

Atrophied Brain T2 Lesion Volume at MRI Is Associated with Disability Progression and Conversion to Secondary Progressive Multiple Sclerosis

Antonia Valentina Genovese, MD • Jesper Hagemeier, PhD • Niels Bergsland, PhD • Dejan Jakimovski, MD • Michael G. Dwyer, PhD • Deepa P. Ramasamy, MD • Alexis A. Lizarraga, MD • David Hojnacki, MD • Channa Kolb, MD • Bianca Weinstock-Guttman, MD • Robert Zivadinov, MD, PhD

From the Buffalo Neuroimaging Analysis Center (A.V.G., J.H., N.B., D.J., M.G.D., D.P.R., R.Z.) and Jacobs MS Center (A.A.L., D.H., C.K.), Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, 100 High St, Buffalo, NY 14203; Institute of Radiology, Department of Clinical Surgical Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy (A.V.G.); and Center for Biomedical Imaging at Clinical Translational Science Institute (M.G.D., B.W., R.Z.), University at Buffalo, State University of New York, Buffalo, NY. Received February 9, 2019; revision requested April 2; revision received July 6; accepted August 9. **Address correspondence** to R.Z. (e-mail: rzivadinov@bnac.net).

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Background: Atrophied T2 lesion volume at MRI is an imaging measure that reflects the replacement of T2 lesions by cerebrospinal fluid spaces in patients with multiple sclerosis (MS).

Purpose: To investigate the association of atrophied T2 lesion volume and development of disability progression (DP) and conversion to secondary progressive MS (SPMS).

Materials and Methods: This retrospective study included 1612 participants recruited from 2006 to 2016 and followed up for 5 years with clinical and MRI examinations. Accumulation of T2 lesion volume, atrophied T2 lesion volume, percentage brain volume change (PBVC), and percentage ventricular volume change (PVVC) were measured. Disability progression and secondary progressive conversion were defined by using standardized guidelines. Analysis of covariance (ANCOVA) adjusted for age and Cox regression adjusted for age and sex were used to compare study groups and explore associations between MRI and clinical outcomes.

Results: A total of 1314 patients with MS (1006 women; mean age, 46 years \pm 11 [standard deviation]) and 124 patients with clinically isolated syndrome (100 women; mean age, 39 years \pm 11) along with 147 healthy control subjects (97 women; mean age, 42 years \pm 13) were evaluated. A total of 336 of 1314 (23%) patients developed DP, and in 67 of 1213 (5.5%) the disease converted from clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS) to SPMS. Patients with conversion to DP had higher atrophied T2 lesion volume (+34.4 mm³; 95% confidence interval [CI]: 17.2 mm³, 51.5 mm³; $d = 0.27$; $P < .001$) and PBVC (−0.21%; 95% CI: −0.36%, −0.05%; $d = 0.19$; $P = .042$) but not PVVC (0.36%; 95% CI: −0.93%, 1.65%; $d = 0.04$; $P = .89$) or T2 lesion volume change (−64.5 mm³; 95% CI: −315.2 mm³, 186.3 mm³; $d = 0.03$; $P = .67$) when compared with DP nonconverters. ANCOVA showed that atrophied T2 lesion volume was associated with conversion from CIS or RRMS to SPMS (+26.4 mm³; 95% CI: 4.2 mm³, 56.9 mm³; $d = 0.23$; $P = .002$) but not PBVC (−0.14%; 95% CI: −0.46%, 0.18%; $d = 0.11$; $P = .66$), PVVC (+0.18%; 95% CI: −2.49%, 2.72%; $d = 0.01$; $P = .75$), or T2 lesion volume change (−46.4 mm³; 95% CI: −460.8 mm³, 367.9 mm³; $d = 0.03$; $P = .93$). At Cox regression analysis, only atrophied T2 lesion volume was associated with the DP (hazard ratio, 1.23; $P < .001$) and conversion to SPMS (hazard ratio, 1.16; $P = .008$).

Conclusion: Atrophied brain T2 lesion volume is a robust MRI marker of MS disability progression and conversion into a secondary progressive disease course.

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Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. A secondary progressive clinical course develops in many individuals with MS, typically 20 years after onset, and sustained disability leads to impaired mobility and cognition (1).

Conventional MRI (ie, T2- or proton density-weighted, T2-weighted fluid-attenuated inversion recovery [FLAIR], or unenhanced and contrast material-enhanced T1-weighted imaging) is the main tool used in the diagnosis and routine surveillance of abnormal changes in patients with MS (2,3). Lesion measures (ie, number of new or enlarging or contrast-enhanced

lesions and their respective volumes) enable quantitative assessment of active inflammation. They have been largely used as primary and secondary end points in many clinical trials (3,4). Monitoring the appearance of new lesions and their enlargement is routinely used as an indicator of disease activity and treatment efficacy in a clinical routine. However, the association between lesion MRI markers and MS clinical worsening or transition to secondary progressive MS (SPMS) disease course is weak to modest (5,6).

Assessment of brain atrophy is considered a more robust outcome reflecting neurodegeneration, the end

Abbreviations

CDMS = clinically definite MS, CI = confidence interval, CIS = clinically isolated syndrome, CSF = cerebrospinal fluid, DP = disability progression, EDSS = Expanded Disability Status Scale, FLAIR = fluid-attenuated inversion recovery, MS = multiple sclerosis, PBVC = percentage brain volume change, PVVC = percentage ventricular volume change, RRMS = relapsing-remitting MS, SPMS = secondary progressive MS

Summary

Together with whole-brain atrophy, atrophied brain T2 lesion volume seen with MRI is used to predict multiple sclerosis (MS) disability progression and is the only MRI feature related to conversion of clinically isolated syndrome and relapsing-remitting MS into secondary progressive MS.

Key Results

- The annualized rate of atrophied T2 lesion volume was higher in patients with progressive multiple sclerosis (MS) than in patients with other MS subtypes or in healthy control subjects (111.1 mm³ vs 71.3 mm³ vs 5.4 mm³, respectively; $P < .001$).
- Patients with disease progression had increased annualized atrophied T2 lesion volume (93 mm³ vs 59 mm³, $P < .001$) and percentage brain volume change (-0.9% vs -0.7% , $P = .042$) when compared with patients without disease progression.
- Atrophied T2 lesion volume was the only MRI marker associated with conversion from clinically isolated syndrome or relapsing-remitting MS to secondary progressive MS (82 mm³ vs 56 mm³, $P = .002$).

stage of heterogeneous pathologic processes occurring in MS (7). Brain atrophy can be observed as early as in clinically isolated syndrome (CIS), and its development is a valid indicator of future clinical disease deterioration (3,7–12).

Despite growing interest in the use of neurodegenerative measures to monitor individuals with MS, there is still a lack of reliable MRI outcomes that can be used to detect early disease changes and predict future outcomes of disease progression and conversion to SPMS. A recently introduced MRI marker, brain atrophied T2 lesion volume, may aid in predicting the timing of MS disease progression (13–15). This quantitative measure reflects the amount of lesions being replaced by cerebrospinal fluid (CSF) spaces as a result of atrophy or direct lesion destruction (13–15). Parallel to the evolution of the disease, the inflammatory activity declines, and the neurodegenerative process accelerates (16). This could explain the plateauing of T2 lesion volume in more advanced disease stages (17) and could contribute to the poor correlation found between T2 lesion volume accumulation and clinical disability (5,7,14).

In this study, we aimed to investigate the behavior of atrophied T2 lesion volume accumulation in a large cohort of patients with MS during long-term clinical routine 5-year follow-up. We explored the predictive value of atrophied T2 lesion volume in relation to the development of DP and conversion from CIS and relapsing-remitting multiple sclerosis (RRMS) course to SPMS. In addition, we included a group of control subjects to understand dynamics of atrophied T2-weighted lesion volume accumulation in healthy subjects.

Materials and Methods

This study was approved by the local institutional review board. Written informed consent was waived for the patients with MS because of the retrospective nature of this study. Written informed consent was obtained for the healthy control subjects prospectively, but these data were used retrospectively in this study. Retrospective chart review was conducted in accordance with Health Insurance Portability Accountability Act guidelines and was approved by the local institutional review board.

Study Participants

This retrospective study enrolled 1612 consecutive participants who were observed between 2006 and 2016 at Jacobs MS Center. The inclusion criteria (Fig 1) for the patients with MS and CIS included (a) being diagnosed with MS according to the 2010 McDonald criteria (just for MS) (18), (b) availability of images acquired with both two-dimensional T2-weighted FLAIR and three-dimensional T1-weighted MRI, (c) availability of results from at least two longitudinal MRI examinations within the same participant over a period of 6 or more months, and (d) availability of demographic and clinical information from the first and most recent follow-up examinations. The exclusion criteria included (a) a clinical relapse or corticosteroid treatment within 30 days after MRI and (b) being pregnant or a nursing mother. Healthy control subjects included nonfamilial relatives of patients with MS and participants recruited via local advertisements. Healthy control subjects were enrolled in the study if they had normal neurologic and MRI findings within clinical expectations for their age.

Age, sex, disease duration, and disease course, as defined by the revised Lublin criteria (19), were recorded at clinical assessment and cross-referenced with electronic medical records at the first and most recent follow-up examinations. Disease severity was evaluated with a standardized neurologic evaluation and scored with the Expanded Disability Status Scale (EDSS) (20).

MRI Acquisition and Analysis

Brain MRI was performed at baseline and follow-up by using either 1.5- or 3.0-T GE Signa Excite HD 12.0 Twin Speed eight-channel units (GE Healthcare, Milwaukee, Wis) and an eight-channel head and neck coil that did not undergo any hardware or software changes during the study (Table E1 [online]). Participants were consistently examined with the same 1.5- or 3.0-T unit and the same MRI protocol between 2006 and 2016. The 3.0-T MRI included (a) axial two-dimensional T2-weighted FLAIR (repetition time msec/echo time msec/inversion time msec, 8500/120/2100; flip angle, 75°; phase acquisition matrix, 1 × 1 × 3 mm) and (b) three-dimensional T1-weighted (5.9/2.8/900; flip angle, 10°; acquisition matrix, 1 × 1 × 1 mm) sequences. Similarly, the 1.5-T sequences used 8000/120/2000 and 7.7/3.7/900 for the two-dimensional T2-weighted FLAIR and three-dimensional T1-weighted sequences, respectively.

Image analyses were performed in a blinded manner with respect to disease and clinical status of study participants. The T2 lesion volume was quantified (D.P.R., 15 years of

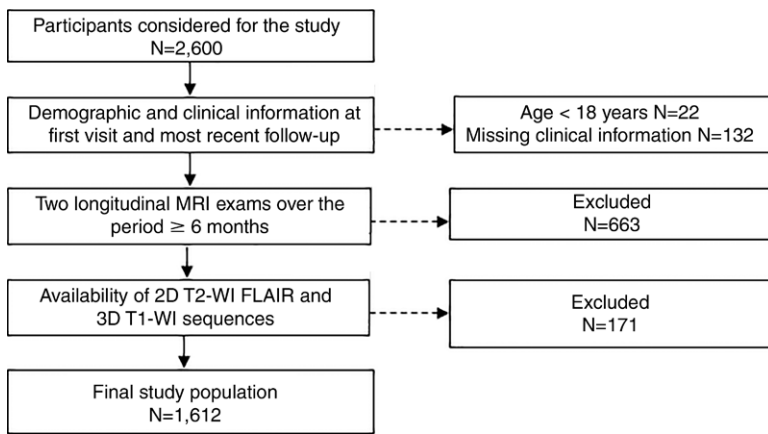


Figure 1: Flowchart shows participant selection criteria. FLAIR = fluid-attenuated inversion recovery, T1-WI = T1-weighted imaging, T2-WI = T2-weighted imaging, 3D = three-dimensional, 2D = two-dimensional.

experience) by using a reliable semiautomated edge-detection contouring and thresholding technique with the T2-weighted FLAIR sequence with Jim software (version 6.0; <http://www.xinapse.com>) (21). The normalized brain volume at the first MRI examination was obtained with the SIENAX method (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>) (22), whereas the percentage brain volume change (PBVC) over the follow-up period was computed with SIENA (FMRIB Software Library, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>) (22) for three-dimensional T1-weighted images that were modified by using an inpainting technique to avoid tissue misclassification (23). The ventricular volume at the first MRI examination and the percentage ventricular volume change (PVVC) over the follow-up MRI examinations were measured on three-dimensional T1-weighted images by using SIENAX (22) and VIENA (FMRIB Software Library, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>) (24), respectively.

To calculate atrophied T2 lesion volume, images were preprocessed with N4 (25) to remove spatially varying intensity inhomogeneities and were standardized by using a piecewise histogram matching technique (26) linearly aligned to the baseline space by using FLIRT software (FMRIB Software Library, <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>) (27). To calculate atrophied T2 lesion volume, rigidly aligned follow-up SIENA CSF maps were overlaid on baseline T2 lesion masks. Voxelwise follow-up CSF partial volume was then integrated over the baseline lesion regions (N.B., 15 years of experience) to determine total volume of periventricular and nonperiventricular lesion tissue subsequently replaced by CSF.

Statistical Analyses

All statistical analyses were performed by authors (A.V.G., J.H., D.J.) and the biostatistician using the Statistical Package for Social Science (version 24.0; IBM, Armonk, NY). For the purposes of demographic, clinical, and MRI overall comparisons, the 217 patients with SPMS and the 35 patients with primary progressive MS were categorized into one group with progressive MS. Patients were divided into two groups based on the presence or absence of disability progression (DP) dur-

ing follow-up. DP converters were classified as patients with an EDSS change of at least 1.5 if baseline EDSS was less than 1.0, those with an EDSS change of at least 1.0 if baseline EDSS was 1.0–5.5, and those with an EDSS change of at least 0.5 if baseline EDSS was 5.5 or higher, as previously reported (28). DP nonconverters were individuals who did not meet the criteria to be DP converters. Furthermore, on the basis of their conversion into SPMS disease phenotype (CIS and RRMS to SPMS), patients were classified as SPMS converters or SPMS nonconverters. We also investigated differences in MRI outcomes between clinically definite MS (CDMS) converters and nonconverters among patients with CIS.

To evaluate demographic and clinical differences, we used the Student *t* test, χ^2 test, and Mann-Whitney *U* test, as appropriate. Baseline and longitudinal percentage changes in MRI measures were analyzed by using analysis of covariance (ANCOVA), adjusted for age. Because there were significant differences in time of follow-up between DP, SPMS, and CDMS converters and nonconverters, all longitudinal MRI analyses were corrected for time to follow-up, and results are presented as actual and annualized values between the first MRI and the most recent follow-up MRI. The Cohen *d* effect size and 95% confidence interval (CI) are provided for the primary longitudinal outcomes in the ANCOVA analyses. To determine the association between the MRI-derived markers (T2 lesion volume, atrophied T2 lesion volume, PBVC, and PVVC) and the conversion to DP or SPMS, we used binary logistic regression models. The significance and rank of the aforementioned variables was determined with forward stepwise criteria. The odds ratio, Wald coefficient, and *P* values are reported, as appropriate.

To further determine the temporal associations between atrophied T2 lesion volume and occurrence of DP (event) versus stable (censored) disease or transition to SPMS status (event) versus stable (censored) disease, age- and sex-adjusted time-to-event Cox regression analysis was performed. Moreover, similar survival analysis was used to determine the temporal associations with transition to the SPMS phenotype. Analogous survival analyses were performed for PBVC and PVVC. The hazard ratio and *P* values are reported.

Results were considered significant at $P < .05$ using two-tailed tests.

Results

Demographic and Clinical Characteristics at Baseline and Follow-up Visits

Demographic and clinical data for the whole study sample are reported in Table 1. A total of 1612 participants were included in this study; of these, 1341 were patients with MS (1006 women; mean age, 45.7 years \pm 11.2 [standard deviation]), 124 were patients with CIS (100 women; mean age, 39 years \pm 10.5), and 147 were healthy control subjects (97 women; mean age, 41.6 years \pm 13). The cohort of 1341 pa-

Table 1: Demographic and Clinical Characteristics of Patients with MS, Patients with CIS, and Healthy Control Subjects

Demographic and Clinical Characteristics	Patients with MS (<i>n</i> = 1341)	Patients with CIS (<i>n</i> = 124)	Healthy Control Subjects (<i>n</i> = 147)	<i>P</i> Value for Patients with MS vs Patients with CIS vs Healthy Control Subjects	<i>P</i> Value for Healthy Control Subjects vs Patients with MS
No. of women*	1006 (75)	100 (81)	97 (66)	.016 [†]	.018 [†]
No. of men*	335 (25)	24 (19.4)	50 (34)	<.001 [†]	.076
Age of women at first MRI (y)	45.7 ± 11.2	39 ± 10.5	41.6 ± 13	<.001 [†]	.001 [†]
Age of men at first MRI (y)	45.7 ± 11.2	38.5 ± 10.1	37.7 ± 13.1	<.001 [†]	.081
Time of follow-up (y)	4.6 ± 2.5	3.7 ± 2.4	2.9 ± 2.2	<.001 [†]	<.001 [†]
Average no. of MRI examinations per year	1.3 ± 1.1	1.5 ± 1.1	2.2 ± 2.6	<.001 [†]	.062
Total no. of MRI examinations during follow-up	4.8 ± 2.9	3.8 ± 1.8	2.8 ± 1.1	<.001 [†]	<.001 [†]
Disease duration from onset to first MRI (y)	12.1 ± 9.8	2.9 ± 4.5	NA	<.001 [†]	NA
Disease subtype*					
RRMS	1089 (81.2)	NA	NA	NA	NA
SPMS	217 (16.2)	NA	NA	NA	NA
PPMS	35 (2.6)	NA	NA	NA	NA
EDSS score at first MRI [‡]	2.5 (1.5–4.0)	1.5 (1.0–2.0)	NA	<.001 [†]	NA
EDSS score change during follow-up	0.4 ± 1.0	0.1 ± 0.5	NA	<.001 [†]	NA
DP at follow-up*	325 (24.2)	11 (8.9)	NA	<.001 [†]	NA
Conversion to CDMS at follow-up*	NA	35 (28.2)	NA	NA	NA
Conversion to SPMS over follow-up*	66 (4.9)	1 (0.8)	NA	NA	NA

Note.—Unless otherwise indicated, data are mean ± standard deviation. *P* values were derived with the χ^2 test, Student *t* test, or Mann-Whitney *U* test, as appropriate. CDMS = clinically definite MS, CIS = clinical isolated syndrome, DP = disease progression, EDSS = Expanded Disability Status Scale, MS = multiple sclerosis, NA = *P* value could not be obtained due to the healthy status of the control subject, PPMS = primary progressive MS, RRMS = relapsing-remitting MS, SPMS = secondary progressive MS.

* Data are numbers of participants, and data in parentheses are percentages.

[†] *P* value indicates a significant difference.

[‡] Data are median and interquartile range.

tients with MS included 1089 patients with RRMS (81.2%), 217 with SPMS (16.2%), and 35 with primary progressive MS (2.6%). As expected, differences were found between patients with MS and those with CIS in EDSS scores at baseline ($P < .001$) and the most recent follow-up ($P < .001$). The patients with MS and healthy control subjects were not matched by age or sex (Table 1).

Over the course of follow-up, of the 1465 patients with MS or CIS, 336 (22.9%) developed DP (246 had RRMS; 66, SPMS; 13, primary progressive MS; and 11, CIS), and 67 (4.6%) converted from RRMS ($n = 66$) or CIS ($n = 1$) to SPMS. Of the 124 patients with CIS, 35 (28.2%) converted to CDMS over the follow-up period. The median time to disability progression was 35.7 months (interquartile range, 18.2–59.9 months), and the median time for conversion from CIS or RRMS to SPMS was 31.1 months (interquartile range, 13.4–50.8 months).

MRI Characteristics at Baseline and Follow-up Visits

The baseline and follow-up MRI characteristics of the study participants are shown in Table 2.

T2 lesion volume ($P < .001$), as well as cumulative atrophied T2 lesion volume ($P < .001$), PVVC ($P < .001$), and

PBVC ($P < .001$) were different between healthy control subjects and patients with MS or CIS. The annualized change of T2 lesion volume over follow-up was numerically but not statistically ($P = .27$) different among the groups. The lowest annualized atrophied T2 lesion volume was observed in healthy control subjects (mean, 5.4 mm³ ± 10.8), followed by patients with CIS (mean, 16.7 mm³ ± 34.7) and patients with MS (mean, 71.3 mm³ ± 140.4) (Table 2, $P < .001$) (Fig 2).

Comparison between patients with RRMS and those with progressive MS showed substantial differences in baseline T2 lesion volume ($P < .001$), while annualized change in T2 lesion volume was not different over the course of follow-up ($P = .35$). Patients with progressive MS accumulated a greater amount of annualized atrophied T2 lesion volume over the course of follow-up (111.11 mm³) as compared with those with RRMS (62 mm³) ($P = .001$) (Fig 2). At post hoc analysis, there was no difference in the rate of annualized atrophied T2 lesion volume between patients with SPMS and those with primary progressive MS (115.1 mm³ vs 86.6 mm³, $P = .32$). At baseline, the normalized brain volume was lower ($P < .001$) and ventricular volume was higher ($P < .001$) in patients with progressive MS than in patients with RRMS. However, there were no differences

Table 2: MRI Outcomes of Patients with MS, Patients with CIS, and Healthy Control Subjects

Measure	Healthy Control Subjects (<i>n</i> = 147)	Patients with CIS (<i>n</i> = 124)	Patients with MS (<i>n</i> = 1341)	Patients with RRMS (<i>n</i> = 1089)	Patients with Progressive MS (<i>n</i> = 252)	<i>P</i> Value for Healthy Control Subjects vs Patients with CIS versus Patients with MS	<i>P</i> Value for RRMS vs Patients with Progressive MS
Lesion volume brain measures							
Baseline T2 lesion volume (mm ³)	2404.7 ± 3090.7	5417.3 ± 5608.1	14242.3 ± 13620.6	12772.9 ± 12244.1	20592.2 ± 17051.2	<.001*	<.001*
Absolute change in T2 lesion volume over follow-up (mm ³)	34.5 ± 2509.7	167.9 ± 1668.1	685.2 ± 4913.5	702.9 ± 4415.1	609.5 ± 6654.1	.24	.62
Annualized change in T2 lesion volume over follow-up (mm ³)	-0.2 ± 1082.1	-33.4 ± 727.8	183.9 ± 1996.3	177.5 ± 1754.2	21.1 ± 2813.2	.27	.35
Cumulative atrophied T2 lesion volume over follow-up (mm ³)	13.1 ± 37	49.9 ± 101.6	315.5 ± 659.9	285.2 ± 639.9	446.5 ± 727.3	<.001*	.011*
Annualized cumulative atrophied T2 lesion volume over follow-up (mm ³)	5.4 ± 10.8	16.7 ± 34.7	71.3 ± 140.4	62 ± 129.5	111.1 ± 174.4	<.001*	.001*
Brain volume measures							
Baseline ventricular volume (cm ³)	31.8 ± 13.4	33.1 ± 12.6	44.9 ± 19.9	42.2 ± 17.9	56.5 ± 23.9	<.001*	<.001*
PVVC over follow-up (cm ³)	6.1 ± 10.8	7.1 ± 10.2	14.5 ± 26.7	14.3 ± 27.4	15.6 ± 24.2	<.001*	.053
Annualized PVVC over follow-up (cm ³)	1.2 ± 4.5	1.9 ± 6.3	3.7 ± 9.3	3.6 ± 9.9	3.7 ± 5.3	.016*	.22
Baseline NBV (cm ³)	1600.2 ± 84.3	1591.3 ± 78.1	1534.3 ± 112.6	1550.1 ± 97.9	1465.6 ± 14.2	<.001*	<.001*
PBVC over follow-up (cm ³)	-1.3 ± 1.9	-2.1 ± 2.2	-3.4 ± 2.8	-3.4 ± 2.8	-3.5 ± 2.6	<.001*	.69
Annualized PBVC over follow-up (cm ³)	-0.3 ± 0.9	-0.6 ± 0.9	-0.9 ± 1.04	-0.8 ± 1.1	-0.9 ± 0.9	<.001	.93

Note.—Unless otherwise indicated, data are mean ± standard deviation. All *P* values are corrected for age and time to follow-up; between-group *P* values are derived from analysis of covariance. CIS = clinically isolated syndrome, MS = multiple sclerosis, NBV = normalized brain volume, PBVC = percentage brain volume change, PVVC = percentage ventricular volume change, RRMS = relapsing-remitting MS.

* *P* value indicates a significant difference.

between the two groups in annualized PVVC (*P* = .22) or PBVC (*P* = .93) over the course of follow-up.

Clinical and MRI Differences between DP Converters and Nonconverters

Table 3 provides demographic, clinical, and MRI characteristics of DP converters and nonconverters. The mean follow-up time was longer for DP converters than for nonconverters (*P* = .001). DP converters were older (*P* = .002) and had longer disease duration at first MRI (*P* < .001) when compared with nonconverters.

At first MRI, DP converters had greater T2 lesion volume than did nonconverters (*P* < .001). Over the follow-up period, the DP converters had greater annualized atrophied T2 lesion volume (+34.4 mm³; 95% CI: 17.2 mm³, 51.5 mm³;

d = 0.27; *P* < .001) but did not have annualized change in T2 lesion volume (-64.5 mm³; 95% CI: -315.2 mm³, 186.3 mm³; *d* = 0.03; *P* = .67). In terms of brain volume changes, the DP converters had greater annualized PBVC (-0.21%; 95% CI: -0.36%, -0.05%; *d* = 0.19; *P* = .042) but did not have greater annualized PVVC (0.36%; 95% CI: -0.93%, 1.65%; *d* = 0.04; *P* = .89).

In individual logistic regression analysis, an increase of 1 mL in annualized atrophied T2 lesion volume was associated with five times higher odds of having DP (odds ratio = 5.04, Wald coefficient = 13.61, *P* < .001), whereas an additional 1% of annualized PBVC was associated with 21.3% higher odds of having DP (odds ratio = 0.78, Wald coefficient = 10.89, *P* = .001). Furthermore, in a stepwise forward analysis including all the significant MRI outcomes, both increase in annualized

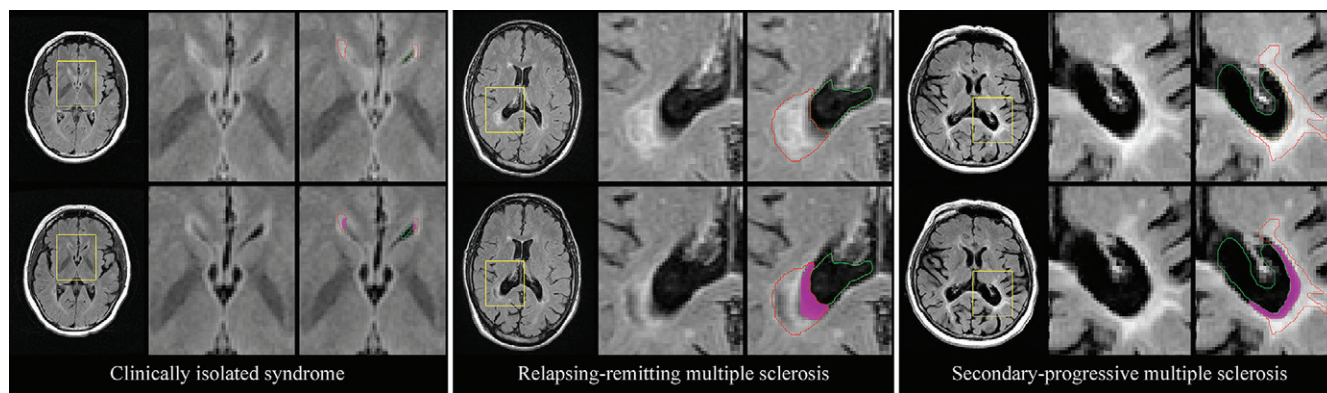


Figure 2: Representative examples of atrophied T2 lesion volume in patients with clinically isolated syndrome, relapsing-remitting multiple sclerosis, and secondary progressive multiple sclerosis. Top row: Baseline images for each case. Left: Axial T2-weighted fluid-attenuated inversion recovery image. Yellow \square indicates the area of interest. Middle: Zoomed-in view of the corresponding area. Right: Outlines of the ventricle (green) and lesion volume (red). Bottom row: Corresponding follow-up images for each case, with the baseline ventricle and lesion volume outlines overlaid on top. The magenta area corresponds to cerebrospinal fluid that was lesioned tissue at baseline (atrophied T2 lesion volume).

Table 3: Demographic, Clinical, and MRI Characteristics for DP Converters versus DP Nonconverters

Demographic and Clinical Variable	DP Converters ($n = 336$)	DP Nonconverters ($n = 1129$)	P Value
No. of women*	260 (77.4)	846 (74.9)	.17
Age at first MRI (y)	47.6 \pm 10	44.3 \pm 11.3	.002 [†]
Disease duration at first MRI	13.1 \pm 10	10.65 \pm 9.4	<.001 [†]
Time over follow-up (y)	5.4 \pm 2.3	4.3 \pm 2.6	.001 [†]
Average no. of MRI examinations per year over follow-up	1.2 \pm 0.8	1.4 \pm 1.3	<.001 [†]
Total no. of MRI examinations over follow-up	5.5 \pm 3.1	4.5 \pm 2.7	.015 [†]
Disease course at first MRI*			
CIS	11 (3.3)	113 (10.0)	<.001 [†]
RRMS	246 (73.2)	843 (74.6)	.83
SPMS	66 (19.6)	151 (13.4)	.015 [†]
PPMS	13 (3.9)	22 (1.9)	.049 [†]
EDSS score at first MRI [‡]	3.0 (2.0–5.0)	2.5 (1.5–4.0)	.002 [†]
EDSS score change over follow-up	1.8 \pm 1.1	–0.1 \pm 0.7	NA
Lesion volume measures			
Baseline T2 lesion volume	16708.3 \pm 15325	12715 \pm 12706.5	.001 [†]
Absolute change in T2 lesion volume over follow-up (mm ³)	776.8 \pm 4998	608.3 \pm 4446.9	.64
Annualized change in T2 lesion volume over follow-up (mm ³)	134.4 \pm 1186.4	198.8 \pm 2226.7	.67
Cumulative atrophied T2 lesion volume over follow-up (mm ³)	495.2 \pm 969.8	230.4 \pm 472.7	<.001 [†]
Annualized cumulative atrophied T2 lesion volume over follow-up (mm ³)	93.4 \pm 176.4	59 \pm 118.5	<.001 [†]
Brain volume measures			
Baseline ventricular volume (cm ³)	47.1 \pm 19.3	43.2 \pm 19.7	.12
PVVC over the follow-up (cm ³)	17.9 \pm 21.8	12.3 \pm 28.6	.009 [†]
Annualized PVVC over follow-up (cm ³)	3.7 \pm 5.4	3.4 \pm 10.8	.89
Baseline NBV (cm ³)	1523.3 \pm 1042.2	1542.8 \pm 9918	.23
PBVC over follow-up (cm ³)	–4.5 \pm 2.9	–2.8 \pm 2.6	<.001 [†]
Annualized PBVC over follow-up (cm ³)	–0.9 \pm 0.9	–0.7 \pm 1	.042 [†]

Note.—Unless otherwise indicated, data are mean \pm standard deviation. P values represent DP converters versus DP nonconverters and were derived using the χ^2 test, Student t test, and Mann-Whitney U test, as appropriate. For MRI measurements, all P values were corrected for age and time to follow-up; between-group P values were derived with analysis of covariance. NA indicates P values are not applicable, as classification of patients into DP converters and nonconverters was defined by EDSS score change. CIS = clinically isolated syndrome, DP = disability progression, EDSS = Expanded Disability Status Scale, NBV = normalized brain volume, PBVC = percentage brain volume change, PPMS = primary progressive multiple sclerosis, PVVC = percentage ventricular volume change, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

* Data are numbers of participants, and data in parentheses are percentages.

[†] P value indicates a significant difference.

[‡] Data are median and interquartile range.

atrophied T2 lesion volume (odds ratio = 4.63, Wald coefficient = 10.16, $P = .001$) and increase in annualized PBVC (odds ratio = 0.89, Wald coefficient = 7.43, $P = .006$) remained associated with the presence of DP status.

These findings were further corroborated in the time-to-event Cox regression analyses. For every 1 mL of additional atrophied T2 lesion volume, there was a 22.8% higher chance of DP event occurrence (hazard ratio = 1.23, $P < .001$). Neither PBVC nor PVVC enabled prediction of a DP transition event in the respective survival analyses.

Clinical and MRI Differences between SPMS Converters and Nonconverters

Further analysis was performed among patients with MS who changed disease course from CIS or RRMS to SPMS. These clinical, demographic, and imaging data are shown in Table 4.

SPMS converters were followed up for a longer time than were nonconverters ($P < .001$), they were older ($P < .001$), and they had longer disease duration at first MRI ($P < .001$). Both at first MRI and at the most recent follow-up MRI, converters had higher EDSS scores ($P < .001$) than did nonconverters.

Over the follow-up period, SPMS converters had greater annualized atrophied T2 lesion volume than did nonconverters (+26.4 mm³; 95% CI: 4.2 mm³, 56.9 mm³; $d = 0.23$, $P = .002$) (Fig 3). There was no difference in annualized change of T2 lesion volume (−46.4 mm³; 95% CI: −460.8 mm³, 367.9 mm³; $d = 0.03$; $P = .93$). SPMS converters had higher ventricular volume ($P = .001$) and lower normalized brain volume ($P = .012$) at first MRI than did nonconverters. However, there were no differences in annualized PBVC (−0.14%; 95% CI: −0.46%, 0.18%; $d = 0.11$; $P = .66$) or PVVC (+0.18%; 95% CI: −2.49%, 2.72%; $d = 0.01$; $P = .75$) over the follow-up period between the two groups.

Similar to the DP individual regression analyses, an increase of 1 mL in annualized atrophied T2 lesion volume was associated with a 4.7-fold higher chance to convert into the SPMS phenotype (odds ratio = 4.73, Wald coefficient = 4.17, $P = .04$). In a forward stepwise model of all MRI measures, only an increase in annualized atrophied T2 lesion volume was a significant predictor of SPMS conversion status (odds ratio = 4.87, Wald coefficient = 4.33, $P = .04$).

At Cox regression analysis, for every 1 mL of additional atrophied T2 lesion volume, there was a 16.3% greater chance of patients with MS transitioning from CIS or RRMS into SPMS (hazard ratio = 1.16, $P = .008$). Neither PBVC nor PVVC enabled us to predict the occurrence of an SPMS transition event in the respective survival analyses.

Clinical and MRI Differences between CDMS Converters and Nonconverters

The clinical, demographic, and imaging data of CDMS converters and nonconverters are shown in Table E2 (online). CDMS converters were observed for a longer time ($P = .001$) and had longer disease duration at first MRI ($P = .045$) when compared with nonconverters. They had greater EDSS score change over the follow-up period ($P = .04$). No MRI differ-

ences at first MRI or during follow-up were detected between CDMS converters and nonconverters.

Discussion

Atrophied T2 lesion volume may aid in predicting the timing of multiple sclerosis (MS) disease progression. Atrophied T2 lesion volume reflects the number of lesions being replaced by cerebrospinal fluid (CSF) spaces as a result of atrophy or direct lesion destruction. In this study, we aimed to investigate the behavior of atrophied T2 lesion volume accumulation in a large cohort of patients with MS during long-term routine clinical 5-year follow-up. This study corroborates the findings of initial reports regarding the utility of atrophied T2 lesion volume as a potential MRI-derived marker of disease progression in a large population-based cohort of patients with MS over the course of routine clinical follow-up. Together with whole-brain atrophy ($d = 0.19$, $P = .042$), atrophied T2 lesion volume ($d = 0.27$, $P < .001$) enabled us to predict development of disability progression (DP) over 5 years of follow-up. Furthermore, unlike percentage brain volume change (PBVC) ($d = 0.11$, $P = .66$) and percentage ventricular volume change (PVVC) ($d = 0.01$, $P = .89$), neither of which showed predictive power, atrophied T2 lesion volume ($d = 0.23$, $P = .002$) was the only MRI measure in the study that was related to conversion of clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS) into secondary progressive MS (SPMS). In contrast, atrophied T2 lesion volume did not enable prediction of conversion from CIS to clinically definite MS, enabling us to confirm that the processes leading to accumulation of atrophied T2 lesion volume occur later in the disease.

Atrophied T2 lesion volume represents the end stage of active inflammation (lesion accrual) and neurodegeneration (brain volume destruction). Because atrophied T2 lesion volume reflects more than one aspect in the heterogeneous pathologic process of MS, it may provide complementary information to explain changes leading to DP and conversion to SPMS beyond individual lesion and brain volume-related MRI outcomes. This hypothesis is supported by two recent studies that investigated whether atrophied T2 lesion volume explains additional independent variance in the prediction of DP (13,15). Thus, the current study extends previous findings from smaller samples of patients with MS.

Many different criteria have been proposed to distinguish between RRMS and SPMS disease courses, but a clear consensus remains elusive (19,29). Imaging and biologic markers may provide more objective criteria to separate these clinical phenotypes than clinical observation alone (19). In a recent study (15), atrophied T2 lesion volume was associated with the development of 10-year confirmed DP for almost all serial time points. This was not the case for whole-brain, cortical, or central atrophy, making atrophied T2 lesion volume a potentially more attractive MRI outcome for clinical monitoring on a year-to-year clinical routine basis in comparison with development of brain atrophy or lesion accrual. The same study showed that atrophied T2 lesion volume is an early predictor of DP, as it took only 6 months to show an association with the development of DP, whereas it took

Table 4: Demographic, Clinical, and MRI Characteristics of SPMS Converters versus SPMS Nonconverters in Patients with RRMS or CIS

Demographic and Clinical Variables	SPMS Converters (<i>n</i> = 67)	SPMS Nonconverters (<i>n</i> = 1146)	<i>P</i> Value
No. of women*	50 (74.6)	875 (76.3)	.74
Age at first MRI (y)	49.8 ± 7.9	42.9 ± 10.8	.001 [†]
Disease duration over follow-up	14.5 ± 10.7	9.5 ± 8.6	<.001 [†]
Time over follow-up (y)	6.2 ± 2.7	4.8 ± 2.8	<.001 [†]
Average no. of MRI examinations per year over follow-up	1.1 ± 0.5	1.4 ± 1.2	.12
Total no. of MRI examinations over follow-up	6.1 ± 2.7	4.8 ± 2.8	<.001 [†]
EDSS score at first MRI [‡]	4.0 (2.5–6.0)	2.0 (1.5–3.0)	<.001 [†]
EDSS score change over follow-up [‡]	1.5 (0.5–2.5)	0.0 (0.0–1.0)	<.001 [†]
Lesion volume brain measures			
Baseline T2 lesion volume (mm ³)	16468.1 ± 14273.6	11171.0 ± 11752.6	.024 [†]
Absolute change T2 lesion volume from first to most recent follow-up MRI (mm ³)	1163.0 ± 4055.4	618.0 ± 4229.6	.32
Annualized change in T2 lesion volume (mm ³)	112.7 ± 695.1	158.6 ± 1720.1	.93
Cumulative atrophied T2 lesion volume over the follow-up (mm ³)	476.3 ± 692.6	248.6 ± 604.2	<.001 [†]
Annualized cumulative atrophied T2 lesion volume over the follow-up (mm ³)	82.3 ± 103.1	55.9 ± 125.0	.002 [†]
Brain volume measures			
Baseline ventricular volume (cm ³)	53.9 ± 19.1	41 ± 17.3	<.001 [†]
PVVC over follow-up (cm ³)	19.1 ± 24.9	13.2 ± 26.2	.22
Annualized PVVC over follow-up (cm ³)	3.5 ± 4.9	3.4 ± 9.8	.75
Baseline NBV (cm ³)	1502.9 ± 1009.7	1557.2 ± 959.4	.011 [†]
PBVC over follow-up (cm ³)	−5.3 ± 2.8	−3.1 ± 2.7	<.001 [†]
Annualized PBVC over follow-up (cm ³)	−0.9 ± 0.6	−0.8 ± 1.1	.66

Note.—Unless otherwise indicated, data are mean ± standard deviation. *P* values represent secondary progressive multiple sclerosis (SPMS) converters versus SPMS nonconverters and were derived by using the χ^2 test, Student *t* test, or Mann-Whitney *U* test, as appropriate. For MRI measurements, all *P* values were corrected for age and time to follow-up; between-group *P* values were derived with analysis of covariance. CIS = clinically isolated syndrome, EDSS = Expanded Disability Status Scale, NBV = normalized brain volume, PBVC = percentage brain volume change, PVVC = percentage ventricular volume change, RRMS = relapsing-remitting multiple sclerosis.

* Data are numbers of participants, and data in parentheses are percentages.

[†] *P* value indicates a significant difference.

[‡] Data are median and interquartile range.

2 years for whole-brain atrophy to show a comparable effect. Furthermore, atrophied T2 lesion volume accumulation accelerated from year 5 to year 10 of the follow-up period, whereas accumulation of total T2 lesion volume decelerated over the same period, suggesting that this MRI outcome could be of particular interest in monitoring the transition from RRMS to SPMS.

Lesion burden is the result of different processes, including demyelination with new lesion accrual, remyelination and repair, and neuroaxonal degeneration (16,30,31). Our results suggest that replacement of the lesions by CSF could be responsible for the decrease in lesion accumulation over time and could partially explain the plateau of T2 lesion volume (17) followed by an ultimate decrease in T2 lesion volume in the advanced stage of the disease (14).

Recent studies have shown a gradient of neuroinflammatory and neurodegenerative disease that is highest in areas close to ventricles and in proximity to CSF spaces (32,33). The presence of diffusible molecules in the CSF may explain greater neuroinflammation and neurodegeneration in periventricular areas. Locally secreted proinflammatory cytokines derived from meningeal and CSF compartments harbor B

cells that reside within the CSF space, promoting greater regional disease (1,34). CSF-based ceramides have been shown to impair neuronal mitochondrial dysfunction and autophagy balance, leading to neuronal loss (35–37). Moreover, in patients with MS, atrophied T2 lesion volume may be partially a substrate of cardiovascular influence on the MS repair processes. Greater accumulation of destructive lesions has been shown in watershed regions, which are at greater risk of hypoperfusion. As the repair mechanisms involved in the lesions around the ventricles require a greater perfusion rate, the failure of such would lead to formation of T1 hypointensities and complete dissolution into CSF. A recent study found greater central brain atrophy (increase in ventricular volume) in patients with cardiovascular comorbidities, which might be directly linked to greater atrophied T2 lesion volume (38). Related to this finding, our study was the first to include healthy control subjects. A minimal amount of atrophied T2 lesion volume was found in these study participants as well. This may be explained by the presence and evolution of white matter hyperintensities and periventricular bands in conjunction with age-related ventricular enlargement. The

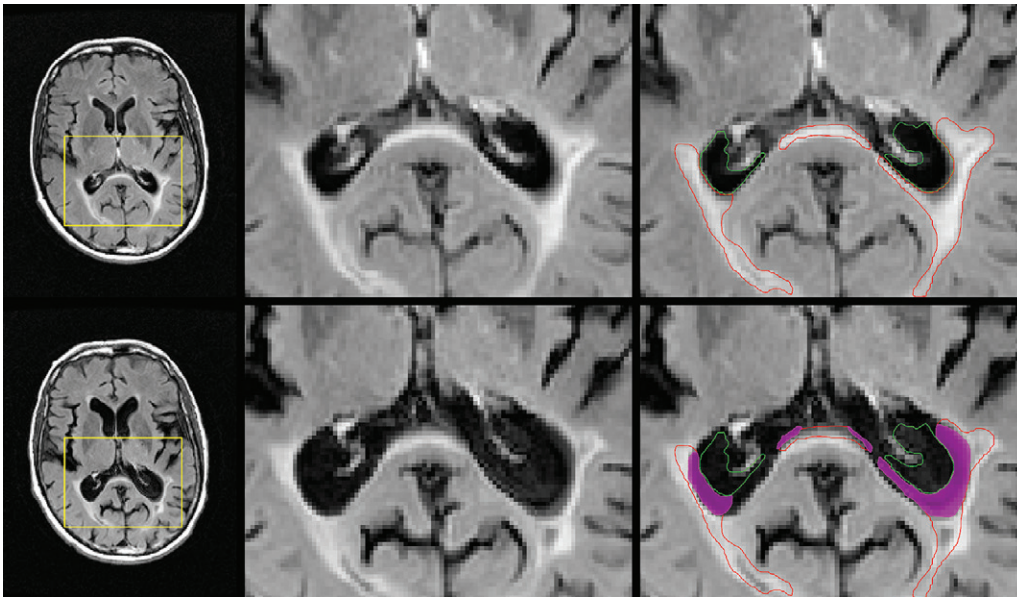


Figure 3: Representative images of atrophied T2 lesion volume in a patient whose disease converted to secondary progressive multiple sclerosis over the course of follow-up. Top row: Baseline images. Left: Axial T2-weighted fluid-attenuated inversion recovery image. Yellow \square indicates the area of interest. Middle: Zoomed-in view of the corresponding area. Right: Outlines of the ventricle (green) and lesion volume (red). Bottom row: Corresponding follow-up images for each case, with the baseline ventricle and lesion volume outlines overlaid on top. The magenta area corresponds to cerebrospinal fluid that was lesioned tissue at baseline (atrophied T2 lesion volume).

investigation of atrophied T2 lesion volume in relation to cerebrovascular disease may be the subject of future studies.

Our study had limitations that must be considered. We did not investigate the spatial predilection of lesion accumulation and atrophy development. However, it has been previously observed that atrophied lesions are mostly located in periventricular areas and at cortical gyri borders (13,15). We also did not investigate the proportion of atrophied T2 lesion volume that was represented by T1 black hole lesions, which are usually characterized by a higher rate of tissue destruction (39,40). Further studies using advanced MRI techniques are needed to explore the underlying mechanism leading to the accumulation of atrophied T2 lesion volume. Another important limitation of the method described is that it cannot be used to distinguish between different causes for tissue motion, such as harmful mechanisms like axonal loss and potentially benign mechanisms like reduction in edema. Although it is unlikely that any current MRI technique could enable one to fully disentangle these contributors, more sophisticated methods, such as Jacobian determinant mapping, might at least enable one to better distinguish edge motion from true atrophy and could be an important avenue of future research. Related to this point, the approach does not currently distinguish between lesions that have been truly subsumed into the CSF and those that have been displaced by ventricular expansion but not fully destroyed. More advanced methods may aid in unraveling whether these two phenomena are equally indicative of clinical disability.

In conclusion, in this large population-based cohort study, we showed that atrophied brain T2 lesion volume represents a viable predictive MRI marker of the development of disability

progression and conversion to secondary progressive multiple sclerosis disease course.

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