Cognition and Mental Health in Patients With Multiple Sclerosis

Neuropsychologic evaluation and treatment can improve quality of life.

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Cognitive impairment and mood disorders are estimated to occur in >50% of patients with multiple sclerosis (MS) early in the disease course, making mental health both a diagnostic and a quality-of-life (QoL) issue that affects relationships, occupational/vocational status, and long-term health outcomes (Figure). Early detection of cognitive impairment and psychiatric distress in this population is critical to allow for earlier treatment intervention, better patient education about treatment options and modifiable lifestyle factors, and engagement in counseling with patients and their families. After the identification of cognitive impairment, clinicians should strive to characterize cognitive dysfunction and assess for the presence of comorbid or symptomatic mental health issues in patients with MS. Evaluation can be done objectively with neuropsychologic assessment of cognition and psychiatric symptoms.

Neuropsychological Evaluation

Goals of Evaluation

The goal of the neuropsychologic evaluation is to characterize the pattern and severity of any cognitive dysfunction and determine whether it is consistent with symptoms of MS and neuroimaging findings or is an alternative or comorbid diagnosis. Neuropsychologic assessment can also assess the relationship between mental health and any functional disabilities that may interfere with the ability to complete activities of daily living. Serial evaluations over time can determine if a neurocognitive disorder or other mental health disorder is present and monitor cognition and psychiatric symptom severity.

A critical part of neuropsychologic assessment includes providing feedback and discussing the results with the patient to give information on cognitive strengths and weakness and educate the patient regarding how competing etiologic factors can exacerbate cognitive dysfunction and mental health conditions. It is vital that during this feedback session the importance of treating the disease as a way of potentially improving cognitive and mental health symptoms is emphasized.

Specific Tests

Neuropsychologic evaluation. Tests should assess multiple cognitive domains to ensure all potential areas of cognitive dysfunction are evaluated. However, specific to the MS population, and particularly in the context of the high prevalence rates of fatigue/somnolence in patients with MS, the battery should be brief (approximately 2-3 hours). Shorter and more efficient assessments are warranted, as performances for patients with MS deteriorate more rapidly compared to control...
subjects during a neuropsychologic evaluation. At the initial stages of assessing cognition in patients with MS, an extended screening evaluation may be appropriate to clarify if a more comprehensive evaluation is indicated. The Brief Repeatable Battery (BRB) takes 20 to 30 minutes to administer, includes measures most sensitive to the cognitive dysfunction associated with MS, and includes measures with available alternate forms, making repeat evaluation(s) over time possible. The BRB is available through the National Multiple Sclerosis Society. Another widely accepted battery used in assessing cognition in patients with MS is the Minimal Assessment of Cognitive Function in MS (MACFIMS), which takes approximately 90 minutes to complete; a strength of the MACFIMS is that it was developed by a consensus of researchers and includes additional measures of emotional functioning and fatigue, relative to the BRB.

Screening evaluation by neurology. As neurologists may have limited time to devote to cognitive testing, the Symbol Digit Modalities Test (SDMT) may help in deciding whether to refer for more extensive neuropsychologic testing. The SDMT is one of 7 subtests comprising the MACFIMS; it does not require extensive training and takes only 5 minutes to administer. The SDMT has emerged as the strongest brief screening instrument for cognitive impairment. In addition, neurologists who specialize in MS are encouraged to familiarize themselves with well-validated brief instruments that screen for cognitive impairment, such as the Montreal Cognitive Assessment (MoCA), which has been validated in persons with MS (Case Study). Self-report measures of subjective cognitive difficulties, such as the Behavioral Rating Inventory of Executive Function–Adult Version (BRIEF-A), may also be helpful in detecting early cognitive changes in patients. A guideline from the American Academy of Neurology is available that covers assessment of psychiatric disorders in individuals with MS.

Cognition
Assessment of Cognition
It is critical to assess for cognitive dysfunction, which occurs in >50% of patients with MS; multiple cognitive domains should be tested (Table). Some patients’ cognitive deficits are relatively mild, whereas others’ are severe enough to warrant diagnoses of neurocognitive disorders.

Although neurocognitive dysfunction may be present in all MS subtypes, diagnostic classification may be useful, as different subtypes are associated with more severe and adverse cognitive outcomes. Patients with secondary progressive MS have greater impairments at the level of encoding of verbal material in memory processing/learning, processing speed, response inhibition, and set-shifting. More profound cognitive dysfunction has been reported in patients with progressive MS compared to those with relapsing MS; patients with primary progressive MS may have more severe cognitive impairments than those with secondary progressive MS. Cognitive changes may also manifest during an acute relapse.

Neuropsychologic correlates of MS vary across the lifespan. Recent work suggests that although adult-onset MS has several features in common with pediatric-onset MS, the cohorts often differ in several regards. Although physical disability progression is reported to be slower among pediatric patients,

Case Study
Mrs. Smith, age 44 is a right-handed, white women who lives alone and has had 12 years of formal education. She was diagnosed with MS 2 years ago and, during a follow-up visit, states that she has become increasingly irritable, is having difficulties focusing and concentrating, and is experiencing significant sadness, anhedonia, apathy, fatigue, and loss of motivation; all of which are a change from her self-reported baseline.

In this example, the neurologist should screen for any cognitive impairment using a validated brief screening measure of gross cognitive functioning (eg, MoCA). The PHQ-2 would help screen for a possible mood disturbance, such as depression. These screening tools can aid the decision of whether to refer the patient for a comprehensive neuropsychologic evaluation.

This highlights the possibility of genuine cognitive disturbance related to central nervous system dysfunction in the context of MS and also addresses the potential role that mood disturbance can play in a patient’s self-appraisal of his or her cognitive symptoms. It is quite common for patients with MS to experience comorbid depression and objective cognitive dysfunction. If the patient has a score of 30/30 on the MoCA, but endorses significant depression on the PHQ-2, it is plausible that the she or he is experiencing a depressive episode resulting in an overappraisal of cognitive dysfunction.

Conversely, if the patient has a score of 22/30 on the MoCA although denies depression on the PHQ-2, it is possible that the patient is experiencing genuine cognitive dysfunction related to MS. In that case, presentation of apathy, fatigue, and anhedonia may be connected to the disease process, rather than a mood disturbance, and the treating neurologist should then ask about the onset, duration, frequency, and intensity of the patient’s irritability, mood disturbance, and cognitive difficulties while considering any medical, situational, or psychosocial factors that could exacerbate those symptoms (eg, metabolic disturbance, social stressors). Regardless of findings during the neurologic examination, a referral for a comprehensive neuropsychologic evaluation, in this example, is indicated, as results from a neuropsychologic examination will aid differential diagnosis and provide detailed and specific treatment recommendations.
profound cognitive dysfunction can occur and more dramatically affects life trajectories in pediatric patients compared to adults. This is presumably related to demyelination and inflammation disrupting typical cognitive development. No longitudinal studies assessing MS across the lifespan are available.

**MRI Lesion Correlations**

The study of the correlation between lesion location, brain networks, and their relation to objective cognitive function among persons with MS is still in its infancy. Cognitive dysfunction is typically relative to observed lesion load on T2 MRI sequences and associated with greater lesion load, location of white matter lesions, microstructural injury, gray matter lesions, cortical and subcortical gray matter volume loss, and abnormal activation during fMRI tasks. Despite these relationships, each patient can present with a distinct pattern of neuropsychological deficits. As a result of this diffuse pattern of cognitive deficits associated with lesion burden, cogni-

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**TABLE. DISPLAY OF COGNITIVE DOMAINS, SUBDOMAINS, AND CLINICAL OBSERVATIONS**

<table>
<thead>
<tr>
<th>COGNITIVE DOMAINS AND SUBDOMAINS</th>
<th>CLINICAL OBSERVATIONS OR SYMPTOMS</th>
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<tr>
<td><strong>Attention and Processing Speed</strong>&lt;br&gt;Simple attention, divided attention, sustained attention, selective attention, information processing speed, and orientation</td>
<td>Daily tasks take longer to complete and work requires more double-checking. It is difficult to concentrate, sustain focus, or attend to sensory input. Disorientation and altered mental status may occur.</td>
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<td><strong>Frontal Systems “Executive” Abilities</strong>&lt;br&gt;Planning and organization, inhibition and self-monitoring, mental flexibility and set-shifting, working memory, initiation and vigilance, conceptualization and problem solving, decision making, and abstract reasoning</td>
<td>Multi-stage projects can be more difficult to complete. It can be more difficult to plan and organize tasks or find solutions to everyday problems. Shifting from one environmental stimuli to another or resuming an interrupted task may be challenging. Self-monitoring may be affected and persons may be more susceptible to financial scams. It is more difficult to remember new information (eg, phone numbers).</td>
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<td><strong>Language</strong>&lt;br&gt;Expressive language (verbal fluency, object naming, writing, calculations) and receptive language (auditory comprehension, ability to follow commands, loss of semantic knowledge)</td>
<td>Persons affected may have trouble finding words or names or have nonfluent, agrammatical, or halting speech, finding speaking more difficult. It may be difficult to track or understand conversation. There may be difficulty with writing, spelling, calculating or solving problems, or following directions, especially multi-step directions. Understanding new words, concepts, and semantic meaning of previously known information can occur, as can an inability to express thoughts.</td>
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<td><strong>Learning and Memory</strong>&lt;br&gt;Encoding sensory input, memory consolidation and storage, prospective memory, memory retention, memory retrieval, and memory recognition</td>
<td>Encoding sensory input can be challenging and it may be difficult to recall details of recent events because the information was either never encoded or because information was not retained or requires cuing to aid retrieval. Patients may need or have compensatory strategies (eg, calendar, grocery lists, appointment reminders).</td>
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<td><strong>Visuospatial/Visuoperceptual/Visuoconstructive Abilities</strong>&lt;br&gt;Visual scanning, visuomotor construction, visual integration, spatial orientation, proprioception, visual agnosia, and prosopagnosia</td>
<td>Patients may have difficulty distinguishing left and right, trouble finding items left in plain sight, get lost or disoriented, or feel out of place. Drawing, reading and recognizing familiar faces or items may be difficult, either as a result of impaired visual integration or insult to focal cortical regions (ie, fusiform gyrus).</td>
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<tr>
<td><strong>Motor</strong>&lt;br&gt;Fine manual dexterity, motor speed, motor apraxia, motor planning and sequencing</td>
<td>Dressing may be difficult due to fine manual dexterity issues or motor sequencing and planning impairments. Executing simple or complex, meaningful or meaningless, skilled or purposeful movements, writing, and using utensils may be challenging.</td>
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*Subdomains that are most commonly associated with MS as a result of nonspecific white matter-lesion load.*
tive dysfunction that results from MS is often best characterized as a subcortical dementia. The cardinal neurocognitive profile of a subcortical dementia is termed frontosubcortical, as the core deficits associated with a frontosubcortical pattern of dysfunction stem from disruption of white matter connectivity between frontal cortical networks and subcortical regions. This often manifests in deficient frontal systems (executive abilities), deficient processing speed, and deficient fine manual dexterity/motor speed. Additionally, there is evidence that cognitive dysfunction in MS cannot be fully explained by white matter injury alone. White matter atrophy is most frequently associated with impairments in the domains of processing speed and working memory, whereas gray matter atrophy is often more associated with focal dysfunction and comorbid psychiatric symptoms including disinhibition or euphoria.

Although the degree of cognitive dysfunction may vary, the frontosubcortical neurocognitive profile in patients with MS is rather stable. MS subtypes differently affect the degree of cognitive dysfunction observed, rather than domain-specific variability. Although the cognitive profile is often associated with lesion load and location (eg, periventricular, juxtacortical, infratentorial, or spinal cord regions), it is disruption of connectivity that largely attenuates processing speed, frontal systems, and motor functions. Nonetheless, periventricular and juxtacortical lesions are more associated with cognitive processing deficits, whereas infratentorial or spinal cord lesions are more associated with motor and sensory-processing deficits.

Specific Cognitive Impairments

Findings from large-scale, controlled studies consistently show that processing speed and episodic memory are the most commonly affected cognitive domains in persons with MS, although concurrent deficits in executive functions, verbal fluency, and visuospatial processing have also been seen. Patients with MS often experience increased difficulty in memory processing, such as difficulty retrieving names, misplacing personal items, forgetfulness in daily life, or difficulties in planning and organizing. Episodic memory deficits are commonly observed on formal neuropsychologic exam. However, one clear distinction between MS and other neurologic diseases (eg, Alzheimer’s disease) is that memory retention remains relatively intact. Instead, patients with MS often have deficient acquisition and learning of new material, particularly at the level of encoding, and this deficit is presumed to be attenuated by slowed processing speed and weak executive control. Although patients may have difficulty retrieving successfully encoded information (often the result of frontal dysfunction), they rarely present as densely amnestic. Patients with MS may also have deficits in aspects of social cognition including theory of mind (understanding and predicting the mental states of others), empathy, and social perception (ie, facial recognition, understanding social or affective prosody), that can significantly affect interpersonal relationships, but the relationship between social cognitive deficits and MS remains unresolved.

Impact of Comorbidities and Disabilities

Comorbid effects of extraneous factors often experienced by patients with MS (ie, depression, fatigue, pain, physical immobility, or sleep disruption) should also be considered for their effects on cognition. Fatigue has been reported in up to 90% of individuals with MS. In addition, the point prevalence of pain in patients with MS is roughly 50%, while approximately 75% of patients with MS report having experienced pain within the past month. These complicating and overlapping factors make a qualitative approach necessary to ensure accurate characterization of cognitive performance.

Objective cognitive performance can be associated with physical disability and disease duration. Evidence of cognitive dysfunction is often observed before physical disability status is documented or even occurs. There is a critical need for establishing the validity of neuropsychologic measures in the context of comorbidities and disabilities, as well as a more robust characterization of various cognitive phenotypes in patients with MS through prospective longitudinal design. Adequate sleep is critical for healthy brain function. Disrupted sleep or the presence of a superimposed sleep disorder can negatively affect cognition and contribute to ongoing psychiatric symptoms. Within the MS population, underlying sleep disorders are common and often remain undiagnosed. Objective sleep measures (eg, polysomnography, actigraphy) have been found to predict cognitive dysfunction in patients with MS; however, self-reported sleep disruption may not be predictive of objective cognitive dysfunction.

Mental Health and Neuropsychiatric Manifestations

Emotional well-being can affect every area of life. Patients with MS often experience significant stress from disease and treatment burden as do their family members, friends, and caregivers. Although changes in emotional state can be related to the situational stressor of living with MS, there are additional neurologic and immunologic changes associated with mental health in MS. In particular, a higher incidence of major depressive disorder, anxiety, frequent mood swings, increased irritability/agitation, and pseudobulbar affect have all been reported in patients with MS. Intrathecal inflammation can induce mood alterations and several biomarkers of neuroinflammation (ie, interleukin-2 CSF levels, TNF-α, interleukin-1β) have been identified to correlate with self-report measures of depression and anxiety in persons with MS. Additionally, psychiatric syndromes are invariably a possible side effect of corticosteroid therapy, which may be used in treating patients with MS, that should be monitored accordingly.
Depression

Estimated prevalence of depression in patients with MS is 20%, with lifetime prevalence as high as 50%, substantially higher than in the general population.27-29 Depression in patients with MS negatively affects QoL, adaptive function, emotional well-being, and treatment adherence.27,32 Routine depression screening is strongly recommended.33,34 The 2-item Patient Health Questionnaire (PHQ-2) is the briefest available screening measure for depression.35 The Beck Depression Inventory-Second edition (BDI-II) is another sound and robust measure for characterizing depressive symptom severity in patients with MS and takes only 5 to 10 minutes to complete.36

Sexual Dysfunction

Sexual dysfunction is a common complication of MS, occurring in 50% to 90% of men with MS and 40% to 80% of women with MS.37 Clinicians should assess for sexual dysfunction, as it can lead to increased interpersonal difficulties, increased rates of anxiety and depression, and decreased QoL.38

Anxiety Disorders

Higher lifetime prevalence rates of anxiety have been observed in patients with MS compared to the general population.28 Generalized anxiety disorder is most commonly reported in the MS literature, followed by panic disorder and obsessive-compulsive disorder.28 Anxiety and fear of future progression of symptoms in MS may be underappreciated and have been found to be associated with increased levels of depressive symptoms.28

Psychotic Spectrum Disorders

Bipolar disorder is the only severe mental illness that occurs with significant frequency in patients with MS compared to the general population. Epidemiological studies have been limited, however, by small sample sizes or weak research design. Few large-scale empirical studies have found a relationship between MS and other psychotic spectrum disorders.

Treatment

Cognitive Rehabilitation

Ongoing research efforts are focused on cognitive rehabilitation and intervention. Restoration of cognitive functioning and enhancement of compensatory strategies continue to be explored; however, which are the best cognitive rehabilitation treatment options for patients with MS are still a matter of debate.15 Cognitive rehabilitation therapy (CRT) is a promising nonpharmacological option that entails learning new cognitive strategies to compensate for cognitive problems; however, the effectiveness of CRT in patients with MS is as yet unproven due to contradictory findings of the methodologically limited studies completed.15,29 Mindfulness-based cognitive therapy (MBCT) is another nonpharmacological treatment combining elements of mindfulness training and cognitive behavioral therapy. Preliminary evidence supports that MBCT has a positive effect on cognition in healthy individuals; findings may be generalizable to persons with MS.40 A systematic review and a meta-analysis on the efficacy of computer-based cognitive training in the neuropsychologic performance of patients with MS found that computer-based cognitive training significantly improved memory performance in patients with MS, relative to healthy controls.41 To date, however, most outcome studies have been limited to focusing exclusively on relapsing-remitting MS, and treatment efficacy remains speculative.42 As in the general population, the act of exercise in patients with MS has been demonstrated to have a positive impact on cognition, perhaps due to secondary improvements related to improved sleep, mood, and vascular health.43 In addition, neurologists are strongly encouraged to reaffirm the importance of a healthy diet, routine exercise regimen, and adequate sleep to their patients, to increase the likelihood of optimal cognitive and emotional functioning.

Treatment for Neuropsychiatric Disorders

There are a number of available psychotherapeutic treatments to alleviate psychiatric distress in patients with MS. Cognitive behavioral therapy (CBT) is effective for treating depression in patients with MS.44,45 CBT focuses on the core principle that psychologic problems are based, in part, on faulty ways of thinking and learned patterns of unhelpful behavior and involves efforts to change distorted thinking patterns or alter maladaptive behavior patterns.53 In patients with MS, the psychologist may focus on a patient’s ability to maintain social relationships or to reduce perceived disease burden and fears of disease progression. Mindfulness-based interventions also successfully treat psychologic symptoms in patients with MS.49 Mindfulness therapies involve bringing one’s attention to experiences occurring in the present, which can be developed through meditation and other stress-relaxation techniques or breathing exercises.

Several systematic reviews show promising findings related to the efficacy of CBT for reducing fatigue in patients with MS.22,46 In the context of ongoing sleep disruption, especially insomnia, CBT for insomnia (CBT-I) is recommended.47 Meta-analyses have shown that relaxation techniques and mindfulness interventions decrease fatigue.48 Because pharmacological interventions are often useful in conjunction with psychotherapeutic interventions, consultation with a psychiatrist to explore mood-stabilizing medications is also recommended. Neurologists are well positioned to refer patients for psychotherapy (eg, CBT) to target mood stabilization.49

Conclusions

Cognitive interventions for persons with MS optimally involve adjunctive pharmacologic treatments in combination with behavioral approaches (eg, cognitive training, psycho-
therapy, sleep hygiene, routine exercise) to optimize cognition. Preventive efforts that increase the likelihood of optimal cognitive functioning and emotional well-being include physical exercise, regular activity and exercise, regular engagement in cognitively stimulating activities, limiting alcohol intake, and smoking cessation. Sumowski and colleagues highlight the importance for treating clinicians to incorporate a holistic approach to clinical intervention, which includes considering the unique circumstances of each patient's life (eg, existing family/social support systems, available financial/health care/educational resources, and medical or psychiatric comorbidities).