MS or CIS.

The influence of comorbidities on cognitive performance

Numerous factors have been identified that may influence cognitive function in patients with MS (Box 1) [10], including depression, anxiety, and fatigue, which are common comorbidities in MS [15–17]. Patient awareness of declining cognitive ability may also increase anxiety and depression, and patients with depression can overestimate their level of cognitive dysfunction, which may further increase their level of depression [18,19].

Fatigue may impair cognitive functions, including processing speed and sustained attention. The potential for central nervous system-active medications (such as anti-epileptics, selective serotonin reuptake inhibitors, and baclofen) to cause fatigue must be considered in patients with MS: impairment of cognitive functions has been reported in patients taking such medications, but a clear causative link has not been shown [20].

Detection of cognitive impairment in MS

The observations that irreversible cognitive impairment will ultimately affect most patients with MS and can occur early in the disease course highlight the need for routine cognitive assessment. Furthermore, little is known about risk factors for cognitive decline, making identification of at-risk individuals difficult. Nevertheless, some risk factors have been described including advanced age, low intelligence quotient or educational level [21], and depression [3]. Cognitive dysfunction in early disease seems to be a major risk factor for ongoing decline, at least in the short term [1,22], but in the longer term, the risk of cognitive decline increases in all patients. Interestingly, patient-reported cognitive decline is not a sensitive marker for actual deficit [19].

Neuropsychological (NPS) testing

The most sensitive method for detecting cognitive impairment is through NPS testing, but NPS tests are generally perceived to be complicated, time-consuming, and expensive, and many must be administered by trained specialists. Therefore, NPS

Box 1 Factors influencing cognitive dysfunction in MS

- Location and extent of pathological lesions
- Disease course (progressive versus relapsing)
- Disease duration
- Fatigue
- Affective disturbance (e.g., depression)
- Central nervous system-active medication

testing is not widely used in the clinic: time limitations alone may preclude its routine use.

Many assessment tools widely used in other indications, such as the Mini Mental State Examination and variants, are insensitive to MS-related cognitive dysfunction or have not been validated adequately in this population. Both single, speed-related cognitive tests and extensive test batteries, such as the Rao's Brief Repeatable Battery (BRB) [23], have been described that accurately assess cognitive function in patients with MS (Table 1) [24–28]. Recommendations for the optimal assessment of cognitive impairment in MS have been published [26]. Research is ongoing to define the minimum battery of NPS tests that will enable the routine assessment of cognitive function in MS [6]. Such a test battery should be sensitive to changes in the cognitive domains most commonly affected by MS but should be insensitive to motor dysfunction [26]. Interestingly, the degree of cognitive impairment reported by patients has been shown to correlate less well with NPS test results than that reported by patient informants, such as a spouse or other family member [24]. Tests that can be completed by patient informants (e.g., the MS Neuropsychological Screening Questionnaire [24]) may, therefore, provide valuable information in addition to that gained from the patient.

Magnetic resonance imaging (MRI)

In recent decades, MRI has become the gold standard tool for assessing brain lesions in MS and has been incorporated into diagnostic criteria [29]: brain imaging may also help to detect patients with, or at risk of, cognitive impairment. Consistent but moderate correlations between cognitive impairment and conventional MRI disease measures have been reported, including T1 lesion load, T2 lesion load, diffuse brain damage, and brain atrophy [30–32]. Furthermore, a recent, cross-sectional analysis of 16-year follow-up data from a pivotal study of interferon (IFN) β-1b in patients with relapsing–remitting MS (RRMS) reported that not only did current MRI disease measures correlate significantly with cognitive performance but also that baseline MRI T2 burden of disease predicted for cognitive test scores at year 16 [33]. Newer, non-conventional MRI techniques with increased specificity have provided further insights into the relationship between lesions in specific brain areas or the extent of brain involvement and cognitive impairment in MS [30,34] and may provide valuable information if incorporated into future trials.

Management of cognitive impairment in MS

Symptomatic therapies, including cognitive behavioral therapy, psychotherapy, and occupational therapy, which aim to optimize cognitive performance, may reduce the impact of cognitive impairment on patients' daily lives [35,36]. Pharmacological treatment of comorbidities that contribute to poor cognitive performance, such as fatigue and depression, may also provide cognitive benefits, but this area has not been studied widely. Acetylcholinesterase inhibitors (e.g., donepezil), which are commonly used in the treatment of Alzheimer's disease, may also benefit patients with MS-associated cognitive impairment [37,38]. Whether approved treatments for MS can prevent, halt, or delay cognitive decline is only starting to be understood.

The rationale for disease-modifying drug (DMD) treatment of cognitive impairment

Since the 1990s, use of DMDs (IFN β-1a, IFN β-1b, and glatiramer acetate [GA]) has significantly improved outcomes for patients with MS. DMDs have been shown to improve clinical (relapses, disability progression) and MRI (T1 and T2) measures of disease [39] and are now licensed as first-line therapy for RRMS. As DMD therapy can attenuate inflammatory processes and prevent the development of new brain lesions or progressive brain atrophy, DMDs may also have cognitive benefits for patients with MS [36].

Table 1 Cognitive test batteries and individual cognitive tests that have been shown to be suitable for the assessment of cognitive function in patients with multiple sclerosis (MS)

Test batteries	Individual cognitive tests
Rao's Brief Repeatable Battery (BRB)	Paced Auditory Serial Addition Test
Rao's BRB plus Stroop Color-Word Task	Symbol Digit Modalities Test (adapted for use in MS)
MS Neuropsychological Screening Questionnaire	California Verbal Learning Test
Minimal assessment of cognitive function in MS	Brief Visuospatial Memory Test – Revised
	Delis–Kaplan Executive Function System, Sorting Test
	Controlled Oral Word Orientation Test
	Judgment of Line Orientation Test

DMDs for the management of cognitive impairment in patients with RRMS

Despite a large body of evidence for the beneficial effects that DMDs have on the physical symptoms of MS, data supporting cognitive benefits of DMDs are scarce (Table 2). Cognitive function was not studied in most large, pivotal trials of DMDs in MS, and only a few smaller trials have been performed specifically to assess the effect of DMDs on cognitive function. Although cognitive function has been assessed retrospectively in some studies, the cognitive benefits of DMDs remain unconfirmed.

The potential cognitive benefits of intramuscular IFN β-1a were assessed retrospectively in the pivotal Phase III study in RRMS [40]. Based on findings in a subgroup of 276 patients (166 of whom completed the cognitive assessments), a significant benefit of IFN β-1a treatment was reported for several cognitive measures after 2 years. The most pronounced effects were seen in the cognitive domains known to be affected most commonly by MS [40]. How high-dose, high-frequency subcutaneous (s.c.) IFN β-1a affects cognitive function in patients with MS remains to be determined.

Cognitive benefits of IFN β-1b have also been reported. Improvements in cognitive function were observed between years 2 and 4 of treatment in a subgroup of patients ($n = 30$) involved in the pivotal randomized, double-blind, placebo-controlled Phase III trial of IFN β-1b in RRMS [41]. Similarly, cognitive benefits of IFN β-1b were reported in a 1-year study of 46 patients with RRMS, 23 of whom received IFN β-1b treatment [42] and an open-label 1-year study of 16 patients with relapsing MS [43]. However, these data should be interpreted with caution, given the small number of patients, the absence of baseline cognitive data in some studies, probable learning effects due to repeat testing, and chance effects due to multiple comparisons.

To date, there is little evidence to suggest that GA has cognitive benefits in patients with RRMS. In one study, similar improvements in NPS performance were reported in patients treated with GA and in those receiving placebo after 2 years, probably reflecting learning effects [44]. However, evaluation of patients treated with GA showed minimal cognitive deterioration from the performance at baseline after approximately 10 years of follow up [11]. Although it was suggested that this might reflect a protective effect of GA, this could not be

Table 2 Studies of the effects of disease-modifying drugs (DMDs) on cognitive function in patients with multiple sclerosis (MS)

DMD	Patient group	Patient number	Study design	Study duration	Key findings	Ref.
IFN β-1a (30 μg i.m. qw)	RRMS	166	Pivotal Phase III randomized, placebo-controlled prospective trial; subgroup analysis	2 years	Significant beneficial effect of i.m. IFN β-1a on information processing, learning, and memory	[40]
IFN β-1b (50 μg or 250 μg s.c. eod)	Relapsing MS	30	Pivotal Phase III randomized, placebo-controlled trial: retrospective subgroup analysis	4 years	Significant improvement in cognitive function over years 2–4 with higher-dose IFN β-1b	[41]
IFN β-1b (250 μg s.c. eod)	Relapsing MS	16	Open-label, prospective	1 year	Positive effect of IFN β-1b on cognitive function, independent of effect on clinical disease measures	[42]
IFN β-1b (250 μg s.c. eod)	RRMS	46	Open-label, longitudinal	1 year	Significant improvement or stable cognitive test performance with IFN β-1b treatment; deterioration in some tests in control group	[43]
IFN β-1a (22 or 44 μg s.c. tiw)	RRMS (EDSS ≤ 4.0)	459	Prospective, observational, cohort study	3 years	Cognitive benefits of IFN β-1a, which may be dose dependent	[44]
GA (20 mg qd)	RRMS (EDSS < 5.0)	248	Pivotal Phase III randomized, placebo-controlled trial	2 years	Cognitive test scores improved from baseline to years 1 and 2; not differences between placebo and GA; learning effects may explain the longitudinal changes seen	[45]
GA (20 mg qd)	RRMS (EDSS < 5.0)		Prospective, open-label extension study to pivotal Phase III trial	10 years	No significant change in test scores of memory or semantic retrieval; decline in attention; test scores during years 0–2 predictive of cognitive function over 10-years	[11]

IFN, interferon; im, intramuscularly; qw, once weekly; RRMS, relapsing–remitting multiple sclerosis; sc, subcutaneously; eod, every other day; tiw, three times weekly ; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; qd, once daily.

demonstrated conclusively owing to the open-label design of this extension study.

Cognitive benefits of DMDs in patients with mild physical disability

The cognitive benefits from IFN β-treatment in patients with early RRMS or mild physical disability are being investigated further in ongoing studies. The potential benefits of IFN β-1a (22 μg or 44 μg s.c. three times weekly) treatment in mildly disabled patients with RRMS (diagnosed according to the McDonald criteria; Expanded Disability Status Scale [EDSS] score ≤4.0) are currently being assessed in the COGIMUS (COGnition Impairment in MS) study. COGIMUS is a prospective, multicenter, observational, dose-controlled, Italian cohort study in which cognitive functioning is being assessed annually during 3 years of treatment using the Rao's BRB and the Stroop Color-Word Task. Preliminary data from the COGIMUS study suggest that IFN β-1a has cognitive benefits in mildly disabled patients with RRMS and that these effects may be dependent on the IFN β-1a dose [45]. The study has now been completed: data have been analyzed and are currently being prepared for publication. In COGIMUS, cognitive function was assessed at baseline to obtain an indication of the prevalence of cognitive impairment in this patient group [32]. How cognitive performance relates to disease measures, affective disorders, and social functioning is also being investigated.

Cognitive function and the pattern of cognitive decline in patients with early MS (diagnosed ≤2 years before study entry) receiving IFN β-1b treatment are being investigated in the CogniMS study [13], an international, longitudinal study in which cognitive performance, depression, and health-related QoL will be assessed at 6 monthly intervals over 2 years. A total of 1520 patients have been recruited in 33 countries, and preliminary baseline data have been reported on 928 (61%) patients: these data indicate that the characteristics of cognitive impairment in this patient population are similar worldwide; no data regarding the influence of IFN β-1b on cognitive function have yet been reported [13].

Cognitive benefits of DMD therapy in patients with CIS

Cognitive impairment can occur in patients with CIS and may be the first manifestation of the disease [13,46]; therefore, the prevention of further cognitive decline should be an important goal of treatment in this patient group. Recent data from the 1-year open-label extension phase of the BENEFIT (Betaferon®/Betaseron® in Newly Emerging MS For Initial Treatment, Schering Berlin, Germany/Berlex Mantville, NJ, USA) trial suggest that early initiation of IFN β-1b therapy in patients with CIS may protect against cognitive decline, in addition to providing physical benefits [47]. An integrated 3-year analysis at the end of the extension phase showed that patients who received IFN β-1b treatment during the initial 2-year placebo-controlled phase of the study ($n = 292$) performed better in the Paced Auditory Serial Addition Test (PASAT; conducted as part of the MS Functional Composite) than those who initially received placebo treatment ($n = 176$; $P = 0.011$) [48].

Pharmacological treatment of cognitive impairment in progressive MS

For patients with progressive disease, or disease that is unresponsive to IFNs and GA, recent evidence from a small study of 27 patients with a mean (standard deviation: SD) disease duration of 13.5 (5.11) years, the majority of whom had secondary progressive MS, suggests that mitoxantrone may have beneficial effects on cognition [49]. Mitoxantrone treatment (mean [SD] duration of treatment: 21.6 [7.23] months) was associated with a trend toward improved cognitive performance, as assessed by the PASAT and Auditory Consonant Triagram tests, in addition to reduced physical disability, evidenced by a reduction in mean EDSS score over the course of the study.

Conclusions

Cognitive impairment is a common feature of MS that is present early in the course of the disease and has a significant negative impact on patients' QoL and on their family and carers. Despite increasing recognition of the impact of cognitive impairment in MS, routine cognitive testing is uncommon, partly due to the lack of reliable, simple, inexpensive, and quick-to-administer tools that have been validated in MS populations. The potential benefits of routine, regular assessment of cognitive function in patients with MS are clear: early detection of cognitive impairment is essential to enable therapeutic intervention to prevent further decline and reduce the impact of cognitive impairment on patients' lives. Furthermore, worsening cognitive impairment may indicate progressive disease in the absence of increasing physical disability. Hence, there is a need for simple cost-effective measures of cognitive function to be integrated into routine patient management. The

optimal treatment of cognitive impairment also requires further study, including whether DMDs can prevent, delay, or even reverse cognitive decline. Although preliminary results suggest that DMDs may help to preserve cognitive function in patients with MS, further studies are urgently needed to enable optimum management of this highly prevalent and disabling symptom. In addition, continuing professional education is needed to raise awareness of the importance and extent of cognitive impairment in patients with MS.

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