

Cognitive Loss in Multiple Sclerosis

Case Reports and Review of the Literature

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● **Neuropsychological and neuroradiologic evidence of cerebral lesions is described for 12 patients with multiple sclerosis in whom cognitive disability was far greater than any other neurologic disability. Cognitive dysfunction resulted in significant functional impairment at work or home in three fourths (9 of 12) of the patients described here, despite mild physical disability (mean Kurtzke Expanded Disability Status Scale score, 3.2). A unique feature of the neurologic examination in these patients was the presence of prominent frontal release signs (gait apraxia and placing response) in the lower extremities. Two new scales, a Cognitive Function Scale and a Frontal Release Scale, were adapted for the investigation of these patients. The extensive literature relating to cognitive dysfunction in multiple sclerosis is reviewed and discussed with regard to its clinical relevance.**

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Recent studies¹⁻³ have clearly demonstrated that neuropsychological deficits in patients with multiple sclerosis (MS) are more frequent than has

been generally recognized. Several facts may account for the prior lack of awareness that functionally important cognitive disturbance can occur in MS as a significant and sometimes predominant problem. First, the degree of cognitive impairment is not significantly related to the degree of neurologic disability.^{1,4} Second, patients with predominant periventricular demyelination, even with longstanding disease, may be considered

See also p 157.

mildly affected or "silent" with respect to neurobehavioral deficits.⁵ Third, the bedside mental status examination normally performed by neurologists may not detect cognitive impairment in persons with MS.^{1,2} We have recently seen 12 patients at our center whose cognitive deficits were far more disabling than any other of their MS-related neurologic impairments. This report briefly describes seven illustrative cases, summarizes the findings in the entire group, and reviews the literature relevant to these findings.

PATIENTS AND METHODS

Patients were tested individually by trained neuropsychological technicians with one of two standardized test batteries: an eight-hour expanded Halstead-Reitan Battery (HRB) or our one-hour Neuropsychological Screening Battery (NSB). A brief overview of these test batteries is presented below. Detailed descriptions of the specific tests and abilities assessed are given elsewhere.^{1,6}

The expanded HRB is a comprehensive, standardized test battery with demonstrated sensitivity to focal and diffuse cerebral lesions.⁷ It assesses the following abilities: problem-solving, attention/con-

centration, learning and delayed recall (verbal and nonverbal), intelligence, academic skills, concept formation, perseveration, perceptual motor speed, visuospatial abilities, sequencing efficiency, sensory-perceptual functions, expressive and receptive language, and motor proficiency. To minimize practice effects, alternate forms of the learning/memory tests were used whenever patients were tested more than once.

The NSB is a briefer set of standardized cognitive tests that were combined in an attempt to provide greater sensitivity to cognitive deficits than clinical mental status examinations.⁶ The NSB also has demonstrated superiority to two widely used standardized mental status examination (the Mini-Mental State examination and the Cognitive Capacity Screening Examination) in the detection of cognitive deficits in MS.⁶ In addition, the NSB summary score was significantly correlated with the extent of white-matter involvement seen with magnetic resonance imaging (MRI).⁶ The NSB consists of 18 subtests that assess the following abilities: verbal learning and memory, nonverbal learning and memory, attention/concentration, visuoconstructive abilities, sequencing efficiency, psychomotor speed, expressive and receptive language, speech articulation, written fluency, and reading comprehension. Standard cutoff values⁶ for normal, mildly impaired, and very impaired were used to classify the degree of cognitive impairment on the NSB subtests and NSB summary score.

The Kurtzke Expanded Disability Status Scale (EDSS)⁸ was used as a measure of physical disability; brain-stem, cerebellar, and pyramidal deficits are heavily weighted in this scale. By contrast, two of the major clinical problems encountered in this series, cognitive impairment and lower-extremity frontal release signs, are poorly represented or not represented, respectively, by the EDSS. Two scales were developed to enable functional classification of these clinical problems (Tables 1 and 2).

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The Cognitive Function Scale (Table 1) is a descriptive method to grade the degree of impairment of activities of daily living (particularly employment) related to clinical cognitive dysfunction. The cases described below are organized (Table 3) according to this method of grading the functional impact of neurocognitive impairment. Similarly, the Frontal Lobe Release Sign Scale is purely a descriptive method to grade the degree of lower-extremity frontal release. In the course of our clinical observation, for example, it was clear that mild placing or grasping in the feet is a less severe sign than gait apraxia. This scale, then, reflects this gradation of lower-extremity frontal release. Both scales were developed for descriptive purposes only; further reliability and validity studies should be done if these scales are applied in studies other than case series.

REPORT OF CASES

Cognitive Function Grade 1 (Table 1)

CASE 1.—Acute exacerbation and progression of cognitive symptoms responding to cyclophosphamide therapy is described.

A 30-year-old woman presented to our center in January 1984 with a three-month history of dizziness and forgetfulness. Although she had been diagnosed with MS in 1983, she had experienced relapsing/remitting symptoms since 1980. Her neurologic examination disclosed poor recent memory and mild left-sided pyramidal dysfunction. The Kurtzke EDSS score was 3.5 (Table 3). A computed tomographic (CT) scan (Fig 1, top left) revealed multiple periventricular lesions, at least three of which appeared acute (ie, contrast enhancing). Comprehensive neuropsychological testing with the HRB revealed a Wechsler Adult Intelligence Scale Full-Scale intelligence quotient of 94 and an HRB summary score in the mildly impaired range. However, she also showed severely impaired learning and delayed recall of both verbal and nonverbal material. Because of lack of response to steroid therapy, the patient was treated with azathioprine for the ensuing six-month period. During this time, she reported fewer memory difficulties. A repeated CT scan in August 1984 revealed that some previously seen lesions had disappeared, but that new lesions had appeared. Azathioprine therapy was discontinued because of hepatic dysfunction. Repeated neuropsychological testing at this time revealed improved concept formation but continued severe memory impairment. By October 1984, the patient reported increased difficulty with cognition in her work as a secretary. An MRI scan disclosed moderately severe periventricular demyelination (Fig 1, top center), as well as multiple corpus callosum lesions (Fig 1, top right). Because of complaints of progressive cognitive difficulty, the patient was admitted to the hospital for cyclophosphamide therapy.⁹ The patient has subsequently had three cyclophosphamide boosts (700 mg/m²) in the one year following initial treatment. No dramatic

Grade	Description
0	Normal function
1	Mild alteration of living pattern; continues to work or function independently
2	Moderate alteration of living pattern; unable to work due to cognitive impairment
3	Severe alteration of living pattern; unable to function independently

Grade	Description
0	No signs
1	Mild lower-extremity placing without gait apraxia
2	Clear lower-extremity placing with mild to moderate gait apraxia
3	Severe gait apraxia; may require aids

Patient No./ Age, y/Sex	Disease Duration, y	Kurtzke EDSS Score	Frontal Release Grade	Disease Course	Neuropsychologic Deficit†
Cognitive Function Grade 1					
1/30/F	4	3.5	0	R/R	VL, VM, NVL, NVM, CPS, NVAP
2/27/F	4	2.5	0	R/R	NVM
3/30/F	6	1.5	1	R/R	NVL, NVM, AC, VSA, LA
Cognitive Function Grade 2					
4/42/F	20	3.5	2	R/R	VM, NVM, CPS, AC, NVAP
5/33/M	1	3.5	1	R/R	NVM, AC, VSA, LA
8/46/F	12	3.0	2	R/R	VL, VM, NVL, NVM, CPS, AC, LA
9/48/F	11	2.5	2	R/R	VL, NVL, NVM, AC, VSA, LA
10/37/F	5	3.5	2	C/P	VL, VM, NVL, NVM, AC, VSA, LA
11/45/F	22	4.0	2	C/P	CPS, AC
12/49/M	6	2.5	2	R/R	VL, NVL, AC, LA
Cognitive Function Grade 3					
6/31/F	4	3.5	3	C/P	VL, NVL, CPS, AC, VSA, NVAP, LA
7/45/F	5	5.0	3	C/P	VL, VM, CPS, AC, LA
Mean . . . /38.6/. . .	8.3	3.2

*EDSS indicates Expanded Disability Status Scale; R/R, relapsing/remitting; C/P, chronic/progressive; VL, verbal learning; VM, verbal memory; NVL, nonverbal learning; NVM, nonverbal memory; CPS, complex problem-solving; NVAP, nonverbal auditory processing; AC, attention/concentration; VSA, visuospatial ability; and LA, language ability.

†All deficits were moderate to severe.

worsening of cognitive function has occurred and her current Kurtzke EDSS score is 2.5. She continues to work full time.

CASE 2.—Cognitive deficits presenting acutely, with subsequent full remission, are described.

A 27-year-old woman presented with a six-week history of cognitive disorganization and poor recall of recent events. These symptoms were noticed quite acutely. She had experienced relapsing/remitting MS symptoms for four years. Results of her neurologic examination, including bedside cognitive testing, were normal except for minor sensory deficits (EDSS score, 2.5). An expanded HRB revealed a moderately severe, isolated deficit in nonverbal memory. Results of a CT scan done at this time

were normal. The patient's cognitive complaints completely abated three months after they began. Results of a repeated HRB at this time were entirely normal.

CASE 3.—Coexistent depression and memory loss are described.

A 30-year-old woman had relapsing/remitting MS for six years prior to treatment at our center. She presented with a chief complaint of intermittent depression and recent memory loss. The depression had been refractory to intensive psychotherapy and antidepressant medication. Her neurologic examination revealed a Kurtzke EDSS score of 1.5. She also exhibited mild lower-extremity frontal release signs. The NSB revealed moderate to severe impairment in memory, attention/concentration, visuospatial ability, and

language ability. An MRI scan disclosed multiple periventricular lesions with moderate supratentorial atrophy (Fig 1, bottom left) as well as both rostral (Fig 1, bottom center) and caudal (Fig 1, bottom right) corpus callosum lesions. It is of note that this patient had been examined by a number of community physicians and therapists, all of whom recognized the depression, but not the cognitive difficulties.

Cognitive Function Grade 2

CASE 4.—Cognitive dysfunction after a long history of benign illness is described.

A 42-year-old woman presented to our center with a 24-year history of relapsing/remitting MS. Her history included bouts of right-leg clumsiness and diplopia. She presented with a two-year history of memory complaints and increasing difficulty in her work as a teacher. Neurologic examination revealed poor recall, impaired calculation ability, moderate gait apraxia, and a clear lower-extremity placing response. The Kurtzke EDSS score was 3.5. The NSB revealed moderate to severe impairment in verbal memory, sequencing efficiency, attention and concentration, and psychomotor speed. An MRI scan revealed extensive and confluent periventricular white-matter disease with mild ventriculomegaly and diffuse supratentorial volume loss (Fig 2, top left and center). Also noted was a linear increase in signal intensity along the length of the corpus callosum (Fig 2, top right). Soon after her visit to our center, the patient was granted Social Security disability compensation based on cognitive dysfunction from MS.

CASE 5.—Cognitive dysfunction coexistent with bipolar disorder is described.

A 33-year-old man with a one-year history of relapsing/remitting MS presented to our center with a one-week history of fatigue and left-sided incoordination. His symptoms improved significantly after a two-week course of oral prednisone. The patient was seen again six months later, when he presented with a one-month history of severe memory complaints and manic-depressive behavior. He had recently lost his job because of thinking difficulties and aberrant behavior. Neurologic examination disclosed prominent memory loss, mild pyramidal and cerebellar signs, moderate lower-extremity placing, and gait apraxia. The Kurtzke EDSS score was 4.0. The NSB revealed moderate to severe impairment in nonverbal memory, sequencing efficiency, attention and concentration, and psychomotor speed. An MRI scan revealed multiple periventricular lesions with severe periventricular volume loss (Fig 2, bottom left) and isolated callosal lesions (Fig 2, bottom center and right). The patient's memory impairment on repeated NSB and clinical examinations improved after high-dose intravenous steroid therapy. His behavioral disorganization has remained stable with maintenance haloperidol therapy (0.5 mg twice each day). He continues to demonstrate cognitive dysfunction that precludes employment.

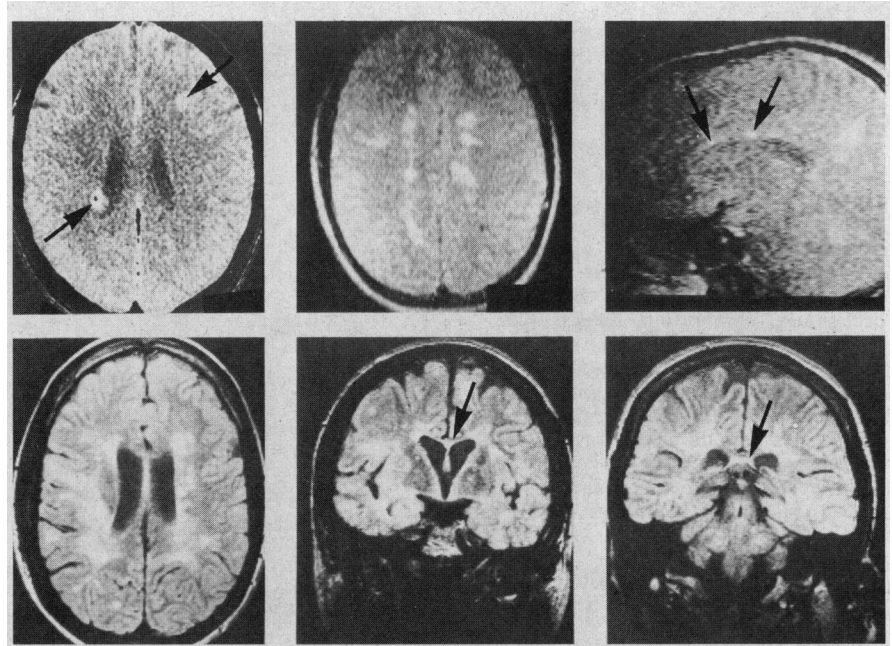


Fig 1.—Top, Patient 1. Acute, contrast-enhancing lesions can be seen on computed tomographic scan (top left). Moderate periventricular demyelination (top center), and multiple corpus callosum lesions (top right) are seen on magnetic resonance imaging. Bottom, Patient 3. Magnetic resonance imaging reveals extensive periventricular demyelination (bottom left), extremely thin rostral corpus callosum (bottom center), and demyelination in posterior corpus callosum (bottom right).

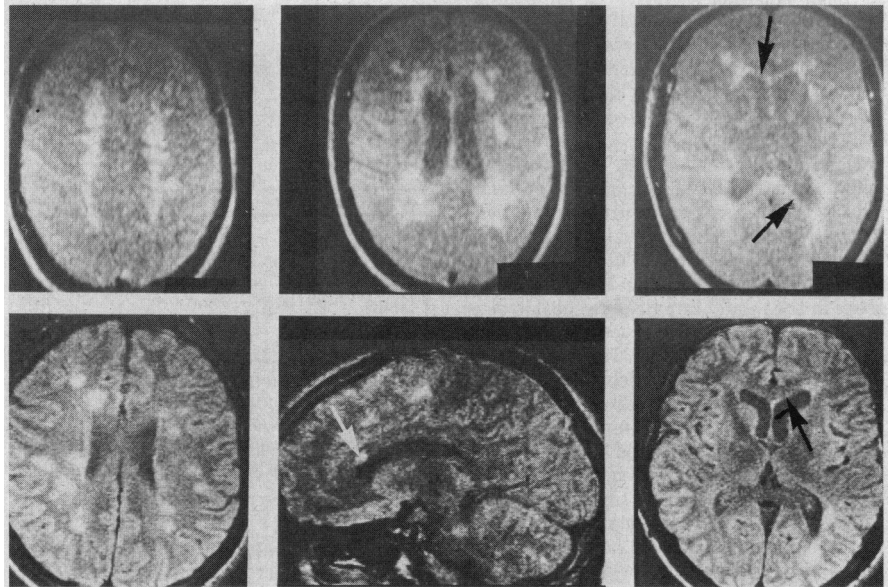


Fig 2.—Top, Patient 4. Magnetic resonance imaging reveals confluent periventricular demyelination (top left), ventricular enlargement (top center), and linear increase in signal intensity in corpus callosum (top right). Bottom, Patient 5. Magnetic resonance imaging reveals periventricular volume loss (bottom left) and isolated callosal lesion (bottom center) in normally thick corpus callosum (bottom right).

Cognitive Function Grade 3

CASE 6.—Isolated cognitive dysfunction with gait apraxia is described.

A 31-year-old woman presented to our center with a four-year history of MS. Her primary complaint was progressive gait difficulty during the preceding two years. She had recently quit her job as an admin-

istrative assistant in a physician's office. The patient had been told that her problems were related to depression. Bedside mental status examination revealed poor concentration, abstraction, and calculations. She exhibited a severely apraxic gait with placing response. Other neurologic dysfunction was minimal. Her Kurtzke EDSS score was 3.5. A CT scan revealed

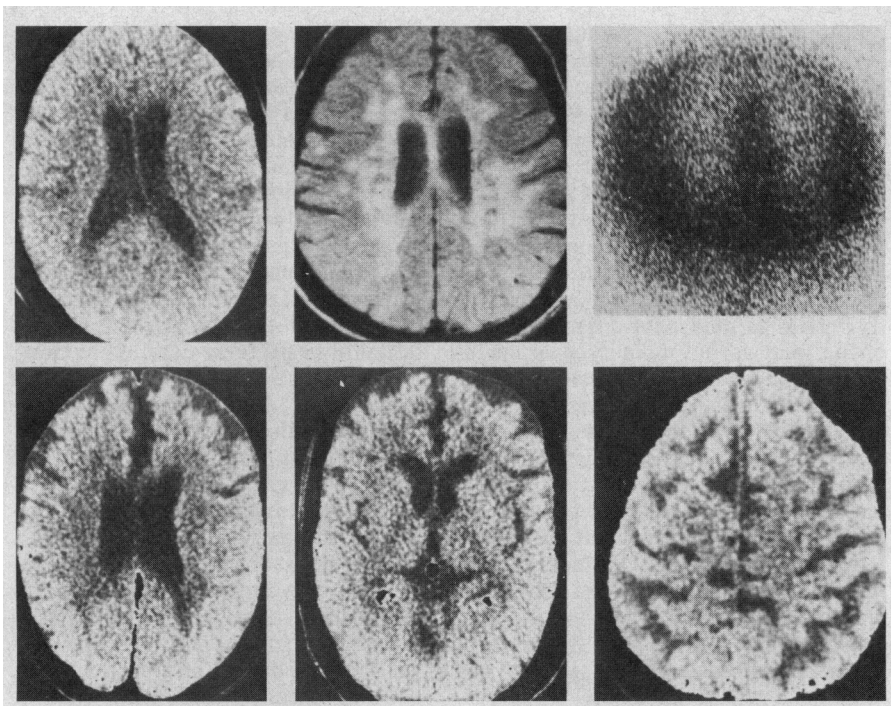


Fig 3.—Top, Patient 6. White-matter attenuation with ventricular enlargement on computed tomographic scan (top left) compared with confluent periventricular demyelination on magnetic resonance imaging (top center) and normal 48-hour cisternogram (top right). Bottom, Patient 7. Computed tomographic scan reveals marked frontal atrophy, ventricular enlargement, white-matter attenuation, and diffuse sulcal enlargement.

diffuse white-matter attenuation and ventricular enlargement (Fig 3, top left). An MRI scan showed confluent demyelination (Fig 3, top center). The expanded HRB disclosed severe impairment across a wide range of functions (especially recent memory) and, in this college graduate, a Wechsler Adult Intelligence Scale Full-Scale intelligence quotient of 82. The patient's cognitive symptoms have continued to deteriorate over the ensuing 1.5 years. Her gait apraxia is now severe enough to require bilateral assistance. A recent isotope cisternogram revealed no evidence of spinal fluid flow disturbance (Fig 3, top right).

CASE 7.—Global dementia and severe gait apraxia are described.

A 45-year-old woman presented to our center in 1985 with progressive gait disorder and difficulty handling her personal and business affairs. Although the diagnosis of MS had been made in 1980, she was noted to have optic atrophy even at that time. Neurologic examination disclosed global dementia and severe gait apraxia. Other neurologic functions, except visual acuity, were minimally impaired. Her Kurtzke EDSS score was 5.0. A CT scan revealed severe white-matter attenuation, diffuse cortical atrophy, and modest ventriculomegaly (Fig 3, bottom).

SUMMARY OF PATIENTS

Table 3 contains a demographic and clinical summary of the patients.

The mean age of the patients (N = 12) was 38.6 years. Disease duration

was five years or less in six patients, six to ten years in two patients, and more than ten years in four patients.

Only four of these 12 patients would have been considered to have a chronic/progressive disease course, the rest having relapsing/remitting histories. The mean Kurtzke EDSS score for the group was only 3.2. The mean number of functional systems involved was 6.2 (maximum number possible is eight). Except for cerebral dysfunction, no predilection for severe involvement in specific systems was noted.

All but two of these patients had frontal lobe release signs seen predominantly in the lower, but not the upper, extremities. Seven of 12 patients had moderate gait apraxia, and two of the 12 had gait apraxia severe enough to eventually require walking aids. All but two patients had a placing response in the feet. This flexor response to plantar stimulation was strong enough in six patients to overcome the Babinski response, which could only be elicited by stimulating the lateral side of the foot. Only the most severely impaired patient (patient 7) exhibited any frontal release signs in the upper extremities.

NEUROPSYCHOLOGICAL FINDINGS

Five of the 12 patients received the expanded HRB, six received the NSB,

and one (patient 7) received only bedside mental status testing. The neuropsychological results are summarized in Table 3. The subtest results can be clinically related to the following broad cognitive abilities: verbal and nonverbal learning and memory, complex problem-solving ability, attention and concentration, visuospatial ability, nonverbal auditory processing, and language abilities.

NEURORADIOLOGIC FINDINGS

Ten of the 12 patients had MRI scans. All scans revealed moderate to severe periventricular disease, including confluent lesions. Ventriculomegaly was noted in ten patients, and three patients had specific corpus callosum lesions or callosal atrophy.

COMMENT

Although an extensive literature prior to 1980 documents cognitive dysfunction in MS,¹⁰⁻¹⁴ major recent reviews of MS^{15,16} have not focused on this aspect of the disorder. Population-based studies, using a brief bedside mental status examination, have suggested that significant cognitive dysfunction may occur soon after onset in 2.0% to 2.9%^{17,18} or after 17 years in as many as 25%¹⁷ of patients. More recent applications of standardized neuropsychological test batteries have demonstrated cognitive dysfunction in 46%¹ of patients with relapsing/remitting courses and in 63%³ to 72%¹ of patients with chronic/progressive courses. It is clear that more rigorous neuropsychological investigations yield higher rates of cognitive dysfunction. There has been, to date, little information on the neurologic and functional relevance of these findings.

The patients presented here were striking to our clinicians in a number of ways:

1. Their functional cognitive impairment was far worse than any other neurologic impairment.

2. Nearly all of the patients had evidence of frontal lobe release signs in the lower extremities.

3. The extent of cognitive impairment was unrelated to neurologic disability status, disease course, or disease duration.

4. Our routine bedside mental status examination could not predict the range and extent of cognitive impairment except in the most severely impaired patients.

5. Cognitive dysfunction, like any other neurologic deficit in MS, can present acutely, subacutely, or chronically.

6. Affective disturbance may herald the presence of cognitive dysfunction.

7. Most of the patients had been followed up for months to years with their cognitive impairment undiscovered.

Although the mean EDSS score was only 3.2 in these patients, two thirds of them experienced cognitive impairment severe enough to preclude employment. In contrast to cognitive function, all other functional systems were mildly impaired. The mean number of functional systems involved (6.2), however, suggests widespread, albeit mild, disease.

Neither cognitive dysfunction nor frontal release signs in the lower extremities are adequately represented in the Kurtzke scale, which is heavily weighted for brain-stem, cerebellar, and spinal cord dysfunction. Formal psychometric studies^{1,4} have found no correlation between degree of cognitive impairment and the EDSS score. The number of lesions on cranial MRI has low correlation with specific neurologic dysfunction,¹⁹ and the degree of cranial lesion burden by MRI does not correlate with the EDSS score even in patients with chronic/progressive courses.⁶ The addition of both cognitive function and frontal release/apraxia components to future scales may permit demonstration of more salient relationships between brain lesions and neurobehavioral deficits.

Except for occasional case reports,²⁰ neither the frontal release signs nor the apraxia, both predominant in the lower extremities, has been previously described in MS. The degree of functional cognitive disability (Table 1) was highly correlated (Spearman's $r = .90$; $P < .001$) with the degree of frontal release/apraxia (Table 2) in the 12 patients described here.

The predominance of the frontal release signs and apraxia in the lower extremities in MS is similar to the pattern seen in patients with normal-pressure hydrocephalus.²¹ Neuroanatomic correlation may be related to the periventricular demyelination seen in both disorders. Although recent reports have suggested abnormal cisternogram patterns in patients with MS,^{22,23} one of our most severely affected patients (patient 6) had a completely normal isotope cisternogram (Fig 3, top right). It seems that periventricular demyelination, rather than an abnormality of spinal fluid flow, accounts for the similarity on CT in these two disorders.

Fifty percent (six of 12) of our

patients developed serious cognitive dysfunction within five years of disease onset, including the two most severely disabled patients. Prior reports have suggested that severe, early cognitive loss can occur in MS.²⁴⁻²⁶ More recent studies using psychometric test batteries have also found that cognitive dysfunction can occur early in a disease course^{2,4,27} or in the presence of mild physical disability.²⁸ Mild to moderate impairment of visual and verbal memory was noted in 60% of patients who presented with MS duration of less than two years or optic neuritis alone.⁴ These findings may correlate with the presence of periventricular demyelination, which occurs in 50% of patients presenting with idiopathic optic neuritis.²⁹

Even among our six patients whose disease duration was more than five years (range, six to 20 years), four were considered to have relapsing/remitting disease. These patients all had evidence of moderate to severe periventricular white-matter disease on CT or MRI scan in spite of a mean EDSS score of only 2.8. Significant cognitive dysfunction may, therefore, occur in those with long disease duration who otherwise appear benignly affected. These findings also suggest that subtle cognitive dysfunction may have been overlooked in patients with "silent" lesions⁵ discovered at post-mortem examination.

Disease duration in this descriptive study had no correlation with degree of cognitive functional impairment. These patients, however, were selected for early or prominent cognitive impairment. In 100 unselected outpatients with MS, the correlation between cognitive impairment and disease duration was significant but low ($r = .22$; $P < .05$).¹ This same level of correlation ($r = .25$; $P < .04$) has recently been described between extent of MRI abnormality and disease duration.³⁰ These weak but statistically significant correlations suggest that, although important, disease duration is not an accurate predictor of either cognitive dysfunction or severe periventricular demyelination in an individual patient.

The nature of the cognitive dysfunction in MS has recently been extensively reviewed.³¹ It is clear both from the results of neuropsychological testing in our cases (Table 3), as well as from the application of a comprehensive psychometric battery in a consecutive series of referral center patients,¹ that the range of cognitive deficits in MS is broad. Specifically, however, the kinds of deficits in mem-

ory and language skills that would normally bring a patient with dementia to the attention of family or physician are less marked than those seen in the dementia of Alzheimer's disease.³² By contrast, disorders of attention³² and difficulties with problem-solving and concept formation^{1,2} may be relatively more severe. Such deficits are not usually apparent in casual interactions, and may only be noticed in everyday situations that require patients to perform detailed or novel tasks. This subtlety of cognitive impairment would help explain the lag time in discovering the functionally significant cognitive dysfunction in some of the cases reported here.

The structural correlates of the cognitive changes in MS are not entirely clear. Both increased ventricular size^{33,34} and atrophy of the corpus callosum³⁵ have been correlated with cognitive impairment. The degree of periventricular demyelination has also been significantly correlated with the extent of cognitive impairment.⁶ Cortical-subcortical or cortical-cortical disconnection, resulting from focal or diffuse periventricular and callosal demyelination, may be the best current explanation for the cognitive deficits in MS.³²

It is clear that cognitive dysfunction, like other neurologic deficits in MS, may occur with relapse and remission (patient 2), relapse and progression (patients 1 and 5), or chronic progression (patients 6 and 7). The CT and psychometric evidence of an acute cognitive relapse with complete clearing in patient 2 has not been previously reported. Patient 1, with relapsing/progressive cognitive deficits, has been stabilized by cyclophosphamide therapy⁹ and remains at work. Evidence for progression of cognitive deficits in MS has been suggested previously.¹⁰

Affective disorder heralded the cognitive dysfunction in two of our cases. Patient 3 was brought to our attention with subacute depressive symptoms that were refractory to counseling. Patient 5 presented with concomitant manic-depressive psychosis and cognitive dysfunction. Recent attention to affective disorders in MS has demonstrated that patients with MS with cerebral involvement have more depressive episodes than those with noncerebral involvement,^{34,36} depression is more common in MS than in amyotrophic lateral sclerosis or temporal lobe epilepsy,³⁷ and MS may present with depressive disorder prior to diagnosis.³⁸ The association of a rapidly cycling bipolar illness with

MS has also been recently reported.³⁹ These findings suggest that affective disorder may be an organic concomitant of MS, possibly related to cognitive dysfunction as well as to specific patterns of subcortical demyelination.³⁴

Serious loss of cognitive function should be considered in patients with MS who (1) have chronic/progressive disease; (2) have demonstrated frontal release signs or apraxia, both prominent in the lower extremities; (3) present with depression or bipolar disorder refractory to treatment; (4) complain of cognitive difficulties at work or home, particularly in the areas of memory, attention, or complex problem-solving skills; and (5)

have moderate to severe periventricular abnormality on MRI scan, even early in the disease course in the absence of progressive neurologic deficit. In cases of suspected cognitive loss, the use of a brief neuropsychological screening battery,⁶ possibly adding tests of concept formation,² would be appropriate. Such a battery, more sensitive to subtle cognitive deficit than either the bedside mental status examination^{1,2} or the Folstein Mini-Mental State examination,⁶ can be used for screening, clinical trial monitoring, or clinical documentation of the progress of cognitive dysfunction over time. A more detailed, extensive neuropsychological battery¹ might be important in determination

of vocational disability due to cognitive dysfunction and in other situations that require a comprehensive assessment of cognitive strengths and deficits. This might prove to be important in applying recently devised methods of cognitive rehabilitation⁴⁰ to those with cognitive deficits and MS. Finally, the application of both traditional and experimental therapies in MS should be done with consideration for cognitive dysfunction as a potentially critical factor in the totality of MS disability.

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References

1. Heaton RK, Nelson LM, Thompson DS, et al: Neuropsychological findings in relapsing/remitting and chronic/progressive multiple sclerosis. *J Consult Clin Psychol* 1985;53:103-110.
2. Peyser JM, Edwards KR, Poser CM, et al: Cognitive function in patients with multiple sclerosis. *Arch Neurol* 1980;37:577-579.
3. Rao SM, Hammeke TA, McQuillen MP, et al: Memory disturbance in chronic/progressive multiple sclerosis. *Arch Neurol* 1984;41:625-631.
4. Lyon-Caen O, Jouvent R, Hauser S, et al: Cognitive function in recent onset demyelinating diseases. *Arch Neurol* 1986;43:1138-1141.
5. Gilbert JJ, Sadler M: Unsuspected multiple sclerosis. *Arch Neurol* 1983;40:533-536.
6. Franklin GM, Heaton RK, Filley CM, et al: Correlation of neuropsychological and magnetic resonance imaging (MRI) findings in chronic/progressive MS. *Neurology* 1988;38:1826-1829.
7. Reitan RM, Davison L: *Clinical Neuropsychology: Current Status and Applications*. Washington, DC, V. H. Winston, 1974.
8. Kurtzke JF: Rating neurological impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983;33:1444-1452.
9. Hauser SL, Dawson DM, Leirich JR, et al: Intensive immunosuppression in progressive multiple sclerosis: A randomized, three arm study of high dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med* 1983;308:173-180.
10. Canter AH: Direct and indirect measures of psychological deficit in multiple sclerosis. *J Gen Psychol* 1951;44:3-50.
11. Ross AT, Reitan RM: Intellectual and affective functions in multiple sclerosis. *Arch Neurol Psychiatry* 1955;73:663-677.
12. Jambor KL: Cognitive functioning in multiple sclerosis. *Br J Psychiatry* 1969;115:765-775.
13. Beatty PA, Gange JJ: Neuropsychological aspects of multiple sclerosis. *J Nerv Ment Dis* 1977;164:42-50.
14. Trimble MR, Grant I: Psychiatric aspects of multiple sclerosis, in Benson DF, Blumer D (eds): *Psychiatric Aspects of Neurologic Disease*. New York, Grune & Stratton, 1982, vol 2, pp 279-299.
15. McFarlin DE, McFarland HF: Multiple sclerosis. *N Engl J Med* 1982;307:1183-1188, 1246-1251.
16. McKhann GM: Multiple sclerosis. *Annu Rev Neurosci* 1982;5:219-239.
17. Kahana E, Leibowitz U, Alter M: Cerebral multiple sclerosis. *Neurology* 1971;21:1179-1185.
18. Kurtzke JF, Beebe GW, Nagler B, et al: Studies on the natural history of multiple sclerosis: 6. Clinical and laboratory findings at first diagnosis. *Acta Neurol Scand* 1972;48:19-46.
19. Crisp DT, Kleiner JE, DePhillip GJ, et al: Clinical correlations with magnetic resonance imaging in multiple sclerosis. *Neurology* 1985;35(suppl 1):137.
20. McLardy T, Sinclair A: A case of pre-senile fulminating multiple sclerosis. *Confin Neurol* 1964;24:417-424.
21. Messert B, Baker NH: Syndrome of progressive spastic ataxia and apraxia associated with occult hydrocephalus. *Neurology* 1966;16:440-452.
22. Bartolini S, Inzitari D, Castagnoli A, et al: Correlation of isotopic cisternographic patterns in multiple sclerosis with CSF IgG values. *Ann Neurol* 1982;12:486-489.
23. Volpi G, Inzitari D, Fratigliani L, et al: CT periventricular hypodensity in multiple sclerosis: Isotope cisternography and clinical correlations. *Ann Neurol* 1986;20:146.
24. Bergin JD: Rapidly progressing dementia in disseminated sclerosis. *J Neurol Neurosurg Psychiatry* 1957;20:285-292.
25. Koenig H: Dementia associated with the benign form of multiple sclerosis. *J Trans Am Neurol Assoc* 1968;93:227-228.
26. Young AC, Saunders J, Ponsford JR: Mental change as an early feature of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1976;39:1008-1013.
27. Grant I, McDonald WI, Trimble MR, et al: Deficit learning and memory in early and middle phases of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1984;47:250-255.
28. Van den Burg W, van Zomeren AH, Minderehoud JM, et al: Cognitive impairment in patients with multiple sclerosis and mild physical disability. *Arch Neurol* 1987;44:494-501.
29. Jacobs L, Kinkel PR, Kinkel WR: Silent brain lesions in patients with idiopathic optic neuritis. *Arch Neurol* 1986;43:452-455.
30. Stevens JC, Farlow MR, Edwards MK, et al: Magnetic resonance imaging: Clinical correlation in 64 patients with multiple sclerosis. *Arch Neurol* 1986;43:1145-1148.
31. Rao SM: The neuropsychology of multiple sclerosis: A critical review. *J Clin Exp Neuropsychol* 1986;8:503-542.
32. Filley CM, Heaton RK, Nelson LM, et al: A comparison of dementia in Alzheimer's disease and multiple sclerosis. *Arch Neurol* 1989;46:157-161.
33. Rao SM, Glatt S, Hammeke TA, et al: Chronic/progressive multiple sclerosis: Relationship between cerebral ventricular size and neuropsychological impairment. *Arch Neurol* 1985;42:678-682.
34. Rabins PV, Brooks BF, O'Donnell P, et al: Structural brain correlates of emotional disorder in multiple sclerosis. *Brain* 1986;109:585-597.
35. Huber SJ, Paulson GW, Rammohan K, et al: Magnetic resonance findings, disability, and cognitive factors in multiple sclerosis. *Ann Neurol* 1986;20:170.
36. Schiffer RB, Caine ED, Bamford KA, et al: Depressive episodes in patients with multiple sclerosis. *Am J Psychiatry* 1983;140:1498-1500.
37. Schiffer RB, Babigian HM: Behavioral disorders in multiple sclerosis, temporal lobe epilepsy and amyotrophic lateral sclerosis: An epidemiologic study. *Arch Neurol* 1984;41:1067-1069.
38. Whitlock FA, Siskind MM: Depression as a major symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1980;43:861-865.
39. Kellner CH, Davenport Y, Post RM, et al: Rapidly cycling bipolar disorder and multiple sclerosis. *Am J Psychiatry* 1984;141:112-113.
40. Ben-Yishay Y, Diller L: Cognitive remediation, in Rosenthal M, Griffith ER, Bond MR, et al (eds): *Rehabilitation of the Head-Injured Adult*. Philadelphia, FA Davis Co Publishers, 1983, pp 367-380.