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 not 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 neurocognitive 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 antidiomyositis antibody, thyrotropin, thyperoxidase 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 anti-phospholipid 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, 0.3–10 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, parasthesias, 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 subacute and fulminant manner. Four of these patients had multiple recurrent attacks of cognitive or psychiatric dysfunction, whereas the remaining 5 had a single severe cognitive attack without full resolution. All 9 patients with a subacute and fulminant onset of cognitive dysfunction developed relapsing-remitting MS, whereas the MS patients with progressive cognitive dysfunction developed was primary progressive MS in 11 and secondary progressive MS in 3.

NEUROIMAGING AND CSF

Neuroimaging was performed at differing points in presentation given the retrospective nature of the study; therefore, limited analysis was performed. Brain magnetic resonance 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 patient 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 abnormalities 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 revealed at least 1 typical small, ovoid, T2-hyperintense lesion consistent with MS. Brain MRI demonstrated diffuse 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 disease 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 acetate, 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 severe decline in cognition or other MS-related neurological 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 disease developed subacute memory impairment, aphasia, and...
apraxia over the course of 2 weeks. Gait and other neuro-
ological functions were normal. Brain MRI (Figure 2A and
B) showed T2 lesions consistent with MS, many of which
enhanced following gadolinium administration. Cerebro-
spinal fluid revealed elevations in both IgG index and oli-
goclonal bands. Results of extensive serological evalua-
tions for connective tissue diseases, vasculitis, paraneoplastic
disease, and infectious etiologies were negative. Brain bi-
opsy was performed at an outside institution, given the atypical
clinical course, and findings demonstrated active demyel-
nylation with relative axonal sparing. Immediate treat-
ment was initiated with intravenous corticosteroids and
subsequent plasma exchange, with only mild and gradual
improvement over 6 months. Despite treatment with inter-
feron 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 neu-
rological disease but had a long history of depression and
cigarette smoking. She was cognitively impaired but en-
tirely alert and had only minor imbalance on tandem walk-
ing on neurological examination. Head MRI demon-
strated extensive T2 signal abnormalities within the
hemispheric white matter and central pons with mod-
erate diffuse cerebral atrophy without associated re-
stricted diffusion or gadolinium enhancement (Figure 2C
and D). Spinal cord MRI demonstrated 2 focal T2 hy-
perintensities within the cervical cord without enhance-
ment, 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, includ-
ing reduced speed of information processing, compro-
mised complex attention, reduced nonverbal reasoning,
complex learning efficiency, and reduced novel prob-
lem solving. Informed decision making was so impaired
that appointment of a guardian and placement in a nurs-
ing home was required.

The patients described herein represent an uncommon
MS clinical presentation characterized by severe cogni-
tive impairment in the relative absence of significant co-
existant MS-related impairment. These hallmark features
are often accompanied by signs of cortical dysfunction (seizures, apraxia, aphasia) that are infre-
fuent in patients with prototypic MS. Patients may pre-
sent with either subacute fulminant or insidiously pro-
gressive cognitive impairment, which corresponds to their
subsequent MS clinical course of relapsing or progressive-
disease, respectively. Over time, the majority of pa-
tients continue to have predominantly cognitive disabil-
ity with little disability in other neurological spheres.
Cognitive dysfunction (particularly when severe) is poorly
represented by the Expanded Disability Status Scale, es-
pecially 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 Res-
search Committee on Multiple Sclerosis registry (N=8983
patients) rates of ever smokers (54.2%) and current smok-
ers (17.3%) and a study of Rhode Island patients with
MS where a current smoker rate of 15.2% was found.12
The smoking rate of the US population is approxi-
mately 19.8%.13 Additionally, cigarette smoking has been
associated with both an increased risk of developing MS14
and subsequent cerebral atrophy in patients with MS.15

Although subcortical MS pathology may produce cor-
tical type symptoms,16 cortical MS lesions may also con-
tribute to the clinical phenotype seen in our patients. Re-
cent neuropathological studies have confirmed that
cortical demyelination may be extensive in progressive
MS17 and does not correlate with white matter lesion bur-
den.18,19 Although conventional brain MRI techniques do
not adequately identify MS lesions within the cortical rib-
on, more recent novel techniques and sequences are
being developed to enhance in vivo detection.20

Limitations of this study include its retrospective na-
ture. Follow-up was limited in some patients and inves-
tigations and therapies were inconsistently applied. Pro-
spective 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 impair-
ment even with relative sparing of other neurological defi-
cits. Therapy appears challenging in these patients and func-
tional evaluation by traditional outcome measures, such as
the Expanded Disability Status Scale, underestimates the
severity of their functional impairment.

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Correspondence: B. Mark Keegan, MD, FRCP, Depart-
ment of Neurology, Mayo Clinic College of Medicine, 200
First St SW, Rochester, MN 55905 (keegan.bmark@mayo.
edu).

Author Contributions: Study concept and design: Staff and
Keegan. Acquisition of data: Staff. Analysis and interpre-
tation of data: Staff, Lucchinetti, and Keegan. Drafting of
the manuscript: Staff and Keegan. Critical revision of the
manuscript for important intellectual content: Staff, Luc-
chinetti, and Keegan. Administrative, technical, and ma-
terial support: Staff. Study supervision: Lucchinetti and
Keegan.

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