Fluid-Attenuated Inversion Recovery Magnetic Resonance Imaging Detects Cortical and Juxtacortical Multiple Sclerosis Lesions

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Background: Autopsy studies showed cortical and juxtacortical multiple sclerosis (MS) plaques. Fluid-attenuated inversion recovery (FLAIR) is an advanced magnetic resonance imaging sequence that reveals tissue T2 prolongation with cerebrospinal fluid suppression, allowing detection of superficial brain lesions.

Objectives: To assess FLAIR, T1-weighted, and T2-weighted images for detecting lesions in or near the cerebral cortex in patients with MS and to explore the relation between cortical lesions and cortical atrophy.

Design, Setting, and Patients: Cross-sectional study in a university MS clinic of 84 patients with MS and 66 age-matched healthy controls receiving 1.5-T fast FLAIR, T2-weighted, and T1-weighted images.

Main Outcome Measures: Regional cortical atrophy was rated vs controls. Cortical and juxtacortical lesions were ovoid hyperintensities involving the cortex and/or gray-white junction.

Results: A total of 810 cortical and juxtacortical lesions were seen by FLAIR in patients (mean, 9.6 per patient), most commonly in the superior frontal lobe. Cortical and juxtacortical lesions were identified in 72 patients and 6 controls. Fourteen percent of cortical and juxtacortical lesions were seen on T1-weighted images and 26% were seen on T2-weighted images. More cortical and juxtacortical lesions were present in secondary progressive disease than relapsing-remitting disease. The total number of cortical and juxtacortical lesions correlated significantly with disease duration and the regional number correlated with the degree of regional atrophy. After taking into account noncortical (white matter) lesions, only the cortical and juxtacortical lesion count predicted atrophy in that region.

Conclusions: FLAIR can detect many cortical and juxtacortical lesions in MS, which were appreciated previously in autopsy studies but usually missed by magnetic resonance imaging during life. Cortical and juxtacortical plaque formation may contribute to cortical atrophy in MS.
SUBJECTS AND METHODS

PATIENTS AND CONTROLS

Subjects were patients from a university-affiliated MS clinic and age-matched healthy controls who underwent the same scanning protocol at a single MRI center during a 2-year period. Patients had clinically definite MS and were 18 to 60 years of age. Exclusion criteria were as follows: (1) other major neurologic or systemic diseases, (2) active substance abuse, (3) pregnancy, (4) poor-quality MRI scans, and (5) primary progressive clinical course. Eighty-four consecutive patients with MS (mean±SD age, 43±9 years) and 66 age-matched healthy controls (mean±SD age, 40±10 years) were included. The MS clinical courses were categorized as relapsing-remitting (RR) in 58 patients or secondary progressive (SP) in 26 patients. The mean±SD duration of MS disease was 10±8.4 years. Neurologic disability was rated by the Expanded Disability Status Scale (EDSS). The EDSS scores ranged from 0 to 8 in the patients with MS (mean±SD, 3.4±1.9). Control subjects, ages 18 to 60 years, in whom MS was excluded clinically were obtained consecutively from a normative MRI database that was compiled by our published method.

MRI PROTOCOL

All subjects were studied on the same 1.5-T MRI scanner using axial 5-mm interleaved (contiguous, no slice gap) FLAIR, T1-weighted, and T2-weighted acquisitions that generated images with approximately a 1×1-mm in-plane resolution. Fast spin-echo FLAIR was performed as previously detailed as follows: repetition time [TR]/echo time [TE]/number of excitations, 8000/150/2; delay time, 2200 milliseconds; echo train length (number of echoes), 20; and scan time, approximately 2 minutes. Multisection imaging technique was used with a section selective inversion pulse. The inversion pulse section was as wide as the imaging section (ie, 5 mm). A presaturation band was placed caudal to the image volume. Fast spin-echo T2WIs (TR/TE/excitations, 2300/120/2; echo train length, 18; scan time, approximately 2.5 minutes) and conventional spin-echo T1WIs (TR/TE/excitations, 400/10/2; scan time, approximately 4 minutes) were also acquired.

MRI ANALYSIS

Two observers masked to clinical details visually assessed the MRIs by consensus. Cortical lesions were defined as hyperintensities compared with normal cortical gray matter that involved or abutted the parenchyma of the cerebral cortex (cortical or juxtacortical). These included lesions that were in the cortex and those in the subcortical U fibers (corticomedullary junction). No effort was made to define lesions as either purely cortical vs adjacent to the cortex, since this was not thought to be feasible by analysis of images. The lesions are referred to as “cortical lesions” throughout the remaining text. Only intra-axial hyperintensities were included (hyperintensities of leptomeningeal matter). In the present study, we assessed the value of FLAIR MRI for detecting MS lesions in or near the cerebral cortical gray matter in a relatively large series of patients with MS compared with age-matched controls.

We compared the sensitivity of FLAIR MRI relative to T1-weighted images (T1WIs) and T2WIs in detecting these lesions and hypothesized that MS cortical gray matter lesions were related to cortical atrophy.

STATISTICAL ANALYSIS

Correlation of number of lesions with age, disease duration, EDSS score, and regional cortical atrophy scores was assessed across all 84 patients with MS by the Spearman rank correlation test. Group differences (RR vs SP) were assessed by the Mann-Whitney test. Linear stepwise regression (F probability to enter = 0.05, F to remove = 0.10) was used to compare the amount of predictive variance in atrophy accounted for by cortical vs white matter lesions. To account for the number of statistical tests, P < .01 was considered significant for all univariate comparisons. This was believed to be an adequate correction because the study is exploratory.
RESULTS

Results are presented in Tables 1, 2, and 3 and in Figures 1, 2, 3, and 4. Cortical lesions were typically seen on FLAIR as focal oval or ovoid hyperintensities (Figures 1-3) or occasionally linear lesions (not shown). Most were confined to cortex (Figures 1-3) but some extended into subcortical white matter (Figures 1 and 4). As shown in Table 1, a total of 810 FLAIR cortical lesions were seen in patients with MS (mean, 9.6 per patient; range, 0-94). Lesions were present in all cortical regions, most commonly in superior frontal cortex (Figures 1-3). Cortical lesions represented 26% of the total number of brain lesions seen on FLAIR images. Thirty-two percent of cortical lesions (n=258) were 5 mm in diameter or smaller (Figure 1), and 48% (n=389) were 6 to 10 mm (Figures 1 and 3), and 20% (n=163) were greater than 10 mm (Figure 2). At least 1 cortical lesion was seen in 86% of patients with MS (n=72). Cortical lesions were poorly shown by T1WIs and T2WIs (Figures 1-4); 14% of cortical lesions were seen as a hypointensity on T1WIs (Figure 1) and 26% were seen as hyperintensity on T2WIs (Figure 1). Thus, 74% to 86% of cortical lesions were missed by conventional MRI. Only 6 total cortical hyperintensities were seen on FLAIR images of controls (mean, 0.1 per patient; range, 0-1). Disease duration correlated positively with the number of regional cortical lesions in the superior frontal (ρ=0.3; P<.005) and temporal (ρ=0.34; P<.001) lobes and total cortical lesions (ρ=0.33; P<.001) but not with inferior frontal, superior parietal, inferior parietal, or occipital number of cortical lesions (P>.16 for all). Cortical lesion counts did not reliably correlate with EDSS score; small nonsignificant correlation coefficients were obtained except in the case of the temporal lobes (ρ=0.33; P<.001), where a weak association was revealed. As shown in Table 2, patients with SP disease had significantly more cortical lesions than patients with RR disease in superior parietal and temporal cortex (P=.01) but not in other cortical regions. Total cortical lesions did not differ between patients with RR and SP disease. As shown in Table 3, cortical lesions were associated with regional cortical atrophy in the same region. In the superior frontal, superior parietal, temporal, and occipital cortex, the number of regional cortical lesions correlated positively and significantly with regional cortical atrophy (ρ<.001 for all). This effect was not seen in the inferior frontal and parietal regions, where there were also lower lesion counts. In each of the regions yielding a reliable lesion count–to-atrophy association, regression analyses were conducted to test whether cortical lesions account for more variance in atrophy than can be accounted for by that region’s white matter lesions. When superior frontal atrophy was regressed on superior frontal cortical and white matter lesion counts, the cortical lesions accounted for the most variance, and the white matter lesions were not retained in the final model. The same results were obtained in the models for the other cortical regions.

COMMENT

This study indicates that lesions of the juxtacortical and cortical region are common in MS and that FLAIR MRI is sensitive for detecting such involvement. The neuropathologic characteristics, pathogenesis, and clinical significance of these cortical lesions are incompletely understood. In a necropsy study of 32 MS brains, Brownell and Hughes16 found numerous plaques in cerebral cortex, mostly in the frontal lobes. Twenty-one percent of the hemisphere lesions were at the corticomedullary junction or in the cortex. In a recent necropsy study16 of 12 MS brains, the 478 cortical lesions showed perivascular demyelination and varying degrees of inflammation. Our MRI observations on the brain during life were similar to previous ones at autopsy. We found 810 cortical lesions of the brain, an average of 9.6 lesions per patient, and 86% of our patients with MS have at least one such lesion. Cortical lesions accounted for 26% of the total brain lesions, and 1 patient had 94 cortical lesions. Thus, cor-

Table 1. Frequency and Distribution of Lesions on FLAIR Scans in 84 Patients With Multiple Sclerosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Total No. of Lesions</th>
<th>Mean No. of Lesions per Patient</th>
<th>Total Cortical Lesions, %</th>
<th>Total Brain Lesions, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal</td>
<td>537</td>
<td>6.4</td>
<td>66</td>
<td>17</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>29</td>
<td>0.4</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>96</td>
<td>1.1</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>10</td>
<td>0.1</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Temporal</td>
<td>95</td>
<td>1.1</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Occipital</td>
<td>43</td>
<td>0.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total cortical</td>
<td>810</td>
<td>9.6</td>
<td>100</td>
<td>26</td>
</tr>
<tr>
<td>Total brain</td>
<td>3072</td>
<td>36.5</td>
<td>. . .</td>
<td>100</td>
</tr>
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</table>

*FLAIR indicates fluid-attenuated inversion recovery magnetic resonance imaging with fast spin-echo (see the “Subjects and Methods” section); cortical, located in cortical gray matter (see the “Subjects and Methods” section).

Table 2. Association Between Cortical Lesions on FLAIR Images and Clinical Course in 84 Patients With Multiple Sclerosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Relapsing-Remitting Disease (n = 58)</th>
<th>Secondary Progressive Disease (n = 26)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior frontal</td>
<td>5.2 ± 7.7</td>
<td>9.1 ± 12.2</td>
<td>.12</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>0.3 ± 0.9</td>
<td>0.4 ± 1.2</td>
<td>.35</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>0.6 ± 1.4</td>
<td>2.2 ± 4.2</td>
<td>.006</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>0.12 ± 0.4</td>
<td>0.12 ± 0.3</td>
<td>.45</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.93 ± 2.1</td>
<td>1.6 ± 1.9</td>
<td>.006</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.4 ± 1.0</td>
<td>0.8 ± 1.6</td>
<td>.21</td>
</tr>
<tr>
<td>Total cortical</td>
<td>7.59 ± 11.8</td>
<td>14.3 ± 19.7</td>
<td>.23</td>
</tr>
</tbody>
</table>

*FLAIR indicates fluid-attenuated inversion recovery magnetic resonance imaging with fast spin-echo (see the “Subjects and Methods” section). †Mann-Whitney test.
tical involvement is common in MS, can represent a significant proportion of total lesions, and can be detected during life by FLAIR MRI in a manner that seems to correlate well with previous autopsy descriptions.

These cortical lesions may have clinical relevance. The number of cortical lesions in the present study was significantly associated with longer disease duration and progressive disease course, although the lesions also occurred commonly in patients with RR disease. Cognitive dysfunction, such as memory and information processing problems, is common in MS and may occur early in the disease course. One study found a relation between cortical plaques detected by FLAIR and cognitive impairment in patients with MS. The number of these lesions corresponded to impaired retention of information in memory tasks. Cortical clinical syndromes may occur in patients with MS. Seizures, occurring in up to 5% of patients, were correlated pathologically with corticomedullary lesions. Depression and other mood disturbances are also common in patients with MS. Recent MRI studies implicated cortical gray matter atrophy in the pathogenesis of primary depression and depression related to MS.

In the present study, T2WIs were insensitive relative to FLAIR for detecting cortical involvement, prob-

<table>
<thead>
<tr>
<th>Location and Atrophy Measure</th>
<th>r</th>
<th>P</th>
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<tbody>
<tr>
<td>Superior frontal cortical</td>
<td>0.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inferior frontal cortical</td>
<td>0.19</td>
<td>.04</td>
</tr>
<tr>
<td>Superior parietal cortical</td>
<td>0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inferior parietal cortical</td>
<td>0.15</td>
<td>.1</td>
</tr>
<tr>
<td>Temporal cortical</td>
<td>0.50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Occipital cortical</td>
<td>0.43</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*FLAIR indicates fluid-attenuated inversion recovery magnetic resonance imaging with fast spin-echo (see the “Subjects and Methods” section).†Spearman rank correlation.

Table 3. Association Between Cortical Lesions on FLAIR Images and Regional Atrophy in 84 Patients With Multiple Sclerosis

Figure 1. A 33-year-old patient with relapsing-remitting multiple sclerosis. A, T1-weighted image; B, T2-weighted image; and C, fluid-attenuated inversion recovery (FLAIR) image. Multiple lesions are seen in the axial FLAIR image involving the dorsal frontal cortex and gray-white junction. Several but not all are detected on the T2-weighted image, and 2 of the lesions show definite hypointensity on the T1-weighted image (arrows). The lesions are most crisply shown by FLAIR. Lesions range in diameter from 2 (open arrow) to 7 mm (curved arrow).

Figure 2. A 40-year-old patient with relapsing-remitting multiple sclerosis. A, T1-weighted image; B, T2-weighted image; and C, fluid-attenuated inversion recovery (FLAIR) image. The patient has a large cortical-subcortical lesion (12 mm in diameter) in the posterior frontal region that is seen on all sequences. The lesion is most conspicuous on the FLAIR image.
able due to 2 factors. The first factor accounting for the poor sensitivity of T2WIs for identifying cortical hyperintensities is partial volume averaging with sulcal subarachnoid CSF. Proton density images, not obtained in the present study, show T2 prolongation and partially suppress CSF and thus might offer greater sensitivity for cortical lesions than T2WIs. The second factor is that gray matter lesions have higher relaxation times than those of normal white matter, leading to poor resolution between gray matter and lesions in the cortex compared with lesions and white matter. This results from the greater cellular density of cortical lesions compared with those of white matter. This high cellular density may not allow a sufficient expansion of the extracellular space to allow an increase in T2 relaxation times in cortical lesions, as in white matter. In the present study, we used a T2-weighted sequence that was optimized for fast scanning time with an acceptable lesion contrast. A T2-weighted study with a higher TR (stronger T2 weighting) might improve lesion detectability with a trade-off of longer scanning time. We showed that T1WIs are also of lower sensitivity than FLAIR for detecting cortical plaques that could relate to the same cortical cellular density and partial volume averaging that affect T2WIs. Also, the detection of MS plaques on T1WIs requires a marked increase in lesional water content (eg, edema or tissue destruction) that does not usually occur in gray matter plaques.

The excellent demonstration of cortical lesions by FLAIR MRI probably relates to its high sensitivity for detecting T2 prolongation in tissue and the nulling of CSF in cortical sulci. Our data extend the results of previous studies that showed cortical lesions detected by FLAIR in patients with MS. One pilot study of FLAIR detection of cortical plaques in MS used an older (conventional spin-echo) FLAIR method on a low-field scanner (0.5 T). Those authors found 60% more cortical lesions by FLAIR than by proton density or T2WIs. Cortical lesions, representing 8% of the total, were rare on FLAIR.
images of healthy controls. Another study35 found a higher number and volume of cortical and subcortical lesions than on conventional sequences.

Cortical plaques may be seen on postcontrast T1WI studies in patients with MS,10,56 indicating that some of these lesions have active blood-brain barrier disruption. A recent large imaging study10 showed a total of 258 enhancing lesions in 172 patients with MS, 16% of which were cortical. However, FLAIR imaging was not performed in that study. Further studies should compare the relative sensitivities of FLAIR and contrast-enhanced T1WIs for detecting cortical plaques.

No direct pathologic correlations of FLAIR findings were performed in our study. However, previous pathologic studies indicated that the cortical lesions reported herein represent direct pathologic involvement of the gray matter or corticomedullary junction by demyelination and inflammation. Neuronal loss and wallerian degeneration could also contribute to cortical hyperintensities on FLAIR images.57,58 Age-related and ischemic changes may cause T2 prolongation as incidental findings in healthy subjects, most commonly after the age of 50 years and usually in periventricular subcortical white matter.59,60 It could be argued that the cortical lesions seen on FLAIR images in our patients with MS were false-positive results due to normal variants, age-related changes, or other diseases. However, incidental cortical hyperintensities were not seen on FLAIR images in healthy adults in the third to sixth decades of life in a separate study61 and were rarely seen in our age-matched controls (6 lesions in 60 subjects). None of our patients with MS had major medical illnesses, such as hypertension, diabetes, or cardiopulmonary diseases, that might have caused cortical lesions.

In our study, cortical lesions were associated with regional cortical atrophy; in a given region, the number of FLAIR cortical lesions was significantly related to the degree of enlargement of the cortical sulci. This relation persisted after taking into account noncortical (white matter) lesions; only the cortical lesions were retained in regression models predicting atrophy in that region. Although not showing cause and effect, this finding indicates that the cortical lesions are closely associated with cortical atrophy.

There is a potential problem with our method, since the MRI readers were aware of the hypothesis that was to be tested. We were not able to blind the readers since the patient’s diagnosis of MS was obvious by the presence of characteristic white matter plaques that could not be deleted from the images and the normal scans were readily apparent. Our method of measuring regional brain atrophy was qualitative and rater dependent. However, our atrophy rating method showed good reliability and validity (see the “Subjects and Methods” section).33 It is likely that improvements in our FLAIR protocol would have allowed a more accurate appreciation and classification of the cortical and juxtacortical lesions in the present study.33 For example, multiplanar imaging and the use of thinner (ie, 3-mm) slices might allow a differentiation of purely cortical vs purely subcortical lesions that we have described. In the present study, we used a FLAIR protocol with a scanning time of 2 minutes, which is applicable to routine clinical care. Thus, our study demonstrates that cortical and juxtacortical lesions can be detected by such a streamlined standard clinical protocol. Future studies using advanced FLAIR protocols would be helpful to extend and confirm our findings.

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