Cognitive presentation of multiple sclerosis: evidence for a cortical variant

M Zarei, S Chandran, A Compston, J Hodges

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, 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 112000 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.
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 leucoencephalopathy</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 (R&gt;L) hypoperfusion of posterior parietal cortices</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</td>
<td>2 years; cerebellar ataxia, INO, bladder involvement, blindness, and progressive cognitive impairment</td>
</tr>
<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 leucoencephalopathy</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</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</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 symptoms were the most common symptoms, occurring in 14 and nine cases, respectively. Two of these case reports21–23 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. Semiological 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%.21 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.22–23 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.25–27 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.28 More recently, depression in multiple sclerosis has been found to correlate with cortical atrophy, especially in superior frontal, superior parietal, and temporal areas.29–31 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...
indicators of demyelination and remyelination. MRI studies have shown a strong correlation between reduced per-ventricular signal intensity and increased CSF oligoclonal bands. The correlation was found to be significant (p < 0.05). However, the exact mechanism responsible for this correlation is not yet understood.

Table 2: Demographic and clinical summary of previously reported cases of cortical multiple sclerosis

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Initial presentation</th>
<th>Paraclinical finding</th>
<th>Follow up period after presentation and progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>43</td>
<td>F</td>
<td>Acute onset of psychotic depression leading to attempted suicide</td>
<td>VER: delayed; CSF: OCB+; MRI (10 years after initial presentation): cerebral atrophy + WM high signal changes</td>
<td>3 months; responded to intravenous methylprednisolone, gait ataxia, poor memory, dyscalculia and dysphasia</td>
</tr>
<tr>
<td>18</td>
<td>41</td>
<td>M</td>
<td>Change in personality, forgetfulness, labile indifference and poor verbal memory</td>
<td>VER: delayed; CSF: OCB+; MRI: WM high signal changes; EEG: diffuse slow activity</td>
<td>8 months; impaired visuospatial skills, frontal lobe dysfunction, impaired abstract thinking, concept formation, judgment, apraxia, poor attention, long tract signs, posterior column signs</td>
</tr>
<tr>
<td>17</td>
<td>37</td>
<td>F</td>
<td>Depression</td>
<td>VER: delayed; CSF: OCB+; MRI: cerebral atrophy + WM high signal changes</td>
<td>13 years; cognitive impairment, personality change, INO, ataxia, incontinence, visual loss</td>
</tr>
<tr>
<td>16</td>
<td>37</td>
<td>M</td>
<td>Depression, memory loss (Korsakoff type)</td>
<td>VER: delayed; CSF: OCB+; MRI (10 years after initial presentation): bilateral high signal in temporal lobes and periventricular area</td>
<td>1 year; bilateral optic atrophy, complete deafness, hemi-pyramidal weakness, reduced sensation on T10 to L4 distribution bilaterally</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>F</td>
<td>Depression</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>5 years; bilateral optic atrophy, complete deafness, hemi-pyramidal weakness, reduced sensation on T10 to L4 distribution bilaterally</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
<td>F</td>
<td>Anxiety, depression, reduced global cognitive function</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>4 years; reduced verbal and performance IQ, dysphagia, diplopia and urinary incontinence. Bilateral optic atrophy, nystagmus, dysarthria, bilateral facial palsy, hyper-reflexia and ataxia</td>
</tr>
<tr>
<td>13</td>
<td>35</td>
<td>M</td>
<td>Depression, cluminess, slurred speech, poor memory, euphoria</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>12 years; facial palsy, slurred speech and gait ataxia, dizziness, nystagmus, clumsiness, dyscalculia, quadriparetic spasticity</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>M</td>
<td>Episodes of anxiety, depression, perseveration, poor attention, memory deficit, dysgraphia</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>8 months; optic atrophy, gait ataxia, progressive cognitive impairment, dyscalculia, dysphasia, lack of insight, reduced verbal and performance intelligence, severe memory impairment, nominal dysphasia</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>M</td>
<td>Depression, memory deficit, dyspraxia, agnosia, and lack of insight</td>
<td>VER: delayed; CSF: pleocytosis</td>
<td>7 years; impaired verbal and performance IQ, change in personality, recovered over 7 months; developed a subacute amnesia plus epilepsy, dysgraphia, and hemipyramidal weakness</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>F</td>
<td>Depression, medically unexplained symptoms, eg, dizziness, blurred vision, &quot;off balance&quot; with no neurological signs</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>5 years; nystagmus, cerebellar signs, neuropsychological deficit (dysexia and somnolence) suggesting cortical dysfunction</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>F</td>
<td>Depression, &quot;histrionic&quot; personality</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>15 years; optic neuritis, neuropsychological deficit including constructional apraxia suggesting cortical dysfunction</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>F</td>
<td>Depression, medically unexplained symptoms, eg, dizziness, blurred vision, &quot;off balance&quot; with no neurological signs</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy; EEG: bilateral slow waves</td>
<td>Nystagmus, cerebellar ataxia, neuropsychological deficit suggesting right temporo-parietal dysfunction</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>M</td>
<td>&quot;Hysterical&quot; type symptoms, progressive psychiatric depression, limb trembling</td>
<td>VER: not done; CSF: increased IgG; LAEG: cortical atrophy</td>
<td>9 years; optic atrophy, dyslexia, limb ataxia, long tract signs, progressive memory loss and non-verbal cognitive skills</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>F</td>
<td>Depression</td>
<td>VER: not done; CSF: increased IgG; no imaging</td>
<td>5 years; nystagmus, cerebellar signs, neuropsychological deficit (dysexia and somnolence) suggesting cortical dysfunction</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>F</td>
<td>Depression, &quot;histrionic&quot; personality</td>
<td>VER: not done; CSF: increased IgG; no imaging</td>
<td>12 years; facial palsy, slurred speech and gait ataxia, dizziness, nystagmus, clumsiness, dyscalculia, quadriparetic spasticity</td>
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</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>Depression</td>
<td>VER: delayed; CSF: OCB+; MRI: cerebral atrophy + WM high signal changes</td>
<td>13 years; cognitive impairment, personality change, INO, ataxia, incontinence, visual loss</td>
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<td>1</td>
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<td>M</td>
<td>Depression, memory loss (Korsakoff type)</td>
<td>VER: delayed; CSF: OCB+; MRI: cerebral atrophy + WM high signal changes</td>
<td>8 months; impaired visuospatial skills, frontal lobe dysfunction, impaired abstract thinking, concept formation, judgment, apraxia, poor attention, long tract signs, posterior column signs</td>
</tr>
</tbody>
</table>

Dementias 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, calculation, and object recognition, and by memory deficit which is greatest in free recall tests, 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. Moriarty 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/juxta-cortical 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. 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.

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’ study, 5% of lesions were cortical but these all came from one of their 22 cases. In contrast, Lumsdaine et al. 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 colleagues 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 colleagues studied 112 cortical lesions which were identified in 110 tissue blocks in 50 patients with multiple sclerosis, and showed that cortical lesions contained 13 times fewer CD3 positive lymphocytes and 6 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 cortical or white matter 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. This reduces the resolution and contrast of lesions against background grey matter on conventional T2W MRI. Catalaa and colleagues used conventional MRI with locally designed software to detect cortical lesions, but failed to correlate global cognitive function with cortical lesions found in 18 patients with multiple sclerosis. However, their study does not exclude a correlation between neuropsychological performance on specific tests relevant to temporal and frontal systems with cortical lesions.

Recent advances in imaging techniques inform this debate. Boggild et al. showed that cortical lesions in multiple sclerosis, not visible on conventional T2W images, could be seen using FLAIR imaging with prolonged inversion time. Rovaris et al. used RARE (dual echo rapid acquisition with relaxation enhancement) and fast FLAIR to show that total cortical lesion loads are significantly greater in cognitively impaired patients. They also showed that average cortical/juxtacortical magnetisation transfer ratio (MTR) is the only parameter strongly associated with cognitive impairment. Lazeron and colleagues used a similar protocol and found that the number of non-cortical lesions correlated with the expanded disability status scale, whereas the number of cortical/juxtacortical lesions correlated with cognitive impairment index. In another study, biochemical abnormality in cerebral cortex was detected in patients with relapsing–remitting multiple sclerosis even in the absence of cortical lesion on conventional brain MRI.

More specific evidence for early involvement of the cerebral cortex in multiple sclerosis is provided by Sokic et al. who used brain MRI with gadolinium pentetate dimeglumine and found that multiple sclerosis presenting with seizures is associated with cortical plaques in anatomical areas that explain clinical and electrophysiological features of the seizure disorder. Collectively, these recent studies suggest that cortical lesions can be identified with increased reliability and correlated with specific cortical syndromes. Cortical atrophy, believed to represent axonal loss, is also often present in multiple sclerosis at the time of diagnosis and may be visualised using newer imaging techniques. Improved detection of cortical lesions using these recently developed imaging techniques has yet to be systematically correlated with specific neuropsychological deficits.

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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REFERENCES

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