Introduction

Multiple sclerosis (MS) is no longer considered purely a white matter demyelinating disease of the central nervous system (CNS). Histological and magnetic resonance imaging (MRI) studies disclose that grey matter inflammation and degeneration constitute a relevant aspect of MS pathology.1,2 Indeed, cortical lesions and atrophy can be observed at disease onset,3,4 can increase over the course of the disease,5,6 and can play a significant role in determining the progressive physical and cognitive deterioration observed in MS patients.7,8 Cortical lesion load has been associated with epilepsy,9 but no association has so far been described between the development of acute cortical lesions and clinical events having the features of acute relapses. We collected five interesting cases of MS patients who had clinical relapses characterized by the acute appearance of cortical symptoms, due to the development of large, snake-like, cortical inflammatory lesions. Symptoms were: acute Wernicke’s aphasia mimicking stroke; agraphia with acalculia, not associated to a motor deficit nor linguistic disturbance; hyposthenia of the left arm, followed by muscle twitching of the hand, spreading to arm and face; acute onset of left lower limb paroxysmal hypertonia; and temporal lobe status epilepticus, with psychotic symptoms.

Results

Report of cases

All of the patients had been diagnosed and are currently being followed at the MS center of the Veneto region of Italy. The diagnoses were achieved according to the MacDonald/Polman Criteria.13 The at time of diagnosis, all the patients had undergone brain (T1, T2, FLAIR, T1-gad and DIR sequences) and spinal cord inversion recovery (DIR)10 and/or phase-sensitive inversion recovery (PSIR)11,12 MRI. Given their unusual clinical pictures, all these patients underwent a detailed diagnostic workup to exclude concomitant (above all, vascular and infectious) pathologies; but no better explanation than MS was found as a cause of the symptoms, which indeed recovered completely after high-dose steroid therapy.

Keywords:
Case study, cortical lesions, grey matter, inversion recovery, magnetic resonance imaging, multiple sclerosis, relapse, relapse symptoms, relapsing–remitting multiple sclerosis
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Table 1. Demographic, clinical and MRI findings of the five patients included in the study, at the time of the cortical relapse.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age</td>
<td>36</td>
<td>32</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>CIS</td>
<td>RRMS</td>
<td>RRMS</td>
<td>RRMS</td>
</tr>
<tr>
<td>Disease duration</td>
<td>4 m</td>
<td>1 y</td>
<td>5 y</td>
<td>6 y</td>
</tr>
<tr>
<td>IgGOB in the CSF</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>VEP</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dissemination in space</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dissemination in time</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brain T2LV (mm³)</td>
<td>7848</td>
<td>1480</td>
<td>3657</td>
<td>4023</td>
</tr>
<tr>
<td>New T2 or Gad+ lesions in the brain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of cortical lesions in the brain</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Spinal cord lesions</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>New T2 or Gad+ lesions in the spinal cord</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Cortical lesions were scored on DIR images.
CIS: clinically-isolated syndrome; CSF: cerebrospinal fluid; F: female gender; Gad: gadolinium; IgGOB: immunoglobulin G oligoclonal bands; m: months; M: male gender; MRI: magnetic resonance imaging; MS: multiple sclerosis; RRMS: relapsing–remitting multiple sclerosis; T2LV: T2 lesion volume; VEP: visual evoked potentials; y: years

(T1, T2, STIR and T1-gad sequences) imaging. Their diagnostic workup included: cerebrospinal fluid (CSF) examination to detect intrathecally-synthesized immunoglobulin G (IgG) antibodies (by IgG Index or IgG oligoclonal bands), other immunological and viral screenings, and visual evoked potential. Other tests/exams were specifically done in single patients, in order to achieve the criterion of ‘no better explanation’ for the symptoms/signs that he/she complained of. Table 1 summarizes the demographic, clinic and MRI data of the five patients at the time of cortical relapse.

Case 1. A right-handed, 36 year-old man with a recent diagnosis of clinically-isolated syndrome (paresthesias of the left leg, 4 months before) having dissemination in space, but not in time, of lesions and the presence of IgG oligoclonal bands in his CSF, presented at the emergency room (ER) with a clinical relapse that was characterized by acute Wernicke’s aphasia, mimicking an ischemic stroke. The patient had no risk factors for cerebrovascular pathology and an accurate differential diagnosis workup, including a repeated CSF analysis, excluded atherosclerotic or embolic disorders, vasculitis and infectious diseases. His brain computed tomography (CT) scan was normal. DIR and PSIR sequences disclosed a huge, snake-like cortical lesion that selectively involved the superior and middle temporal gyri of the left hemisphere (Figure 1). No trace of the lesion could be identified in the previous MRI done 4 months before, at the time of clinical onset and CIS diagnosis. Moreover, the patient had no other new T2 or gadolinium positive (Gad+) white or grey matter lesions, compared to the previous MRI. Then the patient was treated with high-dose steroid therapy, with a complete recovery from symptoms within 4 weeks. Thus, the criterion of dissemination in time of the lesions was acquired clinically and by MRI, and the definite diagnosis of relapsing–remitting MS (RRMS) was definitely achieved.

Case 2. A 32 year-old left-handed female, with a recent diagnosis of RRMS and not yet treated with disease modifying drugs (DMD), developed an acute agraphia with acalculia that was not associated to motor deficit nor linguistic disturbance. CSF examination confirmed the presence of IgG oligoclonal bands, increased IgG Index, normal (≤ 4) lymphocyte count and normal albumin CSF/serum ratio. The patient had no risk factors for cerebrovascular pathology, and vascular and infectious diseases were carefully excluded. Brain and spinal cord MRI examination did not show the appearance of new T2 or Gad+ lesions in the white matter, but a DIR sequence showed a quite large cortical lesion in the right frontal lobe, involving the premotor cortex (Figure 2), and several small, dot-like lesions in the cortex (up to 25 lesions were scored). High dose steroid therapy was followed by complete recovery from the symptoms.
Case 3. A 45 year-old man with a 5-year history of RRMS, who was being treated with interferon beta, developed an acute, moderate hyposthenia of the left arm. The deficit progressively worsened over the following 48 hours. Then he developed muscle twitching of the hand, spreading to his arm and face. The symptoms were sub-continuous and of variable intensity. Brain MRI did not show the appearance of

Figure 1. Case 1. (a) DIR) and (b) PSIR sagittal images of the brain cortex; showing a huge, worm-like cortical lesion, selectively involving part of the superior and middle temporal gyri of the left hemisphere. The lesion appears hyper-intense on DIR images and hypo-intense on PSIR images. In some points, the lesion involves the subcortical white matter. (c) FLAIR axial image, showing the cortical lesion (arrow) and multiple white matter lesions (arrow heads). (d) 3D reconstruction of the patient’s brain, obtained by means of Freesurfer (freesurfer.net; ttps://surfer.nmr.mgh.harvard.edu) on a 3D-T1 sequence; and image of the lesion (in red) obtained by means of MRIcron (www.mricro.com). 3D: Three-dimensional; DIR: double inversion recovery; PSIR: phase sensitive inversion recovery; FLAIR: fluid-attenuated inversion recovery.
new T2 or Gad+ lesions in the white matter. No trace of any lesion could be identified in the previous MRI. Spinal cord MRI disclosed two very small lesions, affecting the posterior spinal column at the level of C5 and D2, which did not account for the symptoms. DIR and PSIR sequences disclosed a large intracortical lesion, involving the lateral precentral gyrus (Figure 3). The symptoms almost completely disappeared after 5 days of high-dose steroid therapy.

Case 4. A 43 year-old female patient with a 6-year-history of RRMS, who interrupted glatiramer acetate therapy for planning a pregnancy, presented at the ER complaining of the acute onset of left lower limb paroxysmal painful hypertonia. In the prior 2 days, she had repeated sensation of pressure at the left thoracic side. The hypertonia became continuous and highly disabling within 24 hours. Brain MRI did not show the appearance of new T2 or Gad+ lesions in the white matter. The spinal cord MRI was normal. DIR disclosed the presence of a leukocortical (mixed) lesion in the right hemisphere, involving the motor cortical area (Figure 4). The patient was treated with baclofen and high-dose steroids, with an almost complete recovery; however, in the subsequent year, the patient developed left leg hypertonia that required continuous treatment with baclofen. Brain and spinal cord MRI did not disclose new white matter lesions along the cortical-spinal tract and in the spinal cord that could explain the symptoms.

Figure 2. Case 2. Double inversion recovery (DIR) axial images. (a) and (b) Periventricular, juxtacortical (arrow head) and small cortical lesions (arrows) are visible. (c) Six contiguous DIR axial slices (c.1.–c.6.) disclose the extension and the morphology of a frontal (pre-motor cortex), intra-cortical lesion (in red) in the right hemisphere. DIR: double inversion recovery MRI; MRI: magnetic resonance imaging.
Case 5. A 21-year-old man with a recent diagnosis of RRMS and who was treated with interferon beta, having no previous history of psychological problems nor epilepsy, suddenly developed a sub-continuous state of mental confusion with behavioral changes. Encephalitis was suspected, but MRI examination and cerebrospinal fluid analysis (presence of IgG0B, but normal cell count and albumin ratio; plus no detection of viral genomes by PCR) excluded infectious diseases. Possible drug abuse was investigated and excluded. DIR images disclosed the presence of several cortical lesions in the frontal lobes, and a huge cortical lesion in the uncus of the right temporal lobe. Electroencephalograms (EEGs) disclosed a temporal epileptic focus. The symptoms dramatically improved with high-dose steroids and carbamazepine therapy. The diagnosis of temporal lobe epileptic status due to MS-related cortical lesions was definitely achieved.

Discussion
Grey matter pathology has been associated to the progressive phase of MS, characterized by the accumulation of physical and cognitive disability, while acute clinical relapses are usually considered the expression of active inflammatory lesions affecting functional systems or tracts of the white matter. Cortical MS was classically defined as a complex syndrome, characterized by a severe cognitive decline and prominent cortical (including dysphasia, dysgraphia and dyslexia) and psychiatric (depression) symptoms, presenting with a subacute or chronic progressive course. Thus, ‘cortical MS’ was applied to a variant clinical form of progressive MS, with an insidious and often misleading neuropsychiatric presentation. Recently, a high load of cortical lesions (as disclosed by DIR) was found to be common in early MS, sometime preceding the appearance of white matter lesions, and to represent the possible

Figure 3. Case 3. (a) Five contiguous sagittal and (b) four contiguous axial slices of DIR sequence, disclosing the extension of the cortical lesion. In (c), the corresponding PSIR images of (b) are shown. The combined analysis of DIR and PSIR images allowed a better identification of the lesion morphology and size. Entire DIR (D) and FLAIR (E) axial images. The arrow-head indicate a white matter lesion. In (E) a very faint hyperintensity is observed in the cortex (arrow). DIR: double inversion recovery; FLAIR: fluid-attenuated inversion recovery; PSIR: phase contrast inversion recovery.
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pathologic substrate of cognitive impairment\textsuperscript{17} and epilepsy\textsuperscript{8} in RRMS, while minimal cortical pathology was associated with a non-aggressive MS course.\textsuperscript{18} Moreover, the cortical lesion load was positively associated with clinical disability and with brain atrophy.\textsuperscript{19–21}

We showed that the development of large intracortical lesions, sometimes involving several cortical gyri, produced acute cortical symptoms that have the clinical features of MS relapses. Indeed, in the cases we prospectively collected, symptoms had an acute presentation, lasted more than 24 hours, were explained by the MRI findings and recovered after high-dose steroids. In all our cases, the vascular or other possible causes of lesions were carefully excluded.

The dramatic response to high-dose steroid therapy strongly supports the inflammatory nature of cortical lesions in MS and is in line with histological findings. Indeed, the majority of all cortical lesion types in early MS show evidence of active demyelination (presence of myelin-laden macrophages) and active inflammation (perivascular and parenchymal inflammatory infiltrates are invariably present and composed by macrophages, T cells, and fewer B cells and plasma cells, with evidence of blood-brain barrier breakdown).\textsuperscript{2,22} The relatively less inflammatory profile of cortical lesions, compared to that of white matter lesions,\textsuperscript{23} may explain the prompt and excellent effects of high-dose steroid therapy (low inflammation equates a rapid response).

Our findings suggested that a ‘cortical relapse’ has to be considered, when interpreting acute unusual symptoms in MS patients, and that the routine MRI investigation in MS should include sequences aimed at visualizing cortical lesions, such as DIR\textsuperscript{10} or

\textbf{Figure 4.} Case 4. DIR: (a) axial and (b) sagittal contiguous images of a quite extensive, worm-like lesion involving the precentral gyrus of the right hemisphere; (c) DIR axial slice, showing another cortical lesion in the left hemisphere (arrow). (d) FLAIR axial slice showing several white matter lesions. (e) and (f) We observed no spinal cord inflammatory lesion nor other pathology.

DIR: double inversion recovery; FLAIR: fluid-attenuated inversion recovery.
Inclusion of cortical lesions into the MRI diagnostic criteria for MS needs to be considered. Indeed, DIR and PSIR have a quite short time of acquisition (4–5 minutes) and can be included in a MS-specific MRI diagnostic protocol, without significantly increasing time and costs. The presence of cortical lesions which was already demonstrated to help in the acquisition of the dissemination in space criterion,\(^\text{24}\) may also help in acquiring the dissemination in time criterion, as was suggested by our Case 1.

The possibility that MS-related inflammation may produce, at least in some patients, cortical relapses further confirmed that MS is a more complex CNS disorder than being a simple white matter disease. From the etio-pathological point of view, the morphology and the extension of the snake-like cortical lesions (that involve several gyri) are particularly interesting and worthy of further investigation, because they might mark a subgroup of MS patients that have peculiar immuno-pathological features. Indeed, of particular interest is the observation that the appearance of cortical lesions in our patients was a grey matter isolated event, since no appearance of new T2 or Gad\(^+\) white matter lesions was observed, in line with the classical observation that cortical demyelination occurs spatially and is anatomically independent of white matter or deep grey pathology.\(^\text{24,25}\)

**Conflict of interest**

The authors declare that there are no conflicts of interest.

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**References**


