

**COGNITION AND MOOD ARE
COMMONLY AFFECTED IN MULTIPLE
SCLEROSIS PATIENTS. HERE'S A
LOOK AT THE UNDERLYING
MECHANISMS AND ADVICE ON
CLINICAL ASSESSMENT.**

IDENTIFYING NEUROBEHAVIORAL CHANGES IN MS PATIENTS

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Although the most overt symptoms of multiple sclerosis are neuromuscular, prominent cognitive and neuropsychiatric symptoms were described by Jean-Martin Charcot, the 19th-century neurologist who named multiple sclerosis. Subsequent early 20th-century writers on MS ignored the cognitive changes but emphasized the presence of euphoria. As neurologists stressed the white matter nature of multiple sclerosis, they further downplayed any cognitive or other “gray matter problems.” They explained depression among multiple sclerosis patients as a logical reaction to physical disabilities. In recent years, however, investigators have rediscovered that cognitive impairment and biological depression are significant manifestations of multiple sclerosis.^{1,2}

CLINICAL MANIFESTATIONS

The neurobehavioral aspects of multiple sclerosis include both cognitive disturbances and neuropsychiatric disorders. Cognitive difficulties in multiple sclerosis involve memory retrieval, mental processing speed, reasoning and goal-oriented behavior, verbal fluency and visuospatial skills.^{3,4} Neuropsychiatric disturbances are primarily mood disorders. Similar to other neurologic symptoms, the neurobehavioral aspects of multiple sclerosis may be present in either relapsing attacks or in a chronic progressive course. A specific pattern of cognitive decline has been proposed. The first cognitive difficulty refers to a general slowness that affects motor execution and cognitive processing. Verbal fluency and verbal memory appear to be affected early in multiple sclerosis. The pattern of cognitive

decline is further characterized by a decrease in visuospatial learning, followed by delayed recall, and then by attention and information processing speed.

Forty-five to 65 percent of MS patients have deficits on neuropsychological testing,^{3,5-7} although not usually as severe as in comparably disabled patients with Alzheimer’s disease or other dementias.⁸ Moreover, many cognitively impaired MS patients either do not complain of cognitive difficulties or complain of nonspecific forgetfulness or mental fatigue, even though significant cognitive impairment may already exist at the onset of MS. General intelligence, language and certain aspects of primary and implicit memory are preserved,⁵ but individual multiple sclerosis patients may become severely demented or markedly impaired from cognitive effects such as frontal-executive disturbances,⁹ particularly associated with disease progression and increasing age. When dementia is defined operationally as less than two standard deviations below normal on three or more neuropsychological measures, one study found dementia in as many as 28 percent of multiple sclerosis patients.¹⁰ In sum, about one-half of multiple sclerosis patients have a decline in one or more cognitive functions, and about one-fourth have a decline in three or more cognitive functions. These symptoms are sufficient for at least a mild dementia. Significant depression occurs in 37 to 54 percent of multiple sclerosis patients despite outward euphoria and eutonia,¹¹ and multiple sclerosis patients have a two-fold increase in the lifetime risk of bipolar disease.¹²

Severity of cognitive impairment significantly correlates with physical disability¹³ and with depression severity.¹⁴ It has

been suggested that slowed information processing speed and, secondarily, deficient nonspeeded central executive skill may be core to the cognitive deficits characteristic of depressed multiple sclerosis patients.¹⁵ Interestingly, males are especially vulnerable to cognitive deficits.¹⁵ Cognitive impairments are also observed in children with multiple sclerosis. Those with longer disease duration and younger age of onset are at greatest risk.¹⁶

Memory problems are the most common cognitive deficits in multiple sclerosis and may be prominent early in the disease course. The main memory problem is deficient retrieval from secondary (recent and remote) memory of both verbal and visual information.^{8,18} By contrast, primary memory, which is responsible for immediate recall, is generally intact. There is a normal digit span, a normal recency effect on supraspan recall, and normal primary memory decay on the Brown-Peterson Test,¹⁸ but impairments in working memory. Gaudino and colleagues observed that the primary problem in multiple sclerosis with regard to memory functioning is in the acquisition of new information.¹⁹ It has been suggested that automatic memory processing is intact in multiple sclerosis, but impairment in memory, in metamemory, and in other cognitive tasks becomes evident over time when patients rely on conscious processes.²⁰

In addition to memory difficulty, multiple sclerosis patients may have other cognitive deficits. First, there is decreased information processing speed evidenced by psychomotor retardation, slowed complex reaction times, rapid fatigue, and disturbed rates of mental processing on neuropsychological measures.²¹⁻²³ Widespread slowing of automatic and controlled information processing underlies much of the cognitive difficulty of patients with multiple sclerosis. De Sonneville and colleagues²⁴ investigated focused, divided and sustained attention as well as executive function and attempted to pinpoint deficits in attention control to peripheral or central processing stages. The results substantiate the hypothesis that the slowing of attention-demanding (controlled) information processing underlying more complex cognitive skills is general (*i.e.*, irrespective of type of controlled processing), with multiple sclerosis patients being 40 percent slower than controls. Secondary progressive patients show the most extensive range of deficits, closely followed by primary progressive patients; relapsing-remitting patients appear to be much less affected.

There are frontal-executive problems in concept formation, abstract reasoning, planning and organization. Chronic progressive patients particularly may exhibit decreased executive function and poor planning, as demonstrated on the Towers of Hanoi Test.²⁵ Further, MS patients also have impaired ability to generate and apply working strategies when performing novel tasks.²⁶ Third, there is a decline in verbal fluency or word-list generation and a milder decrease in confrontational naming. Other language skills are relatively preserved, and aphasias are

rare. Finally, multiple sclerosis patients may be unable to copy a complex figure such as the Rey-Osterrieth figure or perform on measures of egocentric orientation such as Money's Road Map Test.

Deficits in visual processing may result from decreased planning and organization rather than from primary visuospatial deficits. Benedict and colleagues²⁷ studied the association between regional measures of cortical atrophy and neuropsychological dysfunction and concluded that cerebral atrophy predicts neuropsychological impairments. Regions of cortex most susceptible to atrophic and cognitive changes in multiple sclerosis are the right and left superior frontal lobes. Other authors have also found that frontal atrophy is significantly associated with neuropsychological measures of executive functioning.²⁸

Neuropsychiatric symptoms common in multiple sclerosis can be divided into two categories: (1) disorders of mood (depression, bipolar disorder, euphoria, pathological laughing and crying, and psychosis); and (2) abnormalities affecting cognition (memory, speed of information processing, and executive function). In one study of 44 multiple sclerosis patients, a neuropsychiatric inventory revealed symptoms in 95 percent including depressive symptoms (79 percent), agitation (40 percent), anxiety (37 percent), irritability (35 percent), apathy (20 percent), euphoria (13 percent), disinhibition (13 percent), hallucinations (10 percent), aberrant motor behavior (nine percent), and delusions (seven percent).²⁹ Sleep disorders and high levels of sexual dysfunction are also frequently observed in patients with multiple sclerosis.

Mood disorders occur more frequently in multiple sclerosis than in other chronic disabilities. Depression may present as an early sign in multiple sclerosis and may be followed by cognitive impairment (in particular, deficits in visuospatial short-term memory) before physical disability appears.³⁰ Taken together, major depression, bipolar illness, and dysphoria occur in 37 to 54 percent of patients with multiple sclerosis.^{11,29} Although Surridge found depressive episodes prior to physical symptoms in half of his multiple sclerosis patients,³² others have questioned whether depression occurs as an isolated presenting symptom of multiple sclerosis.³³ Psychological reactions to the disabilities of multiple sclerosis can lead to further depression, anxiety, a feeling of helplessness, loss of control and self-blame. In addition, one should separate depression from the frequent presence among multiple sclerosis patients of pseudobulbar affect with emotional incontinence. Work by Arnett and colleagues suggests that depressed multiple sclerosis patients characteristically have a limited working memory capacity and that the central executive component of the working memory system may be most affected.³⁴

Surridge also found that 26 percent of his MS patients had euphoria or a "mood of cheerful complacency."³² This outward

euphoria, however, was often mixed with inward depression. In fact, multiple sclerosis patients are less “euphoric” than they are “eutonic,” a sense of well-being dissociated from concern for their disability. Eutonia often occurs as part of other personality changes, including emotional lability, irritability and apathy, but many personality reactions are possible. MS patients have a high incidence of manic episodes, panic attacks and obsessive-compulsive symptoms.

The neurobehavioral aspects of multiple sclerosis are related poorly to most other aspects of this disease. Although the first episodes of major depression frequently occur during periods of exacerbation of MS, most cognitive and mood changes do not correlate with other neurologic findings or disability measures. One exception is an association of severe cognitive impairment with frontal gait apraxia and frontal release signs in the lower extremities (placing and grasping with the feet).^{35,36}

Another exception is the association of euphoria and eutonia with significant cognitive impairments, more extensive neurologic disability, and advanced demyelination.³⁷ Second, there is a weak relationship among cognitive deficits, euphoria, eutonia and the severity and disease duration.³⁷ In fact, neurobehavioral changes can occur early with minimal physical changes, and multiple sclerosis may present as a rare isolated dementia. Third, studies indicate that patients with a chronic progressive course are more likely to experience memory difficulties, frontal-executive disturbances, euphoria and eutonia.^{37,38}

ETIOLOGY AND PATHOPHYSIOLOGY

The neurobehavioral changes in multiple sclerosis are secondary to cerebral demyelination. Sperling³⁹ observed that multiple sclerosis lesions show a propensity for frontal and parietal white matter. Lesion burden in these areas is strongly associated with performance on tasks requiring sustained complex attention and working verbal memory. This relationship was consistent over a four-year period, suggesting that disruption of frontoparietal subcortical networks may underlie the pattern of neuropsychological impairment seen in many patients with multiple sclerosis. The severity of subcortical demyelination

may spread to involve the heavily myelinated gray-white junction and even the gray matter itself; it may also result in cortical diaschisis.

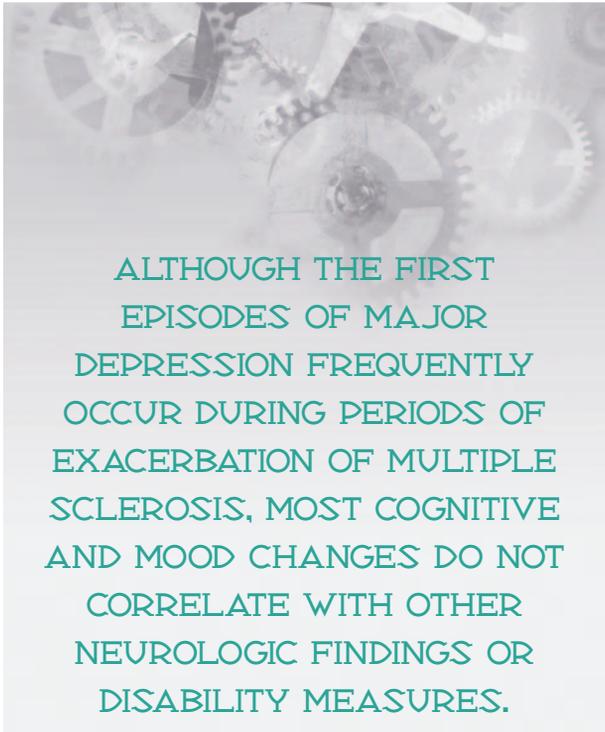
Changes may correlate with demyelination in specific locations, particularly the subfrontal white matter.³⁸ The number of lesions in the corona radiata, insula and hippocampus is especially correlated with cognitive impairment.⁴⁰ Significant cognitive dysfunction often occurs with the extension of white matter changes to areas immediately underlying the cortex.⁴¹ This may relate to an early disturbance of associative fibers, particularly the long associative bundles, disconnecting the frontal lobes from other parts of the cerebral hemispheres.^{41,42}

Significant memory impairment may be linked to demyelinating plaques in the white matter of both hippocampus and in the columns of the fornix.⁴² Involvement of the corpus callosum also promotes cognitive deficits and an interhemispheric disconnection syndrome.^{42,43}

Zivadonov and colleagues found that in the early phase of relapsing-remitting MS the cognitive deterioration correlates more closely with the development of brain parenchymal volume atrophy than with the extent of burden of disease in the brain.⁴⁴ They proposed that the main pathological substrate of brain atrophy in the early stage of the disease is probably early axonal loss, which causes the

progression of neurologic deficits and the development of cognitive impairment. Nocentini found that correlations between the performance in some “frontal” neuropsychological tests and the extent of frontal lobe MRI lesional area were present but nonspecific; the same performance also correlated with the nonfrontal lesional area.⁴⁵ The relationship between cognitive impairments and MRI parameters is moderate, suggesting that cognitive dysfunction in multiple sclerosis has a complex and multifactorial etiology, which is not adequately explained by pathology as demonstrated on conventional MRI.⁴⁶

Rovaris found moderate correlations among symbol digit modalities test scores, verbal fluency test scores, spatial recall test scores, and lesion volume in relapsing-remitting MS.⁴⁷ The authors suggested that the extent and intrinsic nature of the macroscopic lesions contribute to the neuropsychological



ALTHOUGH THE FIRST EPISODES OF MAJOR DEPRESSION FREQUENTLY OCCUR DURING PERIODS OF EXACERBATION OF MULTIPLE SCLEROSIS, MOST COGNITIVE AND MOOD CHANGES DO NOT CORRELATE WITH OTHER NEUROLOGIC FINDINGS OR DISABILITY MEASURES.

deficits. Charil observed a clear distinction between lesion locations causing physical and cognitive disability; lesion likelihood correlated with the Expanded Disability Status Scale (EDSS) in the left internal capsule and in periventricular white matter mostly in the left hemisphere.⁴⁸ Pyramidal deficits correlated with only one area in the left internal capsule that was also present in the EDSS correlation. Cognitive dysfunction correlated with lesion location at the grey-white junction of the associative, limbic and prefrontal cortex. Coordination impairment correlated with areas in interhemispheric and pyramidal periventricular white matter tracts and in the inferior and superior longitudinal fascicles. Bowel and bladder scores correlated with lesions in the medial frontal lobes, cerebellum, insula, dorsal midbrain and pons, areas known to be involved in the control of micturition.

The researchers concluded that there is an evident relationship between the site of lesions and the type of disability in large scale MRI data sets in multiple sclerosis. More recently, Benedict and colleagues found that brain atrophy was a better predictor of cognitive impairments than lesion burden; central atrophy in particular was strongly associated with neuropsychological morbidity.⁴⁹

Depression and other neuropsychiatric symptoms are less related to magnetic resonance measures or to the presence or absence of gadolinium enhancement. Bipolar disorder, euphoria and eutonia may occur with widespread periventricular demyelinated plaques. One report notes that magnetic resonance abnormalities in temporal lobes are common among multiple sclerosis patients with mixed psychopathology.⁵⁰ Brainstem involvement can result in akinetic mutism or peduncular hallucinosis, disorders that may be mistaken for psychiatric symptoms.^{51,52} Depression in multiple sclerosis is worse than in comparably disabling diseases.^{32,50,53} There is no relationship between depression and the severity of multiple sclerosis; however, patients with euphoria and eutonia, compared to those without, are more likely to have cerebral involvement and a moderately advanced disease course.³³

DIAGNOSTIC WORKUP

Clinicians often fail to consider multiple sclerosis in the differential diagnosis of dementia and of depression. This is particularly difficult because multiple sclerosis cannot be definitely diagnosed during life. A clinically probable diagnosis can be made based on the presence of signs and symptoms localized to multiple sites within the central nervous system and relapsing at different times. Multiple sclerosis should be considered in dementing illnesses with a frontal-subcortical profile even in the absence of other neurologic findings.⁵⁴ These dementing illnesses include vascular dementia, leukodystrophies, Huntington's disease and related disorders, the AIDS-dementia com-

plex, chronic meningo-encephalitides, normal pressure hydrocephalus and primary depression. Other considerations are the effects on cognition of depression, of psychoactive medications, and of sensorimotor deficits. A common diagnostic pitfall in neuropsychiatrically disturbed multiple sclerosis patients is the misdiagnosis of their neurologic symptoms as conversion reactions.

The differential diagnosis of white matter changes on magnetic resonance imaging includes Binswanger disease, metachromatic leukodystrophy, adrenoleukodystrophy, CADASIL, Fabry disease, HIV, lymphomatosis cerebri and others.⁶ In addition to tests for multiple sclerosis such as magnetic resonance imaging and cerebrospinal fluid analysis for immunoglobulin measures, a neurobehavioral assessment is essential. A behavioral interview may uncover cognitive and mood changes and may suggest further psychiatric assessment. The routine mental status examination, however, can miss the cognitive impairments of multiple sclerosis. Furthermore, mental status scales, such as the mini-mental state exam, may miss abnormalities of information processing speed, verbal fluency, and frontal-executive abilities.⁵⁵

Investigators recommend supplementing the mental status examination with neuropsychological measures such as a short naming test, a seven-item or more verbal recall test, and frontal-executive tests such as the Symbol Digit Modalities Test or the Wisconsin Card Sorting Test.^{55,56,57} Some investigators have developed brief screening batteries specifically for multiple sclerosis.^{9,58} Recently, the Multiple Sclerosis Impact Scale, a psychometric instrument measuring the physical and psychological impact of multiple sclerosis, was developed.⁵⁹ A minimal neuropsychological examination for multiple sclerosis patients was also recently proposed.

An expert panel composed of neuropsychologists and psychologists from several different countries was convened by the Consortium of Multiple Sclerosis Centers (CMSC) in April 2001. A 90-minute NP battery, the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), emerged from this discussion. The MACFIMS is composed of seven neuropsychological tests, covering five cognitive domains commonly impaired in multiple sclerosis (processing speed, working memory, learning and memory, executive function, visual-spatial processing, and word retrieval). It is supplemented by a measure of estimated premorbid cognitive ability. Recommendations for assessing other factors that may potentially confound interpretation of neuropsychological data (*e.g.*, visual, sensory, and motor impairment, fatigue, and depression) are also included.⁶⁰

Neuroimaging studies may be especially useful in the cognitive assessment of multiple sclerosis.^{61,62} On computerized tomography scans, cerebral atrophy and ventricular enlarge-

ment correlate weakly with cognitive difficulty.³⁷ On magnetic resonance scans, quantitated lesion burden and total lesion size are directly proportional to the amount of cognitive dysfunction.^{38,63,64} Demyelination extending to the gray border,⁴¹ bilateral hippocampal lesions,⁶⁵ white matter volumes,⁶⁶ and atrophy of the corpus callosum^{10,43,63} are also related to cognitive impairment.

Bermel and colleagues quantitatively measured bicaudate ratio, whole-brain atrophy, T2 lesion load, T1 (“black hole”) lesion load and caudate volume using fluid-attenuated inversion recovery, T1-weighted, and gradient-echo magnetic resonance imaging scans.⁶⁷ A Symbol Digit Modalities test was used to assess cognitive function. The bicaudate ratio was increased in multiple sclerosis and was more closely associated with cognitive dysfunction than other magnetic resonance imaging surrogate markers, including whole-brain atrophy. Increased bicaudate ratio was explained by frontal horn ventricular enlargement due to atrophy of deep frontal subcortical white matter. A close relationship between subcortical atrophy and cognitive impairment in patients with multiple sclerosis was suggested.

PET scans may reveal a general reduction in regional cerebral blood flow in the gray and white matter among multiple sclerosis patients.⁶⁸ This reduction correlates with the decrease in cognitive impairment.⁶⁸ Magnetic resonance spectroscopy may reveal subtle frontal neuropathological abnormalities, which contribute to executive dysfunction.⁶⁹

MANAGEMENT AND PROGNOSIS

The mainstays of managing multiple sclerosis are similar in most respects, regardless of the presence or absence of neurobehavioral symptoms. Management includes neurologic care, education and support. Immunosuppressive therapy with corticosteroids and other drugs may cause a remission of cognitive deficits and depression, but may worsen or precipitate mania.³⁸ Fischer and colleagues reported that interferon beta has a significant beneficial effect on information processing, learning and memory, and a mild effect in visuospatial abilities and problem solving.⁷⁰ They conclude that there are significant beneficial effects of interferon beta-1a for relapsing multiple sclerosis. Interferon beta, which decreases the number of relapse attacks and the development of MRI lesions, may worsen or provoke depression. The long-term effects of these medications on neurobehavioral symptoms are as yet unknown.

In addition to therapy with steroids and immunosuppressants, there are other more specific therapies for neurobehavioral symptoms. For cognitive symptoms, therapeutic considerations include cognitive-enhancing drugs and cognitive retraining. Although acetylcholinesterase inhibitor medications can improve memory, investigators have not evaluated donepezil, rivastigmine or galantamine (the major cholinesterase

inhibitors used in the United States) in patients with multiple sclerosis. These patients may benefit from learning compensatory strategies, graded practice on memory tasks, and the use of lists and written clues. For neuropsychiatric symptoms, psychotropic drugs may be useful, particularly antidepressant drugs and lithium. The response rate to antidepressant medication is high, but patients with multiple sclerosis may be unusually sensitive to their side effects.⁷¹ Psychotherapy and support groups are also of potential benefit, and electroconvulsive treatment may be effective.⁷²

Cognitive rehabilitation can have some beneficial effect on multiple sclerosis patients, but results are mixed.⁷³ Lincoln and colleagues found that a detailed cognitive assessment and treatment program designed to help reduce the impact of cognitive problems showed no effect of the interventions on mood, quality of life, subjective cognitive impairment or independence.⁷⁴

The prognosis for neurobehavioral symptoms appears to be just as variable as for other neurologic symptoms. Worse prognostic factors include a shorter interval between the first two relapses, an age of onset of more than 40 years, male sex, and the presence of pyramidal or cerebellar symptoms. The presence of cognitive symptoms or euphoria and eutonia are more likely to indicate a more extensive demyelinating lesion load. Moreover, MS patients with cognitive symptoms or euphoria and eutonia are less likely than multiple sclerosis patients without neurobehavioral symptoms to be employed, engaged in social activities, or independent in daily living activities.^{9,37}

The ability to predict which multiple sclerosis patient will develop neurobehavioral changes is difficult. The clinical findings that best predict cognitive impairment are gait apraxia, frontal release signs in the lower extremities, a chronic-progressive course, moderate to severe demyelination, subgyral demyelination, hippocampal demyelination, and atrophy of the corpus callosum atrophy.^{35,43} Ventricular enlargement may also predict cognitive impairment. Finally, depression (especially bipolar disease) and other neuropsychiatric symptoms may occur in those with a family history of these disorders. Noteworthy, nearly half of multiple sclerosis patients die from complications of their disease. Other major causes of mortality are malignancy (16 percent), suicide (15 percent), and myocardial infarction (11 percent).⁷⁵ **PN**

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