Multiple Sclerosis With Predominant, Severe Cognitive Impairment

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Objective: To describe the characteristics of multiple sclerosis (MS) presenting with severe cognitive impairment as its primary disabling manifestation.

Design: Retrospective case series.

Setting: Tertiary referral center.

Patients: Patients were identified through the Mayo Clinic data retrieval system (1996-2008) with definite MS (McDonald criteria) and severe cognitive impairment as their primary neurological symptom without accompanying significant MS-related impairment or alternative diagnosis for cognitive dysfunction. Twenty-three patients meeting inclusion criteria were compared regarding demographics, clinical course, and radiological features.

Main Outcome Measures: Demographic, clinical, and radiological characteristics of the disease.

Results: Twelve patients were men. The median age of the first clinical symptom suggestive of central nervous system demyelination was 33 years, and severe MS-related cognitive impairment developed at a median age of 39 years. Cognitive impairment could be dichotomized as subacute fulminant (n=9) or chronic progressive (n=14) in presentation, which corresponded to subsequent relapsing or progressive MS courses. Study patients commonly exhibited psychiatric (65%), mild cerebellar (57%), and cortical symptoms and signs (eg, seizure, aphasia, apraxia) (39%). Fourteen of 21 (67%), where documented, smoked cigarettes. Brain magnetic resonance imaging demonstrated diffuse cerebral atrophy in 16 and gadolinium-enhancing lesions in 11. Asymptomatic spinal cord magnetic resonance imaging lesions were present in 12 of 16 patients (75%). Immuno-modulatory therapies were generally ineffective in improving these patients.

Conclusions: We describe patients with MS whose clinical phenotype is characterized by severe cognitive dysfunction and prominent cortical and psychiatric signs presenting as a subacute fulminant or chronic progressive clinical course. Cigarette smokers may be overrepresented in this phenotype.

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Cognitive dysfunction is a common feature of multiple sclerosis (MS), affecting approximately 40% to 60% at some time in their disease course. Cognitive impairment often manifests as deficits in recent memory, attention, information-processing speed, executive functions, and visuospatial perception. The type and degree of cognitive dysfunction is highly associated with disease course (ie, relapsing-remitting, primary or secondary progressive). Even seemingly minor cognitive dysfunction may be troubling and impair employment and daily living; however, it typically does not cause severe disability until late in the disease course when other coexistent neurological impairment also becomes prominent.

Multiple sclerosis rarely presents primarily as debilitating cognitive dysfunction without accompanying disability in motor, sensory, or cerebellar function. When this presentation occurs, it is referred to as “cortical” or “cerebral-type” MS and it presents a diagnostic dilemma, particularly in differentiating primary neurodegenerative dementias or infectious or metabolic disorders. Treatment is challenging in these patients as symptomatic therapies aimed at MS cognitive impairment are of limited benefit. Earlier case series describe some of the characteristics of this presentation; however, the phenotype remains poorly described. Furthermore, risk factors that may predispose patients to primary cognitive forms of MS have not been elucidated. We present 23 patients with predominant, severe cognitive presentations of MS.

METHODS

The study was approved by the Mayo Clinic institutional review board (06-003613). The Mayo Clinic (Rochester, Minnesota) patient database...
was queried for diagnostic coding of both MS central nervous system (CNS) demyelinating disease (and related terms) plus cognitive impairment (and related terms) between January 1, 1996, and June 27, 2008. Study patients had definite MS by the revised guidelines from the International Panel on the Diagnosis of Multiple Sclerosis and MS clinical course was classified by the criteria of the National Multiple Sclerosis Society (USA) Advisory Committee. Patients had severe cognitive impairment as their primary impairing neurological symptom, great enough to impair instrumental activities of daily living. Cognitive impairment was formally assessed by the Kokmen Short Test of Mental Status, a brief 38-point cognitive screening test assessing orientation, attention, learning and recall, calculation, abstraction, construction, and knowledge (mean [SD] normal value of 33.1 [3.3] for patients older than 60 years). A score of 31 of 38 or less for patients younger than 50 years yields a specificity of 93.3% and sensitivity of 86.4% for dementia. In selected patients, comprehensive neuropsychological testing was used to evaluate for dementia, intelligence, memory, language, visual spatial learning, attention, problem solving, and depression. Exclusion criteria were (1) significant impairment in other neurological domains (as determined by the formal Mayo Clinic neurology records) and (2) alternative diagnoses explaining the cognitive impairment (eg, degenerative dementing diseases such as Alzheimer disease, vascular dementia, dementia with Lewy bodies, inherited and sporadic leukodystrophies, CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy], metabolic disturbance or infection). Serological investigations performed, where indicated, included antinuclear antibody titer; levels of rheumatoid factor, angiotensin-converting enzyme, antibody to extracted nuclear antigen, and cyclic citrullinated peptide; erythrocyte sedimentation rate; levels of antideoiumysomal antibody, thyro- tropin, thyroperoxidase antibody, vitamin B12, heavy metals, vitamin E, lactate, pyruvate, ceruloplasmin, and copper; liver function tests; levels of c- and p-antineutrophil cytoplasmic antibodies, myeloperoxidase, proteinase 3 antibody, and antiphospholipid antibodies; skin biopsy for CADASIL; paraneoplastic antibody panel; levels of arylsulfatase A, galactosylceramide B-galactosidase, very-long-chain fatty acids, and hexosaminidase A; and infectious screens for syphils, human immunodeficiency virus, hepatitis, rubella, rubella, JC virus, parvovirus, Lyme disease, Whipple disease, Cryptococcus, toxoplasmosis, West Nile virus, Epstein-Barr virus, human T-lymphotropic virus, and equine encephalitis.

Five patients underwent brain biopsy for diagnostic purposes, of which 3 specimens confirmed demyelinating disease while 2 showed nonspecific gliosis without other diagnostic abnormalities. In the 2 patients with nondiagnostic biopsy specimens, an MS diagnosis was made by clinical history, radiological and cerebrospinal fluid (CSF) findings, and serological exclusion of alternative diagnoses.

Broadly screening for MS, CNS demyelinating disease, and cognitive impairment or dementia identified 549 patients, with 172 having severe cognitive impairment attributable to MS (Figure 1). Twenty-three met our strict criteria for this study, with the others were excluded because of coexistent impairing MS neurological signs and symptoms. All selected patients had either minimal or no impairments in noncognitive neurological domains (pyramidal, cerebellar, brainstem, sensory, bowel/bladder, or visual). Medical records from the Mayo Clinic were abstracted for the following: demographics, MS clinical course, associated neurological and psychological signs and symptoms, smoking history, neuropsychometric testing, laboratory analyses, neuroimaging studies, and treatment responses. Ten patients were seen at Mayo Clinic for 1 visit. In these cases, the clinical course was abstracted entirely from their history and outside medical records. The remaining 13 patients were seen at Mayo Clinic multiple times and had a median of 2 years' follow-up (range, 0.5-10 years).

Statistical analysis was performed using JMP (SAS Institute Inc, Cary, North Carolina) or Microsoft Excel (Microsoft, Redmond, Washington) statistical software. Data were analyzed with either the 2-tailed t test (parametric data) or Fisher exact test (nonparametric data).

### RESULTS

**PATIENT DEMOGRAPHICS**

Twelve patients (52%) were male and the patients had a median age of 33 years (range, 20-56 years) at first onset of symptoms of CNS demyelination (Table). The median age at onset of debilitating cognitive impairment was 39 years (range, 20-56 years). Cognitive impairment was the initial presentation in 17 patients (74%), with the remaining 6 patients presenting with optic neuritis, paresthesias, seizures, or mild leg weakness. Nine patients with MS had a relapsing-remitting course; 11, primary progressive; and 3, secondary progressive.

Associated signs and symptoms of cortical or psychiatric dysfunction were common (Table). Cortical signs and symptoms were present in 9 of 23 patients, including seizures, aphasia, and apraxia. Thirteen patients (57%) had mild cerebellar ataxia. Psychiatric abnormalities were present in 15 of 23 patients, with a combination of depressive (13 of 23) or psychotic (3 of 23) symptoms.

Fourteen of 21 patients (67%) had a history of tobacco use (2 not documented). Twelve were current smokers, with a median 30 pack-year history (range, 2.5-80 pack-years) in the 11 patients where this was clearly documented.

Twenty-one of 23 patients were assessed using the Kokmen Short Test of Mental Status, with a median score of 25 (range, 3-33). Comprehensive neuropsychometric testing was performed in 14 patients and all had results confirming disabling cognitive impairment and dementia not attributable to either depression or non-MS diagnosis. In 14 patients (61%), cognitive dysfunction evolved in a progressive fashion, eventually leading to significant disability. In the remaining 9 patients (39%), cog-
nitive dysfunction occurred in an attack-related sub-
cute and fulminant manner. Four of these patients had 
multiple recurrent attacks of cognitive or psychiatric dys-
function, whereas the remaining 5 had a single severe cog-
nitive attack without full resolution. All 9 patients with 
a subacute and fulminant onset of cognitive dysfunc-
tion developed relapsing-remitting MS, whereas the MS 
patients with progressive cognitive dysfunction devel-
oped was primary progressive MS in 11 and secondary 
progressive MS in 3.

NEUROIMAGING AND CSF

Neuroimaging was performed at differing points in pre-
sentation given the retrospective nature of the study; there-
fore, limited analysis was performed. Brain magnetic reso-
nance imaging (MRI) reports were reviewed in all patients 
and spinal cord MRI, in 16. Neuroimaging review was 
limited to a median of 2 brain scans (range, 1-6) per pa-
tient and those assessed were performed a median of 2 
years following onset of cognitive impairment (range, 0-13 
years). The scans showed no consistently defining ab-
normalities despite the clinical presentation (Figure 2), 
with all patients having numerous typical T2 lesions and 
11 having gadolinium-enhancing lesions on at least 1 scan. 
Twelve of 16 patients with spinal cord MRI available re-
vealed at least 1 typical small, ovoid, T2-hyperintense le-
sion consistent with MS. Brain MRI demonstrated dif-
fuse cerebral atrophy in 10 patients, with accompanying 
cerebellar atrophy in 6 further patients.

Cerebrospinal fluid analysis was available in 20 of 23 
patients and showed abnormalities consistent with MS 
in 19 of 20 (95%). Fourteen had an elevated IgG index, 
16 had elevated unique CSF oligoclonal bands, and 11 
had both abnormalities.

TREATMENT

Eight patients received corticosteroids during their dis-
case course (7 subacute, 2 chronic), and 2 patients with 
subacute severe cognitive attacks subsequently received 
plasmapheresis. Chronic immunomodulatory treatment 
was initiated in 13 patients (with some patients receiving 
more than 1 treatment): interferon beta, 11; glatiramer ac-
etae, 4; and mitoxantrone hydrochloride, 3. One patient 
with a subacute fulminant course and multiple cognitive 
exacerbations had improvement of cognitive impairment 
after initiation of mitoxantrone therapy (as documented 
by 2 neuropsychometric evaluations 5 years apart). There 
was no marked improvement in MS-related dementia in 
the remaining patients despite therapy. Whether long-
term immunomodulatory therapy prevented a more se-
vere decline in cognition or other MS-related neurologi-
cal impairment could not be determined.

ILLUSTRATIVE CASE HISTORIES

Case 1: MS Presenting as Subacute, Fulminant 
Cognitive Impairment

A 43-year-old man without history of neurological dis-

![Figure 2. Magnetic resonance imaging in illustrative cases. Magnetic resonance imaging in our cohort of patients with multiple sclerosis (MS) with severe cognitive impairment is similar to that seen in relapsing-remitting and progressive forms of MS. Brain magnetic resonance imaging from a patient with MS with subacute fulminant cognitive impairment illustrating periventricular T2 hyperintensities (A) with gadolinium enhancement (B). A patient with chronic progressive disease exhibited confluent demyelination, cerebral atrophy (C), and an asymptomatic T2-hyperintense cervical cord lesion (D). See the “Illustrative Case Histories” subsection of the “Results” section in the text for clinical details.](https://www.archneurol.com)
apraxia over the course of 2 weeks. Gait and other neurological functions were normal. Brain MRI (Figure 2A and B) showed T2 lesions consistent with MS, many of which enhanced following gadolinium administration. Cerebrospinal fluid revealed elevations in both IgG index and oligoclonal bands. Results of extensive serological evaluations for connective tissue diseases, vasculitis, paraneoplastic disease, and infectious etiologies were negative. Brain biopsy was performed at an outside institution, given the atypical clinical course, and findings demonstrated active demyelination with relative axonal sparing. Immediate treatment was initiated with intravenous corticosteroids and subsequent plasma exchange, with only mild and gradual improvement over 6 months. Despite treatment with interferon beta-1b, he continued to have clinical relapses and 2 years later he was impaired with dementia and coexisting mild depression.

**Case 2: MS Presenting as Chronic, Progressive Cognitive Impairment**

A 57-year-old woman was found wandering following the nursing home placement of her mother with whom the patient had been living. She had no history of acute neurological disease but had a long history of depression and cigarette smoking. She was cognitively impaired but entirely alert and had only minor imbalance on tandem walking on neurological examination. Head MRI demonstrated extensive T2 signal abnormalities within the hemispheric white matter and central pons with moderate diffuse cerebral atrophy without associated restricted diffusion or gadolinium enhancement (Figure 2C and D). Spinal cord MRI demonstrated 2 focal T2 hyperintensities within the cervical cord without enhancement, consistent with MS and a normal thoracic cord. Cerebrospinal fluid showed an elevated IgG index, 12 unique oligoclonal bands, and mildly elevated protein level (68 mg/dL). Results of investigations for infection and metabolic disease and skin biopsy for CADASIL were negative. Findings of formal neurocognitive testing were consistent with dysfunction typically seen in MS, including reduced speed of information processing, compromised complex attention, reduced nonverbal reasoning, complex learning efficiency, and reduced novel problem solving. Informed decision making was so impaired that appointment of a guardian and placement in a nursing home was required.

The patients described herein represent an uncommon MS clinical presentation characterized by severe cognitive impairment in the relative absence of significant coexistent MS-related impairment. These hallmark features are often accompanied by signs of cortical dysfunction (seizures, apraxia, aphasia) that are infrequent in patients with prototypic MS. Patients may present with either subacute fulminant or insidiously progressive cognitive impairment, which corresponds to their subsequent MS clinical course of relapsing or progressive disease, respectively. Over time, the majority of patients continue to have predominantly cognitive disability with little disability in other neurological spheres. Cognitive dysfunction (particularly when severe) is poorly represented by the Expanded Disability Status Scale, especially at higher levels of disability where ambulation is the primary determinant of score.

We confirmed prior findings of significant coexistent psychiatric symptoms (most commonly depression) in this cohort. An intriguing finding was the apparent high proportion of cigarette use in these patients, which in theory could represent a modifiable risk factor. Sixty-seven percent of our cohort had a history of smoking, 93% of which was active at the time of disease onset. These compare with the self-reported North American Research Committee on Multiple Sclerosis registry (N=8983 patients) rates of ever smokers (54.2%) and current smokers (17.3%) and a study of Rhode Island patients with MS where a current smoker rate of 15.2% was found. The smoking rate of the US population is approximately 19.8%. Additionally, cigarette smoking has been associated with both an increased risk of developing MS and subsequent cerebral atrophy in patients with MS.

Although subcortical MS pathology may produce cortical type symptoms, cortical MS lesions may also contribute to the clinical phenotype seen in our patients. Recent neuropathological studies have confirmed that cortical demyelination may be extensive in progressive MS and does not correlate with white matter lesion burden. Although conventional brain MRI techniques do not adequately identify MS lesions within the cortical ribbon, more recent novel techniques and sequences are being developed to enhance in vivo detection.

Limitations of this study include its retrospective nature. Follow-up was limited in some patients and investigations and therapies were inconsistently applied. Prospective evaluation of a similar cohort would be ideal in better defining the natural history, treatment response, and clinical outcome of this phenotype.

Our study illustrates the importance in considering MS as a cause of acute or progressive severe cognitive impairment even with relative sparing of other neurological deficits. Therapy appears challenging in these patients and functional evaluation by traditional outcome measures, such as the Expanded Disability Status Scale, underestimates the severity of their functional impairment.

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