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Relevance of hypointense brain MRI lesions for long-term worsening of clinical disability in relapsing multiple sclerosis

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Abstract

Background: The accrual of brain focal pathology is considered a good substrate of disability in relapsing–remitting multiple sclerosis (RRMS). However, knowledge on long-term lesion evolution and its relationship with disability progression is poor.

Objective: The objective of this paper is to evaluate in RRMS the long-term clinical relevance of brain lesion evolution.

Methods: In 58 RRMS patients we acquired, using the same scanner and protocol, brain magnetic resonance imaging (MRI) at baseline and 10±0.5 years later. MRI data were correlated with disability changes as measured by the Expanded Disability Status Scale (EDSS).

Results: The annualized 10-year lesion volume (LV) growth was +0.25±0.5 cm^3 (+6.7±8.7%) for T2-weighted (T2-W) lesions and +0.20±0.31 cm^3 (+11.5±12.3%) for T1-weighted (T1-W) lesions. The univariate analysis showed moderate correlations between baseline MRI measures and EDSS at 10 years ($p < 0.001$). Also, 10-year EDSS worsening correlated with LV growth and the number of new/enlarging lesions measured over the same period ($p < 0.005$). In the stepwise multiple regression analysis, EDSS worsening over 10 years was best correlated with the combination of baseline T1-W lesion count and increasing T1-W LV ($R = 0.61$, $p < 0.001$).

Conclusion: In RRMS patients, long-term brain lesion accrual is associated with worsening in clinical disability. This is particularly true for hypointense, destructive lesions.

Keywords

Multiple sclerosis, MRI, brain lesions, longitudinal, disability

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Introduction

In multiple sclerosis (MS), magnetic resonance imaging (MRI) is the modality of choice to identify brain lesions noninvasively, even in "clinically silent" areas. Indeed, MRI-derived measures of white matter (WM) hyperintense lesions as detected on proton density (PD), T2-weighted (T2-W) and fluid-attenuated inversion recovery (FLAIR) sequences represent the disease hallmark.

Accrual of WM lesions is variable among patients with MS. Because the inflammatory process tends to extinguish over time (either spontaneously or after therapy), lesion volume (LV) tends to decrease as well, because of resolution of edema and, possibly, by remyelination.[1] After the acute phase, T2-W hyperintensity usually persists. As MS progresses over the years, brain lesions undergoing several

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reactivations may combine with adjacent lesions, leading to the formation of large confluent lesions. For these reasons, there is an accrual of focal pathology in MS brains, with T2-W LV increasing on average by 5%–10% per year.[2] The assessment of T2-W LV change is considered a clinically relevant measure of disease progression[3] and has been used as an outcome measure in MS clinical trials.[4,5]

Other expressions of MS focal pathology are the hypointense lesions visible on T1-weighted (T1-W) MRI sequences. They are a proportion of MS lesions and have MRI signal intensity equal to or lower than gray matter (GM) on T1-W images.[6] Nonenhancing (after gadolinium injection) T1-W lesions are chronic lesions characterized by marked neuroaxonal damage.[7] Therefore, a T1-W LV increase over time should be an expression of a substantial irreversible MS pathology.

The accrual of focal pathology in the brain represents one of the most relevant substrates of clinical disability in MS, although this does not seem to have a simple relationship with the progression of disability.[8] Indeed, the assessment of the MRI potential in predicting disability in MS patients may require long-term follow-up studies. Few previous MS studies have assessed the long-term clinical relevance of brain lesions at disease onset[9–11] without performing, however, a long-term MRI follow-up.

Against this background, we performed a longitudinal MRI study spanning a decade of follow-up in patients with relapsing–remitting (RR) MS to assess the rate of long-term evolution of brain lesions and to explore the clinical relevance of brain lesion accrual for disability in this long period of time.

Materials and methods

Study population

Seventy-three patients with RRMS were recruited between January 2000 and May 2001 and had a clinical assessment and brain MRI performed at the MR center of the University of Siena. After 10 years, 15 patients were lost to follow-up: Ten patients had moved and thus could not be traced, three patients were unable to participate in the study because of severe disability and two patients had died. In the remaining 58 patients, brain MRI was acquired again after 10±0.5 years. In one patient, the follow-up MRI examination could not be used because of a large signal artifact. Demographic and clinical features of the study patients (n = 57) are reported in Table 1.

Clinical assessment included record of relapses during the study period (for calculation of the annualized relapse rate (ARR)) and scoring on the Expanded Disability Status Scale (EDSS).[12] Relapses during the study period were treated with intravenous administration of methylprednisolone, 1 g/day for three or five days followed by oral prednisone taper. They were defined as the appearance of new or worsening neurological symptoms, or the reappearance of old neurological symptoms that were preceded by a 30-day period of clinical stability.[13] In each patient, EDSS assessment was performed at the time of scanning and by the same neurologist at both timepoints. EDSS change was considered only if confirmed at a three-month visit. Fifty patients were treated with disease-modifying treatment (DMT) during the study period. Seven patients did not receive any DMT during the study period, with the exception of the intravenous administration of methylprednisolone during acute relapses.

Table 1. Baseline demographic and clinical characteristics of the RRMS study population (n = 57).

Age, mean±SD, y	33.8±8.1
Sex, female/male	42/15
Disease duration, mean±SD, y	4.9±4.07
EDSS score, mean±SD	1.8±1.1

RRMS: relapsing–remitting multiple sclerosis; y: years; SD: standard deviation.

All patients signed an informed consent before MRI examination.

The study was approved by the ethics committee of the faculty of medicine of the local university.

MRI examination

All patients were examined with the same MRI protocol at both timepoints. Brain MRIs were acquired using a 1.5 T Philips Gyroscan (Philips Medical Systems, Best, The Netherlands). A sagittal survey image was used to identify the anterior and posterior commissures (AC and PC). A dual-echo, turbo spin-echo sequence (repetition time (TR)/echo time (TE)1/TE2 = 2075/30/90 ms, 256 × 256 matrix, 1 signal average, 250 mm field of view (FOV), 50 contiguous 3 mm slices) yielding PD and T2-W images was acquired in the axial plane parallel to the AC-PC line. Subsequently, T1-W images (TR/TE = 35/10 ms, 256 × 256 matrix, 1 signal average, 250 mm FOV) were acquired, yielding 50 slices, 3 mm thick, oriented to exactly match the PD/T2-W sequence. The MRI protocol did not include the acquisition of post-gadolinium T1-W images for ethical reasons.

Periodical quality control sessions and no major hardware upgrades were performed on the MR scanner during the 10-year study period.

MRI data analysis

Brain lesion count and volume. For each MS patient, MR scans were first visually assessed and then a single observer, unaware of patient identity, performed the count of T2-W hyperintense and T1-W hypointense lesions on the baseline scan, the count of new/enlarging T2-W and T1-W lesions on the follow-up scan and labeling of T2-W and T1-W LV at both timepoints by using a semiautomated segmentation

technique based on user-supervised local thresholding (Jim 5.0, Xinapse System, Leicester, UK). T2-W lesion borders were determined on PD images but information from T2-W and T1-W images was also considered. T1-W lesions were considered as those hypointense lesions corresponding to areas of hyperintensity on PD/T2-W images and with signal intensity in between GM and cerebrospinal fluid on T1-W images.[14] LV was computed by multiplying lesion area by slice thickness.

Statistics

The nonparametric Wilcoxon-paired test was used to compare EDSS and LVs between baseline and follow-up. Change in T2-W and T1-W LV, and count of new/enlarging T2-W and T1-W lesions, were computed as annualized measure (e.g. LV change/y), to account for small differences (months) in the interscan interval among patients. Difference in LV change/y between groups with and without on-study relapses was assessed by the Mann-Whitney U test.

Univariate correlations of brain lesion measures (baseline T2-W and T1-W lesion count, baseline LVs, new/enlarging T2-W and T1-W lesion count, LV changes) with disability (EDSS and EDSS change) were analyzed by using a partial correlation coefficient after adjusting for age, sex, disease duration and baseline EDSS. To assess the extent to which brain lesions can be associated with disability worsening over 10 years, we performed a stepwise multiple regression analysis, with EDSS change as the dependent variable and brain lesion measures (baseline T2-W and T1-W lesion count, T2-W LV, T1-W LV; 10-year change in T2-W and T1-W LV and count of new/enlarging T2-W and T1-W lesions) as the independent explanatory variables. A log-transform was applied to baseline LV variables, and a rank-transform was applied to EDSS and LV changes to smooth the skewed distribution of these variables when analyzed with parametric analyses. Data were considered significant at a two-tailed 0.05 level. SPSS software (SPSS Inc, Chicago, IL, USA) was used to perform statistical analyses.

Results

Clinical features

In the patient population, EDSS worsened from 1.8±1.1 at baseline to 2.5±1.7 after 10 years ($p < 0.001$). Forty-seven of 57 patients had relapses over 10 years (ARR = 0.47±0.34). Ten patients did not experience relapses and did not have EDSS progression during the study period.

Brain lesion evolution

As expected, LV after 10 years was much greater than at baseline (T2-W LV: 8.3±8.1 cm^3 versus 5.8±6.4 cm^3, $p < 0.001$; T1-W LV: 4.4±5 cm^3 versus 2.4±3.6 cm^3, $p < 0.001$), with an annualized 10-year rate of lesion growth (LV change/y) of +0.25±0.5 cm^3 (+6.7±8.7%) for T2-W LV and +0.20±0.31 cm^3 (+11.5±12.3%) for T1-W LV (Table 2). Annualized number of new/enlarging T2-W and T1-W lesions over 10 years is also shown in Table 2.

Increase in T2-W LV was found in patients with on-study relapses ($n = 47$, T2-W LV change/y: +0.31±0.53 cm^3), but was not observed in patients who did not experience relapses during the 10-year follow-up ($n = 10$, T2-W LV change/y: –0.02±0.1 cm^3, $p = 0.001$).

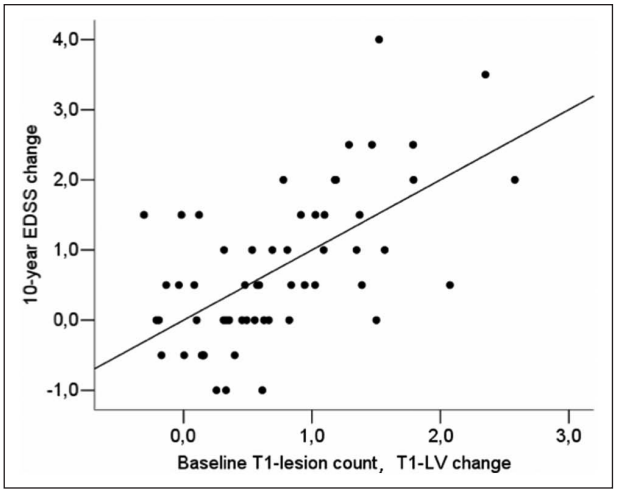

Figure 1. MRI correlates of 10-year disability worsening in RRMS. The stepwise multiple regression analysis shows that in our population of RRMS ($n = 57$), EDSS worsening over 10 years was best correlated with the combined measure of baseline T1-W lesion count and 10-year T1-W LV change ($R = 0.61$, $p < 0.001$). MRI: magnetic resonance imaging; RRMS: relapsing–remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; T1-W: T1-weighted; LV: lesion volume.

Relationship of brain lesions with disability

In the patient population, after adjustment for baseline characteristics, worse 10-year EDSS correlated with greater baseline LV ($r = 0.50$, $p < 0.001$ for T2-W lesions; $r = 0.42$, $p < 0.001$ for T1-W lesions) (Table 3) and with higher count of baseline T2-W lesions ($r = 0.51$, $p < 0.001$) and T1-W lesions ($r = 0.53$, $p < 0.001$).

Over the 10-year follow-up, increasing LV showed moderate correlations with EDSS worsening ($r = 0.37$, $p = 0.007$ for T2-W lesions; $r = 0.47$, $p < 0.001$ for T1-W lesions) (Table 3) and with relapse number ($r = 0.45$, $p = 0.001$ for T2-W lesions; $r = 0.44$, $p = 0.001$ for T1-W lesions). Similar correlations with 10-year EDSS change were found for the number of new/enlarging T2-W and T1-W lesions (Table 3). In the stepwise multiple regression analysis, EDSS worsening over 10 years was best associated with the combination of baseline T1-W lesion count and increasing T1-W LV ($R = 0.61$, $p < 0.001$) (Figure 1).

Table 2. Brain lesion evolution over 10 years is shown in RRMS patients (n=57).

Brain lesion features	Mean (SD)	Median (range)
Baseline T2-W lesion count	22.4±18.5	17 (2 to 80)
Annualized 10-year new/enlarging T2-W lesion count	+1.5±1	+1.3 (0.1 to 4.3)
Baseline T1-W lesion count	12.8±11.5	10 (0 to 50)
Annualized 10-year new/enlarging T1-W lesion count	+0.94±0.7	+0.83 (0 to 3.2)
Baseline T2-W LV, cm^3	5.8±6.4	3.6 (0.1 to 36.9)
Annualized 10-year T2-W LV change, cm^3	+0.25±0.5	+0.11 (–0.09 to 2.4)
Annualized 10-year T2-W LV change, %	+6.7±8.7	+3.7 (–5.6 to 31.8)
Baseline T1-W LV, cm^3	2.4±3.6	1.3 (0 to 18.6)
Annualized 10-year T1-W LV change, cm^3	+0.20±0.31	+0.09 (0 to 1.4)
Annualized 10-year T1-W LV change, %	+11.5±12.3	+7.2 (0 to 53.1)

RRMS: relapsing–remitting multiple sclerosis; T1-W: T1-weighted; T2-W: T2-weighted; SD: standard deviation; LV: lesion volume.

Table 3. Partial correlations (adjusted for age, sex, disease duration and baseline EDSS) between brain lesions and EDSS in RRMS patients (n = 57).

Baseline T2-W lesion count and 10-year EDSS	$r = 0.51, p < 0.001$
Baseline T1-W lesion count and 10-year EDSS	$r = 0.53, p < 0.001$
Baseline T2-W LV and 10-year EDSS	$r = 0.50\ p < 0.001$
Baseline T1-W LV and 10-year EDSS	$r = 0.42, p < 0.001$
Baseline T2-W lesion count and EDSS change	$r = 0.50, p < 0.001$
Baseline T1-W lesion count and EDSS change	$r = 0.54, p < 0.001$
T2-W LV change and EDSS change	$r = 0.37, p = 0.007$
New/enlarging T2-W lesion count and EDSS change	$r = 0.43, p = 0.001$
T1-W LV change and EDSS change	$r = 0.47, p < 0.001$
New/enlarging T1-W lesion count and EDSS change	$r = 0.45, p = 0.001$

EDSS: Expanded Disability Status Scale; RRMS: relapsing–remitting multiple sclerosis; T1-W: T1-weighted; T2-W: T2-weighted LV: lesion volume.

Discussion

Longitudinal imaging permits the evaluation of changes in brain pathology over time. This is particularly important in the setting of a progressive neurological condition such as MS. The present study reports on a long-term (10 years) follow-up of brain lesions in MS using the same MR scanner and imaging protocol at both timepoints and sheds new light on lesion evolution in relation with progression of clinical disability.

We found in our cohort of relapsing MS patients that brain lesions at baseline were associated with disability status after 10 years. Generally, previous long-term studies have shown that the relationship between baseline lesion load and disability status was moderate in patients with clinically isolated syndrome suggestive of MS followed up to 20 years,[9,15] in the patient cohort of the pivotal interferon beta-1b MS trial followed up for 16 years[16] and weak in a cohort of RRMS patients followed up for a median of 15 years.[17] Our findings, obtained in a cohort of RRMS patients with mean disease duration of five years and a 10-year follow-up, add to previous data highlighting that brain lesions at baseline do have predictive ability toward long-term disability.

An important aim of our prospective study was to explore the long-term interplay between changes in brain lesions and clinical disability. Over 10 years, we found that T2-W and T1-W lesion growth, in terms of both volume and count, can show a moderate correlation with disability worsening. Interestingly, multivariate analysis indicated that a higher count of baseline T1-W lesions and 10-year T1-W LV growth were the best MRI correlates of 10-year EDSS worsening.

Indeed, formation and evolution of chronic or persistent T1-hypointense lesions, also known as "black holes," represent markers of destructive WM pathology, in terms of axonal damage/loss.[18] These lesions show more histopathological specificity than T2-W lesions, which can heterogeneously underlie inflammation, edema, demyelination, gliosis and, possibly, remyelination.[19] Relationship of black holes with disability has not been consistently reported in all studies.[20] The finding in our study that the number of black holes at baseline and their volume increase over time were the only significant brain lesion correlates of EDSS worsening over 10 years highlights the role of neurodegeneration in the pathophysiology of long-term disability in MS.[18]

While our results of the multivariate analysis certainly imply a relevant role of focal brain MRI measures on disability progression, they explain 37% (R^2) of the disability worsening in the long term. Indeed, there are many reasons that might contribute to explaining why MRI lesions do not fully account for changes in disability progression, even in the long term. First, WM lesions do not always affect "clinically eloquent" brain regions and, in spite of the high sensitivity to tissue damage, lesions lack pathological specificity.[19] Second, demyelinating lesions in MS also occur in GM and in the spinal cord,[21] which were not considered here. Third, the presence of diffuse tissue damage, which can independently account for disability, and cortical functional reorganization, which may compensate for the clinical damage produced by the focal demyelinating lesions, may further contribute to lessen the clinical relevance of brain lesion monitoring with MRI.[21] Finally, the intrinsic characteristic of EDSS, which is strongly weighted toward impairment of ambulation, certainly contributes to limiting its relationship with MRI measures.[8]

There are limitations in our study. First, it must be stressed that some of the most severely affected patients (three with severe disability and two deceased) were lost to follow-up. This is a limitation of all long-term studies and, although it was here limited to very few cases, it might somehow bias the results and their interpretation. Second, since post-gadolinium T1-W images were not acquired for ethical reasons (i.e. the MRI examination was not diagnostic), we could not assess whether enhancing lesions on the baseline MRI were related to worsened disability in the long term. Third, we focused here on the clinical relevance of focal demyelinating lesion accrual and did not consider markers of diffuse tissue damage such as brain atrophy. In such a relatively small patient group with long follow-up, this measure could be somehow limited by the technical hurdles occurring in the analysis of brains with substantial atrophy between scans.[22] Since the aim of this ongoing longitudinal study is to double the current sample size, we hope to overcome such a limitation and provide this information in the near future.

Usually, long-term MRI studies are difficult to perform because of MR scanner changes, which may lead to different and sometimes incomparable images between timepoints. In this case, however, our longitudinal study benefitted from the fact that periodical quality control sessions and no major hardware upgrades were performed on the MR scanner during the 10-year study period, which made possible the use of the same MRI acquisition protocol and ensured comparable image quality at both timepoints. This ultimately led to the unique occasion of providing evidence that, in the long term, lesion accrual is relevant for the disability worsening occurring in patients with relapsing MS. This seems to be particularly true for hypointense, destructive lesions.

Conflicts of interest statement

AG, MLS, MLB, FR, MB, ADL, LG and PM have nothing to declare. EP serves on scientific advisory boards for Biogen Idec, Merck Serono and Bayer Schering and receives research support and honoraria for speaking from Biogen-Idec, Merck Serono, Bayer Schering, Teva, Novartis and Sanofi Aventis. MPS has received consulting fees or honoraria from Biogen Idec, Merck Serono, Actelion and Synthon. MPA serves on scientific advisory boards for Biogen Idec, Merck Serono, Bayer Schering, Teva and Sanofi Aventis and receives research support and honoraria for speaking from Biogen Idec, Merck Serono, Bayer Schering, Teva, Novartis and Sanofi Aventis. NDS has served on scientific advisory boards, received speaker honoraria, served as a consultant or received research support from BioMS Medical, Biogen Idec, Bayer Schering Pharma, Merck Serono, NeuroRx Research, Novartis, Teva Pharmaceutical Industries Ltd and the Italian Multiple Sclerosis Society.

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