

Identifying Early Neuropsychological Indicators of Cognitive Involvement in Multiple Sclerosis

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Elizabeth S Gromisch¹⁻⁴ 
Zaenab Dhari^{1,2}

¹Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital, Trinity Health Of New England, Hartford, CT, USA; ²Department of Rehabilitative Medicine, Frank H. Netter MD School of Medicine at Quinnipiac University, North Haven, CT, USA; ³Department of Medical Sciences, Frank H. Netter MD School of Medicine at Quinnipiac University, North Haven, CT, USA; ⁴Department of Neurology, University of Connecticut School of Medicine, Farmington, CT, USA

Abstract: Multiple sclerosis (MS) is a debilitating disease of the central nervous system that is most commonly seen in early to middle adulthood, although it can be diagnosed during childhood or later in life. While cognitive impairment can become more prevalent and severe as the disease progresses, signs of cognitive involvement can be apparent in the early stages of the disease. In this review, we discuss the prevalence and types of cognitive impairment seen in early MS, including the specific measures used to identify them, as well as the challenges in characterizing their frequency and progression. In addition to examining the progression of early cognitive involvement over time, we explore the clinical factors associated with early cognitive involvement, including demographics, level of physical disability, disease modifying therapy use, vocational status, and psychological and physical symptoms. Given the prevalence and functional impact these impairments can have for persons with MS, considerations for clinicians are provided, such as the role of early cognitive screenings and the importance of comprehensive neuropsychological assessments.

Keywords: multiple sclerosis, early cognitive impairment, neuropsychological assessment, modifying factors

Introduction

It is estimated that there are 2.8 million people globally living with multiple sclerosis (MS), a chronic neurological condition that is most commonly diagnosed in early to middle adulthood, although it can be seen in children and older adults.^{1,2} About 85% of persons with MS are initially diagnosed with relapsing remitting MS (RRMS), which is characterized by relapses and stable disability in between.^{1,2} A diagnosis for RRMS is based on evidence of dissemination in space (ie, distinct location in the central nervous system) and in time, which is met with ≥ 2 demyelinating episodes and ≥ 2 lesions.² Individuals who have had a single episode are considered to have clinically isolated syndrome (CIS).² Over time, RRMS may evolve to secondary progressive MS (SPMS).² Another 12% are diagnosed with primary progressive MS (PPMS), who have had at least one year of disability progression without relapses and meet two additional criteria (≥ 1 periventricular, cortical/juxtacortical, or infratentorial T2- hyperintense lesions, ≥ 2 spinal cord T2- hyperintense lesions, and/or cerebrospinal fluid-specific oligoclonal bands).^{1,2}

The clinical presentation of MS is heterogeneous, with persons presenting with range of physical and emotional symptoms. A common and often intrusive symptom of MS is cognitive impairment, which can affect up to 70% of the MS population.³ Persons with MS can experience difficulties in several cognitive domains, including

Correspondence: Elizabeth S Gromisch
490 Blue Hills Avenue, Hartford, CT,
06112, USA
Tel +860-714-2154
Fax +860-714-8933
Email elizabeth.
gromisch@trinityhealthofne.org

processing speed, attention, learning and memory, and executive functioning.³ These impairments can have a negative impact on several aspects of persons' with MS lives, including their quality of life and completion of everyday activities.^{4,5} While more severe cognitive impairment is more likely in persons with SPMS,⁶ signs of cognitive involvement can be present early in the disease process.

Within the first year of diagnosis, about half of persons with MS report having either minimal or mild cognitive difficulties, with greater complaints over the first decade.⁷ Although uncommon, some persons with MS present with cognitive impairment as their primary symptom.⁸ Individuals with an aggressive form of cognitive impairment at this early stage can exhibit severe deficits reaching the level of a major neurocognitive disorder.^{9,10} In addition, cognitive issues may be present preclinically, with one study finding that men who developed MS two years later performed six points lower on an intelligence quotient test compared to a control group.¹¹ As such, there is a strong need to evaluate and monitor cognitive functioning beginning early in the disease so as to detect these issues as soon as possible.

That being said, understanding the prevalence and types of cognitive involvement early in the disease process comes with challenges as there is not a clear definition of what is considered the early stage of MS. The literature is mixed, with studies characterizing early MS by disease duration (either since diagnosis or symptom onset),^{12–112} level of disability (such as with the Expanded Disability Status Scale; EDSS),^{113–120} or a combination of both metrics.^{121–158} Furthermore, the time frame of disease duration for early MS varies greatly. For instance, some studies defined early MS shortly after symptom onset or diagnosis (eg, six months or less),^{13,15,18,24–26,29,31,32,34,35,37,41,48,54,65,72,94,112,153,156,158} while other studies used broader time frames, such as 10 years or less.^{33,46,78,89,113,121,129–131} As some studies were investigating the signs of cognitive involvement soon after the onset of initial symptoms, persons with CIS suggestive of MS were included, either comprising the entire early stage group^{17,21,26,37,47,48,54,57,58,61–64,66,68,71,79,84,92–94,99,101,103,107,137,142,148,153,156} or as part of a mixed sample with persons with early RRMS.^{12,18,20,22,28,44,53,56,67,73,75,77,80,82,83,87,105,106,108,109,112,122,143,145,146} In contrast, studies that have examined early MS in relation to late MS have defined the latter as a disease duration of >10²³ or >12 years.^{19,104}

Given the need to understand the early signs from a clinical perspective, we aimed to review the current literature on cognitive impairment that occurs early MS in order to answer

the following questions: 1) what is the prevalence of cognitive involvement in early MS; 2) what types of cognitive deficits are seen in early MS and how are they measured; 3) how does early MS cognitive involvement evolve over time; and 4) what clinical factors are associated with early MS cognitive involvement and its progression. In order to provide a comprehensive review of the literature in this area, we utilized a broader definition of early MS (ie, 10 years or less disease duration and inclusion of persons with CIS) and discuss how the different criteria may contribute to discrepancies. Finally, we will discuss implications for clinicians, such as screening batteries for early detection and the importance of comprehensive neuropsychological assessments.

Methods

A search was conducted of articles published in English between 1991 and 2020 using PubMed, MEDLINE, and CINAHL using a combination of the search terms cognition, cognitive, neuropsychological, early, multiple sclerosis, and clinically isolated syndrome. Both pediatric-onset and adult-onset cohorts were included. A total of 2003 entries were found (Figure 1). After removing duplicate entries (n = 1126) and articles where only the abstract was in English (n = 1), literature reviews, protocols, corrections, case studies, working group reports, letters to the editor, and conference abstracts (n = 299) were excluded. The titles and abstracts were then screened, with articles removed if they were not about MS, including animal model-based studies (n = 87), or were not about cognitive functioning (n = 107). The remaining 383 articles were split between the two authors for review. Articles were excluded if they did not fit our definition of early MS (n = 138), only used self-reported cognitive measures (n = 4), or were not related to our study questions (n = 94). If one author was unsure if an article met the inclusion criteria, it was reviewed by the other and a consensus was reached. Due to the breadth of literature that examines neuroimaging and biomarkers with cognitive functioning in MS, it was decided to exclude these articles from the current review in order to focus on neuropsychological indicators. A total of 147 studies were included in this review.

Results

Prevalence of Cognitive Impairment in Early MS

Fifty studies provided an estimate on the prevalence of cognitive involvement in early MS, with rates being as

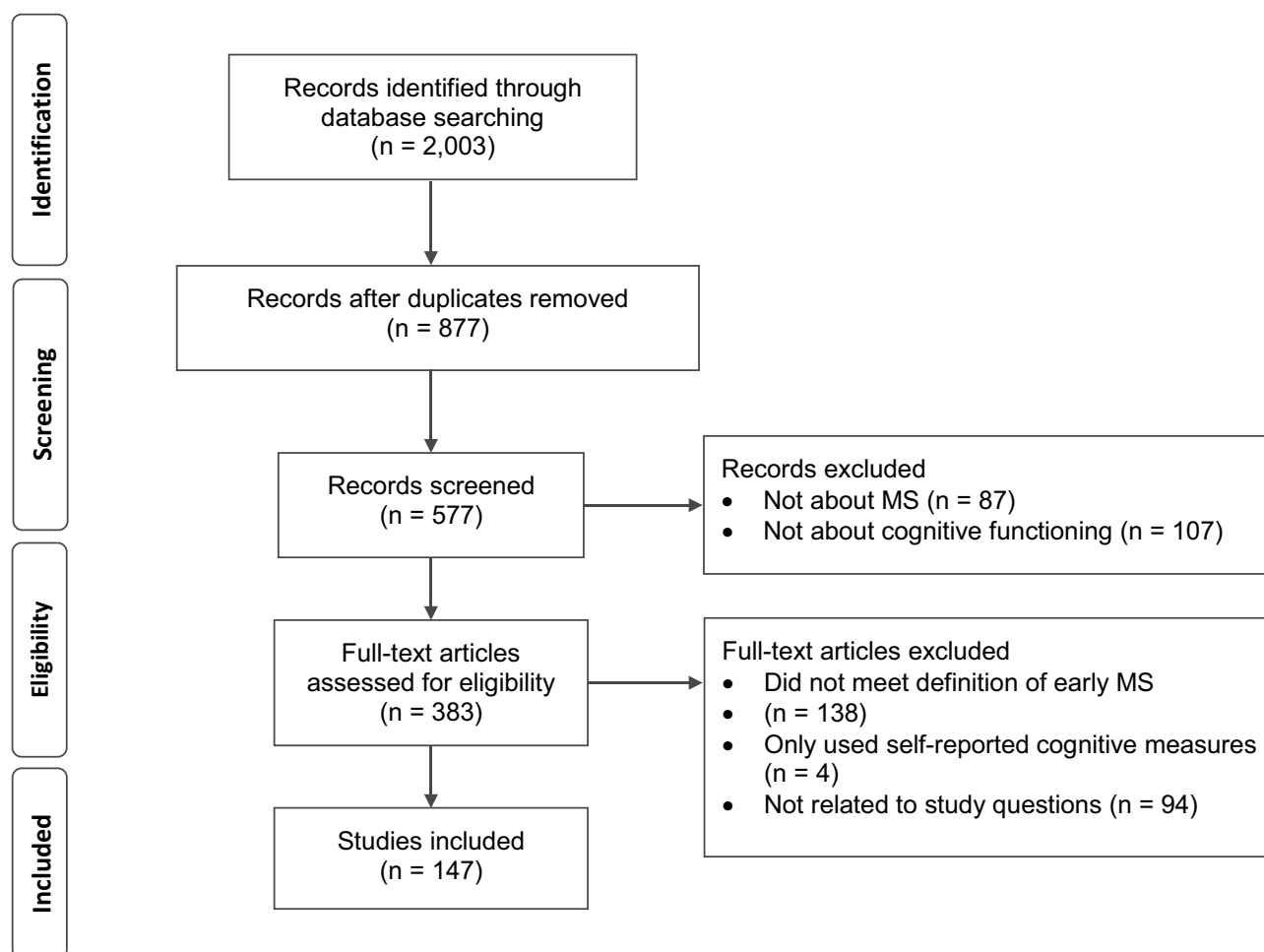


Figure 1 PRISMA flow diagram of article screening and selection for literature review.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.¹⁸³

high as 61%,⁸² however, the numbers vary greatly between studies. Besides the variable definitions of early MS, there are several different criteria employed for classifying persons as cognitively impaired. Fischer et al¹⁹ identified 20 distinct approaches for defining cognitive impairment in the literature, which could be broadly grouped by 1) the number of impaired measures, 2) a composite score (ie, a z-score calculated by performance on all measures in a domain), and 3) a combination of the first two strategies. Furthermore, different stringencies for impairment have been used, such as the number of required “failed” measures and the cut-off for impairment (eg, 1.5 standard deviations (SD) below the mean). Fischer et al¹⁹ noted that using more liberal criteria could result in the prevalence of cognitive impairment in early MS being overestimated: in their own sample, the rate of cognitive impairment ranged from 0% to 68% using the 20 identified criteria. In addition, it should be kept in mind that healthy

controls may demonstrate impairment, and some researchers have adjusted for this in the quantification of impairment in early MS. For instance, Baysal Kırac et al¹² adjusted the number of impaired measures required (ie, four or more measures) based on performance of their healthy controls. Deloire et al,⁴¹ on the other hand, calculated the attributable risk for impairment on one or two measures in their early MS cohort based on the percentage of “failures” in their control group.

As demonstrated in Table 1, several criteria have been used to define cognitive impairment during the early stage of MS. While the number of “failed” measures varied in those studies, it was often influenced by the assessment battery used. For instance, the Brief International Cognitive Assessment for MS (BICAMS)¹⁵⁹ consists of three measures (Symbol Digit Modalities Test (SDMT), five learning trials of the California Verbal Learning Test-Second Edition (CVLT-II), and three learning trials of the Brief Visuospatial Memory Test-

Table I Rates of Impairment in the Literature by Different Criteria

Definition	Rates
Impaired on a composite score (<1.3 SD) ⁴⁰	39.1%
Impaired on one or more neuropsychological measures (<1.5 SD or 5th percentile) ^{22,41,44,46,85,113}	32.3–53.7%
Impaired on one or more neuropsychological measures (<2 SD) ^{12,29,125,129,145,146}	29.3–56.1%
Impaired on one or more cognitive domains (<2 SD) ^{47,51}	22–29%
Impaired on two or more neuropsychological measures (<1.5 SD or 5th percentile) ^{18,22,25,31,32,34,39,41,44,62,84,85,113,135,153}	10.8–52.3%
Impaired on two or more neuropsychological measures (<2 SD) ^{12,17,21,29,37,52,57,82,88,130,134}	6.6–61%
Impaired on two or more cognitive domains (<1.5 SD or 5th percentile) ^{27,58,59,115}	34.5–57.5%
Impaired on three or more neuropsychological measures (<1 SD) ¹²⁰	21.4%
Impaired on three or more neuropsychological measures (<1.5 SD or 5th percentile) ^{25,32,49,62,64,71,85,92,96,113,133,138}	4.6–47.8%
Impaired on three or more neuropsychological measures (<2 SD) ^{12,13,17,29,45,150}	11–39.6%
Impaired on four or more neuropsychological measures (<1.5 SD or 5th percentile) ⁶²	13%
Impaired on four or more neuropsychological measures (<2 SD) ¹²	19.6%
Impaired on one-third of the neuropsychological indices (<1 SD) ^{67,106}	32–37.3%

Revised (BVM-T-R)), and impairment on one measure is considered the threshold.¹¹³ Using that criterion, 32.3% of Marstrand et al' sample¹¹³ were categorized as cognitively impaired; if held to the standard of three impaired measures (ie, the entire battery), the percent of participants categorized as impaired dropped to 4.6%. On the other hand, with a more extensive battery, a higher number of “failed” measures would be more appropriate. For instance, Jönsson et al,²⁷ who had 30 cognitive variables, identified mild impairment if at least five measures were impaired, while severe was defined as 20 or more. They also defined mild, moderate, and severe cognitive impairment by the number of impaired cognitive domains.

Types of Deficits and the Measures Used to Identify Signs of Cognitive Involvement in Early MS

Eighty studies detailed the specific measures where persons with early MS have been impaired, with deficits in

several cognitive domains, including attention, processing speed, working memory, verbal learning and memory, visual learning and memory, executive functioning, language, and to a lesser extent visuospatial ability and theory of mind ([Supplementary Table 1](#)). These signs of cognitive involvement were identified either through persons with early MS performing below a specific threshold (eg, 1.5 SD below the normative mean) or in comparison to a matched cohort of healthy controls. Even if persons with early MS do not meet the threshold for being categorized as cognitively impaired, they may still exhibit relative difficulties. For instance, Pitteri et al⁴⁹ found that their “cognitively normal” group performed worse on measures of verbal learning and memory, attention and processing speed, and executive functioning compared to healthy controls.

Although the measures used varied between studies, two of the most commonly used measures that have

detected early cognitive involvement were the SDMT and the Paced Auditory Serial Addition Test (PASAT). Forty-one studies found impairments in early MS using the SDMT, a 90-second measure where the examinee orally matches numbers to corresponding symbols as quickly as possible.¹⁶⁰ The SDMT has emerged as a particularly sensitive measure, with one study finding that it correctly classified 75.4% of their sample with cognitive impairment.⁴¹ Thirty-four studies identified deficits with either the 3-second or 2-second version of the PASAT, where the examinee attends to and calculates numbers that are presented auditorily via a tape recording.¹⁶¹ Besides issues with complex attention, processing speed, and working memory, persons with early MS have also demonstrated slowed reaction time on attentional measures, although measurement of this metric was less common in the identified studies.

Issues with learning and memory can emerge early in the disease process. Thirty-six studies showed that persons with early MS exhibit difficulty learning and recalling verbal information. The most commonly used measure was the Selective Reminding Test (SRT), which 18 studies found impairments on, particularly on the Long Term Storage, Consistent Long Term Retrieval, and Delayed Recall indices. Besides the SRT, other measures that detected impairments were the CVLT-II (four studies) and the Rey Auditory Verbal Learning Test (RAVLT; six studies). Difficulty learning and remembering visual material was also observed, as noted by 34 studies. The Spatial Recall Test (SPART) was used the most frequently, with issues being identified in 15 studies, particularly on the Delayed Recall index. Impairments were also found in nine studies using the BVMT-R.

While several studies have focused on attention, processing speed, and memory impairments in early MS, executive dysfunction can also occur, as noted by 26 studies. Pitteri et al⁴⁹ found that 71% of their sample exhibited deficits on a composite executive functioning index, although other studies have found much lower rates of impairment.¹²⁵ As executive functioning in a broad term, several different processes such as set-shifting (eg, Trail Making Test Part B; TMT-B; eight studies), inhibition (eg, Stroop; 10 studies), and abstraction (eg, Similarities from the Wechsler Adult Intelligence Scale; four studies) can be included in this domain. Verbal fluency has sometimes been included as executive functioning tasks,⁴⁹ in addition to being a language-based task. Deficits in both phonemic (ie, letter) and semantic

(ie, category) fluency have emerged in 15 studies and 16 studies, respectively, as signs of early cognitive involvement. Furthermore, with persons with CIS, both verbal fluency tasks were able to classify individuals with cognitive impairment with 64–82% sensitivity and 66–79% specificity.¹⁷

However, because of the heterogeneity of these samples, the types of impairments observed are not consistent across studies. For instance, in their sample of persons with CIS, Viterbo et al noted only 5–7% were impaired on the SDMT and PASAT, while other studies^{103,121} did not find differences between healthy controls and persons with early MS on PASAT or SDMT performances. In addition to the different definitions for early MS, another consideration may be in how the measure is utilized and scored, such as in the case of the PASAT where examiners may look at total correct scores, dyads, and/or performance at different points of the test. When Berard et al¹²¹ used it to measure cognitive fatigue (eg, performance on the last third of the task compared to the first third), persons with early MS exhibited significantly greater difficulties.

In addition to cognitive involvement becoming more prevalent in late MS,^{19,58,79,84,88,104} as the disease progresses, some of these cognitive difficulties may become more apparent. For instance, Achiron et al⁷⁹ found that the percent of persons with MS with cognitive impairment significantly increased after five years of MS onset, while Štecková et al⁸⁷ noted greater impairments among persons who had had MS for 10 years compared to persons with CIS and persons with MS for five years. In terms of specific deficits, while Caputi et al¹²⁸ found that persons with early RRMS did not differ from healthy controls in terms of object naming and visual discrimination, deficits were more pronounced in later stages of the disease (ie, SPMS). Processing speed and memory performances have also been shown to be lower in late MS compared to early MS.^{23,104,157}

Evolution of Early Cognitive Impairment

In addition to studies comparing MS cohorts at different stages of the disease, there have been 24 longitudinal studies with persons with early MS. While some studies did not observe a decline on individual¹²¹ or a battery of measures,^{106,131,153} several identified an increase in cognitive impairments over time. For instance, Amato et al¹³³ noted that the number of persons with MS with no cognitive impairment decreased from 74% at baseline to 44% at

the 10-year follow-up, with a particular increase in the number with mild cognitive impairment (8% to 34%). Increases in the number of persons with cognitive involvement have also been observed at two years,^{134,149} three years,^{115,135} four years,¹³² five years,^{47,51,60,112,136} seven years,^{31,116} and nine years¹⁵⁸ since the initial neuropsychological evaluation.

Several studies have found that the SDMT is sensitive to progression, with greater impairments noted over time.^{15,28,60,135,136,143} While declines in attention, processing speed, or memory were detected in several cohorts,^{31,47,60,112,116,134,158} this was not observed by Wybrecht et al.⁵⁰ Instead, they found a greater number of persons with MS impaired in executive functioning 10 years later, particularly on the TMT-B, Digit Spans Backwards, and both phonemic and semantic fluency.⁵⁰ Declines in executive functioning, including verbal fluency, have been noted in other longitudinal early MS cohorts.^{47,134}

While longitudinal cohorts can provide insight into the progression of early MS cognitive impairment, there are potential confounders that may skew results. Some studies have noted improvements on certain measures at the second assessment, which has been attributed to factors such as practice effects, short intervals between the initial and follow-up testing, anxiety at baseline, and initiation of disease modifying therapies (DMT) after the first evaluation.^{18,27,121} Besides judging the length of time between assessments and using an equivalent alternative form of a measure, clinicians may consider calculating the reliable change to determine if a reduction in performance (or improvement) represents meaningful change.

Clinical Factors Associated with Early Cognitive Involvement and Its Progression

Demographics

When examining their patients' performances and determining whether there is evidence of cognitive impairment, clinicians should be mindful of factors that may be associated with reduced performance. Although 10 studies did not find a significant relationship between age or gender with cognitive performances in early MS,^{12,21,37,39,46,47,65,82,125,135} nine noted worse performance with older age or among men.^{18,24,26,30,44,52,111,133,139} For instance, men with early MS have demonstrated greater impairments in aspects of

executive functioning and verbal learning and memory.^{30,139} One study⁷⁸ also found that low free testosterone levels in men were related to more longitudinal changes on the SDMT.

The contributions of race and ethnicity in early MS cognitive involvement have been studied less extensively. While Black and Hispanic persons with MS had lower scores on the oral SDMT compared to White persons with MS, Amezcua et al.²⁰ attributed these findings to underlying population differences (eg, sociodemographic factors) rather a more severe disease course. The authors highlighted the importance of using appropriate normative data to identify persons in the early stages of MS who are exhibiting cognitive involvement. Julian et al.⁶⁷ did not find race to be a significant contributor to cognitive performance, but noted a trend with lower scores and identifying as Hispanic.

Seven studies did not demonstrate an association between education level and cognitive performance,^{39,44,46,47,65,125,135} while 10 showed that persons with fewer years of education have greater levels of impairment.^{17,18,21,30,37,52,72,111,113,144} For instance, Bonnet et al.⁷² found that persons with early MS who had low educational levels (<12 years or no schooling) were impaired on 13 out of 15 cognitive tests, while persons with high education levels were only impaired on three measures. Persons' education level has also been utilized as a marker for cognitive reserve. For instance, Barbu et al.¹³¹ used years of education and performance on the North American Adult Reading Test to calculate cognitive reserve. While they did not find that cognitive reserve predict change in cognitive functioning three years later, their sample did not exhibit significant decline over time. In addition, Planche et al.⁸⁰ hypothesized that their sample's high education level contributed to the lack of impairment in memory impairments.

Level of Disability

There has been mixed evidence on the connection between level of disability and cognitive impairment. Fifteen studies have found relationships between disability and cognition,^{16,18,24,26,34,43,54,67,83,105,111,113,114,116,122} with seven studies noting that cognitive performances predicted disease progression^{13,24,32,35} or disability predicted cognitive deterioration.^{45,132,133} In 15 other cohorts, disability and cognitive performance were not significantly associated.^{12-17-29-37-39-44-46-82-107-109-123-125,135} The discrepancies in these findings may be due to the

heterogeneity of the study populations. In the studies that identified a significant relationship between cognitive impairment and disability, three included participants' EDSS score in their definition of early MS (ie, ≤ 4 ¹²² and ≤ 5 ^{113,132}). Comparatively, three of the studies that did not find an association had a narrower EDSS inclusion criterion (ie, ≤ 2 ¹²³, ≤ 2.5 ¹²⁵, and ≤ 3.5 ¹³⁵).

Disease Modifying Therapies

Seven studies have evaluated the impact of starting a DMT on cognitive functioning. Overall improvement in cognitive functioning have been noted with interferon beta-1a three years after initiation.¹²⁰ In a pediatric cohort,¹⁰⁰ persons with MS who had an escalation of their DMT (ie, changing to fingolimod or natalizumab) had better overall cognitive performance than individuals who remained on a first-line DMT. In terms of specific tests, improvements on the SDMT have been found with interferon beta-1a,^{91,151} interferon beta-1b,^{91,151} glatiramer acetate,¹⁵¹ and natalizumab,¹⁵⁵ with a non-significant increase with the latter in a pediatric cohort with aggressive MS.¹⁵⁴ The PASAT-2⁹¹ and PASAT-3⁹³ have been noted to improve following treatment with interferon beta-1a and interferon beta-1b, respectively. Interferon beta-1a, interferon beta-1b, and glatiramer acetate have also been associated with improvements on total learning of the CVLT-II and BVMT-R.¹⁵¹ In addition, Mokhber et al⁹¹ noted improvements on the SPART Delay with interferon beta-1a, as well as on the SRT Delay and WLG with one version of interferon beta-1a (Avonex).

Vocational Status

Given that the average age of diagnosis is 32,¹ employment is a significant concern for many persons with MS. Cognition has been associated with vocational status changes,¹⁶² and these issues can be apparent early in the disease course, as noted by two studies. Jongen et al⁵³ showed that persons with MS who wanted to work fewer hours had poorer focused attention and processing speed, while individuals who wanted to change their jobs had worse episodic memory. Furthermore, the number of days that participants worked were positively associated with their working memory, focused attention, and processing speed performances.⁵³ Evidence of early cognitive involvement may also predict later employment. Ruet et al³¹ demonstrated that baseline processing speed, as well as participants' decline in cognitive functioning, predicted their vocational status seven years later.

Psychological Symptoms

While depression is prevalent in MS,¹⁶³ there is mixed evidence on its relationship with cognitive functioning. Ten studies did not find an association between performance and level of depressive symptom severity,^{29,34,37,46,83,85,113,124,135,141} while 14 studies found a negative impact,^{16,18,22,30,44,45,69,70,74,98,105,107,125,142} such as higher levels of depression among persons with cognitive impairment or worse performance on verbal fluency, aspects of executive functioning, multitasking, working memory, and processing speed tasks. There is also mixed evidence with quality of life and cognition, with two studies not finding a relationship^{82,115} and four studies noting a significant association.^{22,66,113,125} In addition, baseline memory performance has been found to predict persons' with MS health-related quality of life seven years later,³¹ while improvement in cognition was associated with improvement in mental health-related quality of life longitudinally.⁷³

Less research has been done on the impact of anxiety on cognitive performance in early MS. Although six studies did not find a significant relationship,^{16,30,85,113,142,147} five studies^{26,45,74,98,107} showed that greater anxiety symptomatology was associated with worse performance on aspects of executive functioning, working memory, processing speed, immediate structured verbal learning (ie, story memory), and delayed structured verbal memory. Simioni et al¹²⁵ also found a higher prevalence of anxiety among persons with cognitive involvement.

One study⁵⁶ examined the relationship between self-efficacy and cognitive performance, finding that not only was self-efficacy strongly associated with several domains, it predicted 40% of the variability of persons' with MS performance on Power of Attention and Speed of Memory and 3% on their Reaction Time Variability. While another study⁸¹ found that psychological resilience was correlated with processing speed, it was not significant after adjusting for multiple comparisons or fatigue and mood.

Physical Symptoms

Subjective reports of fatigue have not been found to be consistently related to objective cognitive performance in the wider MS literature.¹⁶⁴ This is similar in early MS, with seven studies finding no significant relationship between fatigue and cognitive impairment.^{12,29,34,46,89,113,135} Seven studies found an association,^{22,30,68,74,75,125,142} such as higher rates of fatigue among persons with cognitive involvement or worse

performance on measures of verbal fluency, verbal memory, aspects of executive functioning, working memory, and processing speed. However, part of the discrepancy may be due to the measures being used. For instance, while Hyncicova et al¹⁴² showed that the SDMT was significantly related to the Energy/Fatigue scale on the Short Form-36, it was not associated with the Fatigue Severity Scale.

Two studies investigated the association between pain and cognition in early MS, with one¹⁴² noting a significant relationship between performance on the SDMT and pain ratings in persons with CIS. While the other study⁷⁷ found that impaired cognitive functioning contributed to baseline unspecified pain, other factors such as fatigue played a more significant role. Furthermore, the authors did not find that it significantly impacted follow-up unspecified pain or baseline and follow-up neuropathic pain.

Five studies have evaluated the relationship between cognition and difference aspects of eye functioning. One study⁵⁵ has investigated pupillary dilation with regards to cognitive functioning in early MS. The authors found that while it was not related to performance on the BICAMS when examining their entire cohort, persons with early MS who had low cognitive scores had smaller pupillary responses compared to controls with low cognitive scores. One study¹⁰² noted that saccadic initiation time was associated with performance on the written version of the SDMT, as was hand functioning, but not with the PASAT. Similarly, Clough et al¹⁰⁸ only found a relationship between visually guided latency saccades with late MS and not early RRMS. With regards to anti-saccades, performance on the PASAT has been correlated with latency,¹⁰³ error proportion,¹⁰⁸ and error times,¹⁰⁸ while processing speed (ie, SDMT and the Computerized Speed Cognitive Test) has been correlated with error rate.^{103,110}

In terms of sleep, one study¹¹⁷ found that self-reported daytime sleepiness was negatively correlated with performance on the BICAMS. The authors also found positive associations between cognition and pulmonary and respiratory muscle functioning, suggesting impaired functioning in these areas are related to cognitive involvement.

Discussion

Despite differences in definitions of early MS and impairment, cognitive involvement in common within the first 10 years of MS. During the early stage of MS, persons may exhibit deficits in attention, processing speed, working

memory, verbal and visual learning and memory, executive functioning, and verbal fluency. Over time, these impairments can become more significant, with a greater number of individuals exhibiting cognitive involvement. While the SDMT has been shown to be sensitive to both initial cognitive impairment^{13,22,26–28,30,31,33,34,36,41,44–46,48,57,59,62,64,65,68,70,76,82,86,94,97,107,109,113,114,118,127,135,140,142–144,148,151,156} and progression,^{15,28,60,135,136,143} a number of longitudinal early MS cohorts demonstrated declines in executive functioning and verbal fluency,^{47,50,134} signaling the importance of evaluating and monitoring these domains over time. The evidence of modifying factors is mixed; however, several studies noted a positive influence on cognitive functioning with DMT usage^{91,93,100,120,151,154,155} and cognitive reserve may help protect against decline.^{80,131}

Given the evidence that cognitive involvement can occur early in MS and its relationship to later changes in functioning, such as vocational status,³¹ there is a strong need to evaluate persons' with MS cognition early and monitor over time. It is currently recommended that persons with MS should receive early baseline screening, with annual reassessment with the same measure, and a follow-up comprehensive evaluation if there is evidence of impairment.¹⁶⁵ The minimal recommended screening tool is the SDMT or a similar validated measure,¹⁶⁵ which coincides with our findings of its sensitivity to early cognitive involvement in MS. That said, as not all persons with MS-related cognitive impairment will demonstrate reductions on the SDMT, clinicians should strongly consider using a short screening battery that assesses several domains. The most commonly used battery is the BICAMS, which includes measures of verbal (CVLT-II) and visual (BVM-T-R) learning in addition to the SDMT.¹⁵⁹ Besides taking 15 minutes to administer, there is an international standard for validation, allowing it to be used in different countries.¹⁶⁶

An alternative battery is the abbreviated Minimal Assessment of Cognitive Function in MS (aMACFIMS), which includes shortened versions of the SDMT, CVLT-II, BVM-T-R, and verbal fluency, with both phonemic and semantic fluency in the expanded version.^{167–170} Deficits in verbal fluency have been noted in several early MS cohorts,^{12,13,16,17,21,23,27,29,30,38,41,42,57,59,61–66,74,76,82,94,97,101,118,148} and both types have been shown to have good detection of cognitive impairment in persons with CIS,¹⁷ which supports its use as a screening battery for persons with early MS. Regardless of which screening battery

a clinician chooses, they should be aware that they may not be capturing persons with MS whose deficits are primarily in executive functioning. Although the aMACFIMS was initially developed with an abbreviated executive functioning task (ie, one Card Sort from the D-KEFS),¹⁶⁸ it did not significantly contribute to the battery in terms of detecting cognitive impairment and was subsequently removed.¹⁶⁹

If there are concerns about a patient's executive abilities and/or they demonstrate impairments on a screening battery, a comprehensive neuropsychological assessment may be warranted. Besides considering the influences of demographics such as age, education, race/ethnicity, gender, and premorbid functioning on performances, a neuropsychologist can evaluate whether the person's with MS impairments are influenced by other factors such as comorbidities,¹⁷¹ including psychological and physical symptoms. Two of the most common batteries used in MS are the MACFIMS¹⁷² and the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).¹⁷³ Both of these batteries assess the domains frequently affected in early MS, including attention and processing speed (SDMT in both), working memory (PASAT in both), verbal learning and memory (CVLT-II in the MACFIMS and SRT in the BRB-N), visual learning and memory (BVRT in the MACFIMS and 10/36 SPART in the BRB-N), and verbal fluency (Controlled Oral Word Association Test in the MACFIMS and Word List Generation in the BRB-N). The MACFIMS also includes measures of visuospatial functioning (Judgment of Line Orientation) and executive functioning (Delis-Kaplan Executive Function System). As the MACFIMS and BRB-N are considered minimal assessment batteries, clinicians may consider adding ones that evaluate aspects of executive functioning. For instance, a number of studies^{34,41,49,71,120} that used the BRB-N also included the Stroop test, which taps into inhibition. However, despite the prevalence of cognitive impairment and its impact, even in early MS, neuropsychological services may be underutilized.^{174,175} While there are many factors that may influence service utilization, such as cost and accessibility, increased awareness of the deficits observed at the different stages of the disease and how to screen for them may lead to more patients who need these services to receive them.

While there is a large body of literature investigating early cognitive involvement in MS, there are still limitations with the available data. The first is the lack of a consensus over what is considered "early." As previously noted, the varying

definitions have likely contributed to discrepancies in the types of observed cognitive deficits and their relationships with clinical factors. Although a longer duration like ≤ 10 years may allow for inclusion of more persons with MS from a clinical sample, it begins to encroach upon some definitions of late MS,²³ making it difficult to differentiate between these stages of disease duration. Given that the rate of impairment has been shown to significantly increase after having MS for five years,^{47,51,79,112} classifying persons with MS with less than five years of disease duration may provide insights into the earliest signs of cognitive involvement.

In addition, the definition used for impairment can affect how many persons with MS are classified as cognitively impaired. The majority of the reviewed studies used at least a cut-off of >1.5 SD, which is a fair stringency.¹⁹ Furthermore, the number of impaired measures is also an important factor and is dependent on the size of the battery. Several of the established batteries have a recommended number of impaired measures to consider an individual cognitively impaired: for instance, one for the BICAMS¹¹³ and two measures for the aMACFIMS^{169,170} and MACFIMS.¹⁷⁶ With larger batteries, using a cut-off of one or two measures may overestimate the prevalence of cognitive impairment.

Finally, there is a need to evaluate how engagement in different activities and co-occurring conditions may influence cognitive functioning early in the disease process. For instance, research in the broader MS population has shown that cognitive leisure activities, which have been used as a marker for cognitive reserve, is a protective factor for cognitive decline.¹⁷⁷ While persons with early MS tend to engage in fewer reserve-building activities, particularly organized sports, job-related exercise, and high and low impact exercise,¹⁷⁸ their contributions to cognitive functioning has not been explored at this stage. Furthermore, although there is evidence that there are relationships between diabetes,¹⁷¹ body mass index (BMI),^{171,179,180} and cholesterol level^{179,181,182} with cognition in MS, these studies were not specific to early MS. Understanding if these factors contribute to cognitive deficits early in MS may help with management of patients' multimorbidities and general health, and subsequently mediate their impact on cognitive functioning.

Conclusions

Even early in the disease process, many persons with MS can present with signs of cognitive involvement. Although the definitions for early MS and cognitive impairment vary between studies, up to 61% of persons with early MS

demonstrate some type of cognitive involvement. Besides impairments in attention, processing speed, and memory, executive dysfunction can occur, which can include reductions in verbal fluency. As cognitive impairment can progress over time and early involvement is associated with later functional difficulties, there is a strong need for early screening and follow-up comprehensive neuropsychological assessments when indicated.

Disclosure

The authors have no conflicts of interest to report.

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