MRI phenotypes based on cerebral lesions and atrophy in patients with multiple sclerosis

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</table>
MRI phenotypes based on cerebral lesions and atrophy in patients with multiple sclerosis

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**A B S T R A C T**

**Background:** While disease categories (i.e. clinical phenotypes) of multiple sclerosis (MS) are established, there remains MRI heterogeneity among patients within those definitions. MRI-defined lesions and atrophy show only moderate inter-correlations, suggesting that they represent partly different processes in MS. We assessed the ability of MRI-based categorization of cerebral lesions and atrophy in individual patients to identify distinct phenotypes.

**Methods:** We studied 175 patients with MS [age (mean ± SD) 42.7 ± 9.1 years, 124 (71%) women, Expanded Disability Status (EDSS) score 2.5 ± 2.3, n = 18 (10%) clinically isolated demyelinating syndrome (CIS), n = 115 (66%) relapsing-remitting (RR), and n = 42 (24%) secondary progressive (SP)]. Brain MRI measures included T2 hyperintense lesion volume (T2LV) and brain parenchymal fraction (to assess whole brain atrophy). Medians were used to create bins for each parameter, with patients assigned a low or high severity score.

**Results:** Four MRI phenotype categories emerged: Type I = low T2LV/mild atrophy [n = 67 (38%); CIS = 14, RR = 47, SP = 6]; Type II = high T2LV/mild atrophy [n = 21 (12%); RR = 19, SP = 2]; Type III = low T2LV/high atrophy [n = 21 (12%); CIS = 4, RR = 16, SP = 1]; and Type IV = high T2LV/high atrophy [n = 66 (38%); RR = 33, SP = 33]. Type IV was the most disabled and was the only group showing a correlation between T2LV vs. BPF and MRI vs. EDSS score (all p < 0.05).

**Conclusions:** We described MRI-categorization based on the relationship between lesions and atrophy in individual patients to identify four phenotypes in MS. Most patients have congruent extremes related to the degree of lesions and atrophy. However, many have a dissociation. Longitudinal studies will help define the stability of these patterns and their role in risk stratification.

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1. **Introduction**

While clinically-defined disease categories of multiple sclerosis (MS) are well established [1], there remains heterogeneity of the disease among patients that appears to exist within the confines of these subtypes. This heterogeneity includes the concepts of patient-dependent longitudinally-consistent immunopathological lesion subtypes [2] and clustering of patient subgroups based on MRI-defined lesion characteristics and the level of tissue destruction [3,4]. Consistent with the concept of disease heterogeneity, clinical progression and treatment response are difficult to predict in individual patients. Furthermore, there is a topographic uncoupling of structural changes such as the lack of a relationship between brain and spinal cord involvement [5]. Taken together, these data suggest that the pathogenesis of tissue injury may differ among patients with MS.

Among the types of CNS tissue injury that typify the disease, the two broadest categories include inflammatory demyelinating foci (lesions) and tissue destruction (neurodegeneration; axonal and neuronal loss). The most commonly-used and readily-available MRI measure of lesion load is hyperintensity on T2-weighted images. To assess overall tissue destruction, MRI-quantified normalized whole brain volume is an established measure of brain atrophy [6]. Several lines of evidence indicate that lesions and atrophy represent somewhat unrelated aspects of the disease process. This includes the observation that in both cross-sectional [6,7] and longitudinal [6,8] studies, lesions show a weak relationship to current and subsequent atrophy. Furthermore, the two measures provide complementary information in predicting treatment efficacy [9]. The objective of this study was to assess the ability of MRI-based categorization of the relationship between the severity of cerebral lesions and atrophy in individual patients to identify distinct MS phenotypes. This work was presented in preliminary form at the 2013 annual meeting of the American Academy of Neurology, San Diego.
2. Methods

2.1. Subjects and clinical evaluation

Demographic and clinical characteristics of the subjects are summarized in Table 1. This was a single-center cross-sectional retrospective study of 175 consecutive patients who met the following inclusion criteria: 1) Diagnosed with a relapsing form of MS including a clinically-isolated demyelinating syndrome (CIS), relapsing-remitting (RR), or secondary progressive (SP) [1]; 2) Evaluated clinically by an MS specialist provider at the Brigham and Women’s Hospital MS clinic (Partners MS Center) within three months of MRI; 3) age 18–60 years. Nearly all patients were receiving disease modifying therapy, as is the common practice at our center [7]. Baseline characteristics, including demographic, clinical, and MRI (Table 1), were comparable to those of large MS cohorts [10,11], indicating that our cohort represented a wide range of the MS spectrum that includes the continuum CIS–RR–SP. We did not include primary progressive MS patients because of the challenging diagnosis [1], the small numbers of those patients available, and that concept that this group may represent a separate entity. This study was approved by our institutional review board.

2.2. MRI acquisition and segmentation

Brain MRI was obtained in all subjects at 1.5 T with a 3 mm thick, gapless, T2-weighted, axial dual-echo protocol that included the entire brain. With few exceptions, the protocol was performed on the same scanner and included the following consistent acquisition parameters: repetition time 3000 ms, echo time 30/80 ms, and 0.93 × 0.93 mm pixel size. Using automated template-driven segmentation (TDS++) from the dual echo images, total brain T2 hyperintense white matter lesion volume (T2LV) and normalized whole brain volume [brain parenchymal fraction (BPF) – a surrogate of whole brain atrophy] [6] were automatically determined [12], after which expert manual correction was applied to each output map to ensure accuracy.

2.3. Creation of the MRI-defined phenotypes

Patients were stratified into MRI phenotype groups based on a median split (0 or 1) of T2LV and BPF. As shown in Fig. 1, all patients were assigned to one of four unique groups as:

- Type I (mild atrophy) (0) and low T2LV (0)
- Type II (mild atrophy) (0) and high T2LV (1)
- Type III (high atrophy) (1) and low T2LV (0)
- Type IV (high atrophy) (1) and high T2LV (1).

2.4. Statistical analysis

The demographic, clinical and MRI characteristics were compared across the four groups using one-way analysis of variance for continuous outcomes (age, disease duration, BPF, and T2LV), a proportional odds model for ordinal outcomes (EDSS) and a chi-square test for nominal variables (gender and disease category). If a significant difference was observed in the four group comparison, pairwise group comparisons were completed and Holm’s correction for multiple comparisons was applied to adjust the p-values. In addition, we assessed the relationship among the MRI measures and the relationship between MRI and EDSS score using the Spearman’s correlation coefficient. These were analyzed for the whole cohort and within each MRI phenotype group.

3. Results

Four categories emerged from the median split analysis (Table 2, Fig. 2). Regarding clinical and demographic group comparisons (Table 2), Type IV patients had higher disease duration, higher EDSS scores, and a higher proportion of SP patients than the other three groups (all p < 0.05). Type III and IV patients were each older than the Type I and II patients. Otherwise, there were no differences in age, disease duration, EDSS score, or clinical disease category distribution among groups (p > 0.05). There were no differences in the gender breakdown across the groups (p > 0.05).

Regarding the MRI parameters that comprised the phenotypes (Table 2), all pairwise comparisons showed significant differences in T2LV among the groups (p < 0.05), except for Type I vs. Type III (p > 0.05). In addition, all pairwise comparisons showed significant differences in BPF among the groups (p < 0.05) except Type I vs. Type II (p > 0.05). These results confirm the rationale of defining unique MRI phenotypes on the basis of different T2LV and BPF characteristics.

We also tested the relationships between lesions and atrophy and between MRI and disability (Table 3). The correlation between T2LV and BPF was significant in the overall cohort (p < 0.0001) and in the Type IV patients (p < 0.0001) but not in the other three groups (p > 0.05). Similarly, the correlation between each of the two MRI parameters (T2LV and BPF) and EDSS score was significant in the overall cohort (p < 0.0001) and in the Type IV patients (p < 0.0001) but not in the other three groups (p > 0.05).

4. Discussion

A major finding in this study is that 25% patients had a discordance of where their brain lesions and atrophy fell with regard to the medians of the full cohort. The discordance was equally bidirectional in that about half of the discordant patients had a high degree of atrophy
1.5 T and 3 T [6,15] rather than white matter atrophy, consistently seen in MRI studies at not onset that whole brain atrophy in MS is dominated by gray matter that are not captured by overt lesion load. Considering the prevailing degree of atrophy, there may be other contributions to tissue destruction or other resistance to the downstream effects of white matter injury in these patients may be the presence of enhanced repair capacity [14] or other disease duration (years); T2LV = total brain T2 hyperintense lesion volume (cc); BPF = brain parenchymal fraction.

II (mild atrophy/high T2LV); Type III (high atrophy/low T2LV); Type IV (high atrophy/high T2LV); RR = relapsing-remitting; EDSS = Expanded Disability Status Scale score; DD = disease duration (years); T2LV = total brain T2 hyperintense lesion volume (cc); BPF = brain parenchymal fraction.

Another noteworthy finding in this study is that the MRI phenotypes belie the confines of the current MS disease categories (i.e. clinical phenotypes), readily crossing those boundaries, suggesting that the MRI categorization provides unique information about disease severity. For example, RR and SP patients were identified in each of the four MRI phenotype groups, in a manner that would contradict the intuitive understanding of these clinical stages of MS. In particular, 9% of the Type I (mild) MRI phenotype patients had a SP (advanced) clinical despite a low lesion load (Type II MRI phenotype) and vice-versa (Type III). This was further underscored by the poor correlation in both groups between T2LV and BPF. Taken together these findings suggest that subgroups of patients have an uncoupling between focal immunemediated demyelination in white matter (inflammation) and overall global cerebral tissue destruction (neurodegeneration).

Regarding the Type II patients, who have a high T2LV but low atrophy, this might relate in part to the long held view that T2 hyperintense lesions are non-specific for pathologic changes, reflecting a wide range of severity [13]. We hypothesize that Type II patients have a T2LV that is dominated by mild changes such as mild inflammation, edema, and partial demyelination. Another factor serving to limit overall atrophy in these patients may be the presence of enhanced repair capacity [14] or other resistance to the downstream effects of white matter injury on neuronal and axonal integrity.

Regarding the Type III patients, who have a low T2LV but higher degree of atrophy, there may be other contributions to tissue destruction that are not captured by overt lesion load. Considering the prevailing notion that whole brain atrophy in MS is dominated by gray matter rather than white matter atrophy, consistently seen in MRI studies at 1.5 T and 3 T [6,15–17], the Type III patients may be affected by gray matter injury due to a variety of mechanisms that are separate from white matter lesions (and were not assessed in the present study) such as microglial activation [18], cortical lesions [19,20], meningeal inflammation [21], and iron deposition/oxidative stress [22].

Type I and Type IV phenotypes were characterized by a congruent level of lesions and atrophy with each either of a lower (Type I) or higher (Type IV) degree. Comparing these two groups, Type I patients tended to be at an earlier stage of disease on other disease characteristics, showing a lower age, lower disease duration, and lower level of disability. In addition, the Type I group was represented by a preponderance of CIS and inflammation, edema, and partial demyelination. Another factor serving to limit overall atrophy in these patients may be the presence of enhanced repair capacity [14] or other resistance to the downstream effects of white matter injury on neuronal and axonal integrity.

Another noteworthy finding in this study is that the MRI phenotypes belie the confines of the current MS disease categories (i.e. clinical phenotypes), readily crossing those boundaries, suggesting that the MRI categorization provides unique information about disease severity. For example, RR and SP patients were identified in each of the four MRI phenotype groups, in a manner that would contradict the intuitive understanding of these clinical stages of MS. In particular, 9% of the Type I (mild) MRI phenotype patients had a SP (advanced) clinical severe stage.

**Table 2**

Demographic, clinical and MRI characteristics of the MRI-defined phenotypes.

<table>
<thead>
<tr>
<th>Disease category:</th>
<th>Type I (mild atrophy/low T2LV)</th>
<th>Type II (mild atrophy/high T2LV)</th>
<th>Type III (high atrophy/low T2LV)</th>
<th>Type IV (high atrophy/high T2LV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>n = 67 (38%)</td>
<td>n = 21 (12%)</td>
<td>n = 21 (12%)</td>
<td>n = 66 (38%)</td>
</tr>
<tr>
<td>Disease category:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Clinically isolated syndrome</td>
<td>14 (21%)</td>
<td>0</td>
<td>4 (19.0%)</td>
<td>0</td>
</tr>
<tr>
<td>• Relapsing-remitting MS</td>
<td>47 (70%)</td>
<td>19 (91%)</td>
<td>16 (76%)</td>
<td>33 (50%)</td>
</tr>
<tr>
<td>• Secondary progressive MS</td>
<td>6 (9%)</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
<td>33 (50%)</td>
</tr>
<tr>
<td>Number of women (n, %)</td>
<td>n = 51 (76%)</td>
<td>n = 16 (76%)</td>
<td>n = 14 (67%)</td>
<td>n = 43 (65%)</td>
</tr>
<tr>
<td>Age (mean ± SD) (range) (years)</td>
<td>37.3 ± 8.3 (21.0–54.1)</td>
<td>36.9 ± 7.9 (21.7–50.2)</td>
<td>43.7 ± 7.8 (21.0–54.3)</td>
<td>44.0 ± 8.6 (26.5–60.2)</td>
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<tr>
<td>Expanded Disability Status Scale score</td>
<td>1.5 ± 1.8 (0–8.5)</td>
<td>1.9 ± 2.0 (0.7–6.5)</td>
<td>1.7 ± 1.8 (0–6.5)</td>
<td>3.9 ± 2.2 (1.0–8.5)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.5 ± 5.7 (0.26–26.0)</td>
<td>8.6 ± 6.6 (0.57–22.0)</td>
<td>8.6 ± 8.1 (0.4–26.0)</td>
<td>14.3 ± 9.4 (0.25–48.0)</td>
</tr>
<tr>
<td>T2LV (cc)</td>
<td>2.3 ± 1.0 (0.46–421)</td>
<td>8.2 ± 4.9 (4.5–22.2)</td>
<td>2.3 ± 1.1 (0.8–4.1)</td>
<td>17.3 ± 11.8 (4.4–57.1)</td>
</tr>
<tr>
<td>Brain parenchymal fraction</td>
<td>0.888 ± 0.025 (0.85–0.93)</td>
<td>0.875 ± 0.025 (0.85–0.93)</td>
<td>0.834 ± 0.016 (0.78–0.85)</td>
<td>0.791 ± 0.041 (0.67–0.85)</td>
</tr>
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</table>

Key: T2LV = total brain T2 hyperintense lesion volume. Regarding the breakdown of women vs. men, no significant differences were observed across the groups (p > 0.05). Regarding age, Types III and IV were significantly older than Types I and II (p < 0.05). Regarding disease category (i.e. clinical phenotype), EDSS, and disease duration, Type IV was significantly more likely to be SPMS, disabled, with higher disease duration than the other three categories (p < 0.05). Regarding T2LV, all pairwise differences except Type I vs III were statistically significant (p < 0.05). Regarding brain parenchymal fraction, all pairwise differences except Type I vs. Type II were statistically significant (p < 0.05).
course, and 50% of the Type IV patients had a RR clinical course (not yet progressed to SP). This paradox is underscored by the fact that the range of EDSS scores was similar between Type I and Type IV groups. Spinal cord involvement (not considered in the present study) might explain the presence of SP patients in the Type I MRI group, given that spinal cord atrophy is a hallmark of SPMS [23] and such involvement is poorly reflected in MRI brain measures of pathology [5]. Why are there so many patients with Type IV pathology in the RR (rather than SP) stage and carrying relatively low levels of disability? These patients may have enhanced cerebral reserve capacity [24], sparing of eloquent substructures/pathways of the brain [25], or relative little spinal cord involvement [5] (analyses which were not performed in the present study). Because this was a cross-sectional study, we were not able to determine if the more mildly affected Type IV patients were at risk for imminent clinical progression. As further evidence of the unique information provided by the MRI phenotype grouping, Type II and Type III patients showed a similar number of RR and SP patients.

A longstanding challenge in the MS field has been the poor correlation between brain MRI and neurologic status [26]; this clinical–MRI paradox has traditionally referred to focal brain lesions. While measurement of brain atrophy has improved MRI correlations with disability and cognitive impairment, the association with clinical status has remained inconsistent (and moderate at best) [5–8, 15–17, 19, 26–28]. In the present study, we found a striking difference among groups in modeling the relationship between brain MRI and disability in that three of the groups (Types I, II and III) showed no relationship between either T2LV or BPF and EDSS score; while, Type IV patients showed significant but moderate associations. Our data thus indicate that disease heterogeneity is one factor contribution to the relationship between global MRI and physical disability. Moreover we can bring forward a “two-hit” hypothesis based on these results that both inflammation and neurodegeneration need to be substantially present in a given patient to exceed cerebral reserve capacity and thus cause clinical impairment.

Perhaps the first use of a clustering method to classify patients with MS on the basis of MRI-defined inflammation or neurodegeneration was introduced by Bielekova et al. [3]. These investigators used the presence of gadolinium-enhancement on three consecutive monthly scans to initially stratify patients as having either low or high active inflammation. Subjects were then subdivided further by BPF and the ratio of T1 hypointense to T2 hyperintense lesions. Although related, ours was a more simplified classification system requiring only one imaging time point and the availability of T2LV and BPF, which does not consider acute/recent inflammatory activity. We focused disease severity rather than disease activity in creating these MRI phenotypes.

Our exploratory study should serve as a basis for confirmation and extension in future studies. A prospective study is warranted to confirm and extend these findings. While the overall sample size was large for an MS–MRI clinical correlation study, the numbers of patients assigned to Type II and Type III were relatively small. It remains to be determined whether consideration of other advanced structural aspects of MRI-defined CNS related damage [7] such as imaging parameters focused on the gray matter, spinal cord, normal–appearing white matter, destructive potential of lesions, or mapping of specific sites/tracts of involvement would help to further refine the MRI phenotype definitions. Given the emerging data suggesting a link between genetics, immune regulation, and inflammatory or neurodegenerative aspects of MS disease pathogenesis [29–35], it would be of interest to investigate if the MRI phenotypes are associated with specific biomarkers. Because most of our patients were treated with disease modifying medications, this might alter the natural rate or degree of development lesion and atrophy metrics. It would be of interest to assess if these phenotypic definitions persist when considering untreated patients. This may not be feasible in the current treatment era, requiring access to historic data sets. Finally, it remains to be determined in longitudinal studies, the treatment response and rate/factors associated with a change in a patient’s MRI phenotype.

Conflict of interest and source of funding

None.

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References


Table 3

MRI–MRI and MRI–disability correlations.

<table>
<thead>
<tr>
<th>Correlation examined</th>
<th>Type I (n = 67)</th>
<th>Type II (n = 21)</th>
<th>Type III (n = 21)</th>
<th>Type IV (n = 66)</th>
<th>Entire cohort (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2LV–BPF</td>
<td>−0.06 (0.656)</td>
<td>−0.16 (0.491)</td>
<td>−0.32 (0.158)</td>
<td>−0.49 (0.001)</td>
<td>−0.66 (&lt;0.001)</td>
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<tr>
<td>BPF–EDSS</td>
<td>−0.35 (0.003)*</td>
<td>−0.21 (0.356)</td>
<td>0.30 (0.185)</td>
<td>−0.46 (0.001)*</td>
<td>−0.57 (&lt;0.001)*</td>
</tr>
<tr>
<td>T2LV–EDSS</td>
<td>0.11 (0.383)</td>
<td>0.18 (0.433)</td>
<td>0.28 (0.225)</td>
<td>0.36 (0.003)*</td>
<td>0.56 (&lt;0.001)*</td>
</tr>
</tbody>
</table>

Key: r, (p) values are shown for Spearman correlation coefficients; Type I (mild atrophy/low T2LV); Type II (mild atrophy/high T2LV); Type III (high atrophy/low T2LV); Type IV (high atrophy/high T2LV); EDSS = Expanded Disability Status Scale score; T2LV = total brain T2 hyperintense lesion volume (cc); BPF = brain parenchymal fraction.

* p < 0.05.


