Cognitive presentation of multiple sclerosis: evidence for a cortical variant

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Background: Although neuropsychiatric complications are well recognised, the presentation of multiple sclerosis with cognitive or neuropsychiatric symptoms has generally been considered a rare occurrence and to reflect subcortical pathology.

Objectives: To document the clinical, neuropsychological, and radiological features of six cases of cognitive presentation of multiple sclerosis, to review the relevant literature, and to propose a possible cortical basis for this clinical presentation.

Subjects: Six patients (five women; age range 38 to 60 years) presented to the memory and cognitive disorders clinic in Cambridge with an initially undiagnosed cognitive/neuropsychiatric syndrome. All underwent neuropsychological evaluation, brain imaging, and ancillary investigations to establish a diagnosis of multiple sclerosis.

Results: The six cases all had a progressive dementia syndrome with prominent amnesia, often accompanied by classic cortical features including dysphasia, dysgraphia, or dyslexia. Mood disturbance was ubiquitous and in three patients there was a long history of preceding severe depression. All six developed characteristic physical signs on follow up, with marked disabilities. A review of 17 previously reported cases highlighted the prominence of memory impairment and depression in the early stages.

Conclusions: On clinical, pathological, and radiological grounds, the neuropsychiatric presentation of multiple sclerosis may represent a clinicopathological entity of “cortical multiple sclerosis.” Failure to recognise this will delay diagnosis and may expose patients to potentially dangerous and invasive investigation. Because the neuropsychiatric features of cortical multiple sclerosis are a major cause of handicap, their early recognition may be particularly important in view of emerging treatments.

Although once considered uncommon or late features, cognitive and neuropsychiatric symptoms are now well recognised as early manifestations of multiple sclerosis. Estimates vary but Lyon-Caen and colleagues reported that 85% of patients with clinically definite multiple sclerosis of less than two years’ duration, and 66% of those with only optic neuritis, showed some form of cognitive impairment. Similarly, Swingler and Compston reported a prevalence of 40% for neuropsychiatric symptoms and signs in 301 patients with established multiple sclerosis during routine clinical interview. Others have since confirmed this observation and reported that the prevalence of symptoms such as memory deficit or depression and focal cortical syndromes was as high as 60%.

Despite the recognised high prevalence of cognitive symptoms in early established multiple sclerosis, a presentation with predominant or pure cognitive or neuropsychiatric symptoms is rarely described. In a retrospective study, Skegg identified 91 patients with multiple sclerosis in a prevalent population of 112,000 of 29 with neuropsychiatric manifestations, 18 (62%) had been initially referred for psychiatric assessment, often several years before the diagnosis of multiple sclerosis. In addition, there have been eight previous reports of an exclusive neuropsychiatric or cognitive presentation of multiple sclerosis, four detailing single cases, and the collective experience amounting to 17 individuals.

We report six patients with multiple sclerosis who presented with predominant cognitive or neuropsychiatric syndromes or both. We suggest that, together with emerging pathological and radiological evidence for discrete cortical involvement in multiple sclerosis, these clinical observations suggest a subclass of multiple sclerosis in which the cerebral cortex is predominantly or exclusively involved. Self evidently, the availability of emerging treatment opportunities highlights the importance of early recognition of cortical multiple sclerosis.

METHODS

Patients and diagnostic criteria

This was a retrospective study of six cases that were referred to the memory and cognitive disorders clinic at Addenbrooke’s Hospital, Cambridge, between 1996 and 2001. All patients had an undiagnosed cognitive/neuropsychiatric syndrome at initial presentation and were eventually found to have multiple sclerosis. All cases fulfilled recently revised diagnostic criteria of multiple sclerosis.

History and examination

Information about handedness, education, occupation, risk factors for cognitive disorders (for example, thyroid disorders) or white matter diseases (such as vaculitides), other medical history, psychiatric background, drug history, and family history was collected. A detailed neurological examination was undertaken.

After evaluation by a behavioural neurologist (JH) in the memory clinic, all patients were also referred to a senior neurologist with an interest in multiple sclerosis (AC) for assessment of the clinical and paraclinical evidence and confirmation of the diagnosis of multiple sclerosis. The patients were followed up for between two and five years thereafter.

Investigations

To exclude other causes of cognitive impairment or white matter disease, a comprehensive series of investigations was carried out. Blood tests included urea and electrolytes, erythrocyte sedimentation rate, full blood count, vitamin B-12 and...
### Table 1  Demographic and clinical summary of the cases described

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Initial symptoms</th>
<th>Paraclinical findings</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47/F</td>
<td>2 year history: progressive amnesic syndrome, emotional lability and depression.</td>
<td>VER: delayed CSF: OCB+ MRI: diffuse and marked cerebral atrophy Brain biopsy: very mild hypercellularity and moderate diffuse microglial activation with no evidence of vasculitis, leucodystrophy, or progressive multifocal leukoencephalopathy Neuropsychology: impaired retrograde memory, poor verbal fluency, anosmia, and dyscalculia</td>
<td>3 years; spastic paraplegia, dysarthria, optic atrophy, and urinary incontinence; wheelchair-bound, full time care, severe cognitive impairment</td>
</tr>
<tr>
<td>2</td>
<td>52/F</td>
<td>3 year history: depressive illness + progressive amnesic syndrome; difficulty in autobiographical and semantic memory and face recognition</td>
<td>VER: delayed CSF: OCB+ MRI: periventricular high signal changes SPECT: bilateral (RL&gt;R) hypoperfusion of posterior parietal cortices Neuropsychology: dyscalculia, dysgraphia, visuo-constructive and visuo-spatial dysfunction, impaired anterograde and retrograde memory</td>
<td>4 years; optic atrophy, continued to deteriorate cognitively</td>
</tr>
<tr>
<td>3</td>
<td>60/F</td>
<td>5 year history: progressive amnesia, inattention, and personality changes</td>
<td>VER: normal CSF: OCB− MRI: cortical atrophy with multiple high signal lesions in white matter SPECT: marked hypoperfusion of cortical perfusion particularly in frontal regions Neuropsychology: anterograde and retrograde memory impairment, reduced digit span, reduced verbal fluency, and mild arithmetic and visuospatial difficulty</td>
<td>2 years; cerebellar ataxia, INO, bladder involvement, blindness, and progressive cognitive impairment</td>
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<tr>
<td>4</td>
<td>38/F</td>
<td>15 months history: progressive amnesic syndrome and difficulty in writing, reading, spelling, use of words associated with depression, and later ataxia and alien limb phenomenon</td>
<td>VER: delayed Brain MRI: marked cortical atrophy with widespread periventricular high signal lesions Brain biopsy: no evidence of vasculitis, leucodystrophy, or progressive multifocal leukoencephalopathy Neuropsychology: severe impairment of retrograde memory, comprehension, attention, working memory, and verbal fluency together with marked executive dysfunction, constructional apraxia, and pervasive psychomotor retardation but normal visual-perceptual skills</td>
<td>18 months; severely demented, without verbal communication, blind, spastic quadriparesis, doubly incontinent and required full care</td>
</tr>
<tr>
<td>5</td>
<td>42/F</td>
<td>4 year history: recurrent depression, before signs and symptoms of cerebellar dysfunction</td>
<td>VER: delayed CSF: OCB+ MRI: bilateral high signal changes in the cerebrum, corpus callosum, and cerebellum Neuropsychology: impairment of anterograde and semantic memory and poor abstract reasoning</td>
<td>2 years; developed INO, spastic paraparesis, marked cerebellar signs and bladder instability, as well as progressive amnesic syndrome</td>
</tr>
<tr>
<td>6</td>
<td>57/M</td>
<td>3 year history: depression, episodes of confusion, disorientation, delusional ideation, memory impairment, preceding an episode of ataxia, double vision and unilateral facial palsy</td>
<td>VER: normal CSF: OCB+ MRI: marked cortical atrophy with widespread periventricular high signal lesions SPECT: hypoperfusion of both frontal and temporal regions Neuropsychology: impaired verbal fluency and anterograde memory suggestive of fronto-temporal dysfunction</td>
<td>3 years; bilateral pyramidal signs with extensor plantar response, severe cognitive deterioration requiring nursing home care</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; F, female; M, male; MRI, magnetic resonance imaging; OCB, oligoclonal bands; INO, internuclear ophthalmoplegia; VER, visual evoked response.
 Physicians habitually depend on the presence of physical symptoms before considering the diagnosis of multiple sclerosis. The true prevalence of this variant is therefore probably underestimated.

In previous reports documenting 17 cases (table 2), the patients' ages at presentation ranged from 19 to 43 years, with a female predominance as expected, in a clinical series of patients with multiple sclerosis. The diagnosis of multiple sclerosis was made within weeks to 10 years of the initial neuropsychiatric presentation. Depressive and amnesic syndromes were the most common symptoms, occurring in 14 and nine cases, respectively. Two of these case reports 19 20 had acute presentations; the rest were indolent for many years before classic symptoms and signs of multiple sclerosis appeared. Neuropsychological data on previously reported cases are limited, making it difficult to derive a pattern of neuropsychological deficit from these patients; however, reduced verbal IQ and amnesia appear to be the most common findings.

The presentation of our patients and their clinical course is broadly consistent with other published reports. We found depression and amnesia to be the most common neuropsychiatric presentations of multiple sclerosis. Neurological and neuropsychological analysis of all the cases show a consistent pattern of neuropsychiatric symptoms, including amnesia, aphasia, dyscalculia, dyslexia, dysgraphia, dyspraxia, and visuospatial disabilities. This consistency leads us to suggest that most of these symptoms could largely be attributed to cortical dysfunction. Clinical, radiological, and pathological evidence to support this contention is presented below.

Depression and cortical dysfunction in multiple sclerosis

Depression is well recognised as a complication of multiple sclerosis, with an estimated lifetime prevalence of almost 50%.19 There is evidence that depression represents a feature of multiple sclerosis rather than simply a reaction to the disease or comorbidity in a study controlled for physical disability.21 22 The present and previous series suggest that multiple sclerosis can be heralded by a long period of depression (13 of 17 cases in previous case reports, and five of the six in the present series).

As in many other neurological disorders, depression in multiple sclerosis is commonly thought to reflect white matter pathology. Depression can, however, be associated with pathology affecting the orbital and medial prefrontal cortices.24 Several studies into the biology of depression have shown that depressive symptoms, both in primary affective disorders and in association with organic neurological disease, are associated with reduced temporal and frontal cortical function.25 26 Dysfunction of these structures may also result in impairment of language, memory, or executive processes. Interestingly these symptoms were recognised in our case series as well as in those reported previously (table 2). A recent study of the anatomical correlation of cortical lesions and depression in multiple sclerosis using SPECT and MRI showed an association between reduction of perfusion in orbital, mesial temporal, and anterior and posterior cingulate cortices and depressive symptoms, but with no lesion load in the white matter.27 More recently, depression in multiple sclerosis has been found to correlate with cortical atrophy, especially in superior frontal, superior parietal, and temporal areas.28 29 These studies support our hypothesis that depression in multiple sclerosis could have an underlying cortical mechanism and such a mechanism might be of particular importance in patients with multiple sclerosis who present with predominant cognitive symptoms.

Cognitive presentation of multiple sclerosis

Progressive impairment in more than one domain of intellectual function without alteration in arousal (dementia) may result from cortical or subcortical dysfunction. Cortical

RESULTS

We describe six cases, five female and one male, aged 38 to 60 years at the time of presentation. None of the cases had the initial sensory or motor symptoms typically seen in multiple sclerosis at the time of referral. Three of these cases (Nos 2, 3, and 6) had a long course of depression preceding cognitive impairment. In four cases (Nos 1, 3, 4, and 5) dementia was characterised by a progressive amnesic syndrome. Case 4 presented with distinct pure cortical dysphasia, dysgraphia, and dyslexia in the context of an amnesic syndrome. All patients became demented on follow up, severely enough to require full time care. Disability in two patients (Nos 2 and 4) was essentially cognitive. Case 2 never developed any significant physical disability and case 4 developed a mild physical impairment. The other four cases developed severe physical disability; two became blind (Nos 3 and 4) and four (Nos 1, 3, 4, and 5) developed urinary sphincter involvement.

Four cases (Nos 1, 3, 4, and 6) had cerebral atrophy. Brain MRI scan of case 1 did not show high signal changes in the white matter. Two cases (Nos 3 and 6) had normal VER. Two cases (Nos 4 and 3) were negative for CSF oligoclonal band. Other aspects of CSF examination were unremarkable in all cases. All other laboratory investigations, in particularly vasculitis screen, immunological profile, and search for evidence of leucodystrophy, were entirely normal. Details of each patient’s clinical presentation and their laboratory findings are shown in table 1.

The diagnosis of multiple sclerosis was often delayed for several years after the initial presentation. In five of our six cases depression and progressive dementia were prominent features. Our case series shows that patients with cortical multiple sclerosis can remain free from physical manifestations of the disease for many years (case 2), follow a relapsing–remitting course (case 6), or show a primary progressive pattern (cases 3 and 5).

DISCUSSION

A cognitive or psychiatric presentation of multiple sclerosis appears to be rare. This is surprising considering the overall frequency of neuropsychiatric symptoms at all stages of multiple sclerosis. It may reflect underdiagnosis, as most physicians habitually depend on the presence of physical
Cortical multiple sclerosis

Dements are classically associated with dysphasia, dyscalculia, dyspraxia, agnosia, and severe amnesia in the absence of significant primary sensorimotor dysfunction. Subcortical dementia is characterised by early psychomotor retardation and mood disturbance, with relative preservation of language, and memory deficit which is greatest in free recall tasks, improving with cueing and recognition paradigms.

Although regarded as a typical subcortical dementia, a subgroup of patients with multiple sclerosis shows marked impairment of abstract-conceptual reasoning, dependent on intact frontal functions and impaired language, suggesting cortical dysfunction. In addition, memory impairment is a common complaint in patients with multiple sclerosis and was a prominent feature in our cases. Moriarity and colleagues showed a strong correlation between reduced performance on the Rey auditory verbal learning test and the number of cortical lesions detected with Fast FLAIR (fluid attenuated inversion recovery) images (detecting 154 lesions at the cortical/juxtacortical area compared with 10 using conventional imaging). These investigators concluded that cortical lesions in patients with multiple sclerosis correlate...
with impaired retention of information in memory tasks. In another study, PET imaging showed hypofunction of the hippocampus, cingulate gyrus, associative occipital cortex, prefrontal cortex, and inferior parietal cortex in patients with multiple sclerosis and memory impairment.17 Bilateral hippocampal hypometabolism in these patients correlated with impairment of episodic memory, suggesting that the amnesic syndrome in multiple sclerosis is the direct result of cortical involvement. A recent study has shown that impairment of verbal learning, spatial learning, attention, and conceptual reasoning correlates with bilateral superior frontal cortices dysfunction.18

**Cortical pathology in multiple sclerosis**

The relatively few neuropathological studies of cortical lesions in multiple sclerosis have not sought to establish correlations with cognitive impairment. In Brownell and Hughes’ study10 5% of lesions were cortical but these all came from one of their 22 cases. In contrast, Lumsden11 reported that cortical involvement occurred in 93% of patients with multiple sclerosis. Most cortical lesions in these studies were at the white–grey matter junction. More recently, Kidd and colleagues12 studied cortical lesions in multiple sclerosis and categorised these into four groups according to cortical vasculature. They provide some evidence that intracortical lesions are located around the intracortical vein (V4), in contrast to juxtacortical lesions that are associated with gyral veins located at the white–grey matter junction. Peterson and colleagues13 studied 112 cortical lesions which were identified in 110 tissue blocks from 50 patients with multiple sclerosis, and showed that cortical lesions contained 13 times fewer CD3 positive lymphocytes and six times fewer CD68 positive microglia/macrophages than subcortical lesions. Taken together, these and other studies support the existence of multiple sclerosis with exclusive or predominant cortical lesions. It does not, however, necessarily follow that these lesions correlate with symptoms, either at presentation or later in the clinical course of the disease. This remains to be demonstrated.

**Radiological evidence for cortical involvement in multiple sclerosis**

Several workers have tried, with limited success, to correlate neuropsychiatric symptoms in multiple sclerosis with cortical14 or white matter15 lesion load. The lack of success may reflect the limitations in imaging methods for identifying cortical lesions in multiple sclerosis, and the variability of neuropsychological methods used to identify cognitive deficits. The former problem arises from the fact that the cerebral cortex has a longer relaxation time than white matter during MRI. The relatively few neuropathological studies of cortical lesions in multiple sclerosis have not sought to establish correlations with cognitive impairment. In Brownell and Hughes’ study10 5% of lesions were cortical but these all came from one of their 22 cases. In contrast, Lumsden11 reported that cortical involvement occurred in 93% of patients with multiple sclerosis. Most cortical lesions in these studies were at the white–grey matter junction. More recently, Kidd and colleagues12 studied cortical lesions in multiple sclerosis and categorised these into four groups according to cortical vasculature. They provide some evidence that intracortical lesions are located around the intracortical vein (V4), in contrast to juxtacortical lesions that are associated with gyral veins located at the white–grey matter junction. Peterson and colleagues13 studied 112 cortical lesions which were identified in 110 tissue blocks from 50 patients with multiple sclerosis, and showed that cortical lesions contained 13 times fewer CD3 positive lymphocytes and six times fewer CD68 positive microglia/macrophages than subcortical lesions. Taken together, these and other studies support the existence of multiple sclerosis with exclusive or predominant cortical lesions. It does not, however, necessarily follow that these lesions correlate with symptoms, either at presentation or later in the clinical course of the disease. This remains to be demonstrated.

**Conclusions**

Although it is difficult to distinguish the contributions of white and grey matter lesions to cognitive symptomatology in multiple sclerosis, we believe that the neuropsychiatric presentations described, along with well documented examples of focal cortical syndromes such as aphasia, epilepsy, and cortical sensory loss, support our hypothesis of a cortical variant of multiple sclerosis. It follows, therefore, that multiple sclerosis should be considered in the differential diagnosis of unusual and intractable depression as well as in dementia—particularly with cortical features—even in the absence of hard neurological signs. While depression appears to be the most common cortical presentation of multiple sclerosis, to screen all patients with depression for ancillary evidence of this disease would be inefficient and a poor use of finite resources. Therefore, we suggest that routine questioning and physical examination for possible evidence of cryptic demyelination should be part of the routine assessment of patients who present with depression or early onset dementia. Consideration of paraclinical investigations that support the diagnosis of multiple sclerosis and formal neuropsychological assessment should be undertaken, especially in younger patients with cognitive abnormalities.

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