Enhancing Magnetic Resonance Imaging Lesions and Cerebral Atrophy in Patients With Relapsing Multiple Sclerosis

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Objective: To examine the relation between the frequency of enhancing magnetic resonance imaging lesions and their characteristics of enhancement and atrophy in patients with early relapsing multiple sclerosis.

Design: Analysis of number of enhancing lesions, ventricular volumes and diameters, and lesion characteristics on monthly magnetic resonance imaging scans during natural history follow-up.

Setting: A clinical research institution.

Patients: Sixteen patients with confirmed early relapsing multiple sclerosis.

Main Outcome Measure: Cerebral atrophy as measured by ventricular enlargement.

Results: Numbers of enhancing lesions correlated well with an increase of ventricular size. This correlation was strongest for patients with a high proportion of concentric ring–enhancing lesions with central contrast pallor. Patients with a high proportion of lesions with central contrast pallor, which is likely associated with more extensive tissue damage, have a higher rate of atrophic changes.

Conclusions: Inflammatory events, especially those within lesions with associated blood-brain barrier breakdown, affect the ensuing loss of brain parenchyma. Patients with a high proportion of lesions with central contrast pallor, which is likely associated with more extensive tissue damage, have a higher rate of atrophic changes.

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Patients with multiple sclerosis exhibit a varying degree of cerebral atrophy. Little is known about the underlying mechanisms and individual disease characteristics that affect the rate at which brain parenchyma decreases. Loss of neurons, oligodendrocytes, the formation of glial scars, and the effects of therapeutics, such as corticosteroids, may contribute to reduction of brain matter and atrophy. Magnetic resonance imaging (MRI) has had a major impact on the understanding and management of multiple sclerosis. Blood-brain barrier breakdown is a consistent early feature of new lesion development in patients with relapsing and secondary progressive multiple sclerosis, which usually correlates with active inflammation and myelin breakdown. On the MRI scan, these lesions are visualized by T1-weighted, contrast-enhanced images. Characteristics of enhancing lesions vary greatly, with individual patients often having predominant types regarding size, location, or ring enhancement. T2-weighted brain imaging remains the standard diagnostic tool; however, it is limited by poor pathological specificity.

To assess the impact of ongoing disease activity on atrophy development, we correlated the increase of ventricular volume and diameter with the cumulative number of contrast-enhancing lesions and their characteristics on serial monthly MRI scans. In contrast to the spinal cord, most supratentorial lesions do not affect primary efferent pathways. Their effects on neurologic function may be, therefore, less readily assessable. Disability as a function of ventricular enlargement or cumulative lesion count was, therefore, not a primary objective of this study. Contrast enhancement is a transient feature of some acute lesions. In general, lesions do not remain enhancing for more than 2 to 4 weeks and the volume of enhancement varies with time after the onset of blood-brain barrier breakdown. Since MRI scans were performed monthly, we elected to account for the number and the characteristics of the lesions rather than the volume of enhancement.

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PATIENTS AND METHODS

Patients were enrolled in clinical research protocols approved by the Institutional Review Board; provided signed and informed consent; and were followed up monthly in the Neuroimmunology Clinic, National Institute of Neurological Disorders and Stroke, Bethesda, Md. Sixteen patients were identified according to the following inclusion criteria: (1) relapsing remitting course of disease; (2) a diagnosis within 2 years of the first scan; (3) at least 2 gadolinium-enhancing lesions during the first 3 monthly MRI scans; (4) a natural history follow-up of at least 16 months (mean±SD, 23.0±11.7 months); and (5) no treatment with immunomodulatory medication other than methylprednisolone sodium succinate, 1 g/d given intravenously for 3 to 5 days, for acute exacerbations. Five individuals did not have clinically significant exacerbations during the study period. The remaining patients had between 1 and 3 attacks per year requiring treatment with corticosteroids (Figure 2). The mean±SD age of the cohort (9 women and 7 men) at the time of diagnosis was 29.7±6.4 years. Four normal volunteers (2 women and 2 men [mean±SD age, 34.7±10.9 years]) were followed up for up to 5 years (mean±SD follow-up, 3.8±3.2 years) with unenhanced MRI scans.

Magnetic resonance imaging was performed on a 1.5-T MRI unit (General Electric, Milwaukee, Wis) with a quadrature head coil. Unenhanced and gadopentate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ), 0.1 mmol/kg, enhanced T1-weighted sequences were analyzed (echo time, 20 ms; and repetition time, 600 ms) for this study. Reproducible head positioning was attempted by application of vitamin E–containing capsules in the external acoustic meatus and over the lateral canthus of the orbit. Depending on when enrolled, patients and volunteers underwent imaging with either a 5-mm (n=9) or a 3-mm (n=7) slice thickness. Measurement of third ventricular width and the diameter of the lateral ventricles was performed on all scans. Images with 3-mm section thicknesses were evaluated with computer analysis of ventricular volume after 3-dimensional reconstruction and with linear measurements to cross validate the 2 methods.

Reconstruction and coregistration of scans with 3-mm section thicknesses were performed with image processing software (MEDx; Sensor Systems Inc, Sterling, Va). A graded caliper with a 0.1-mm scale was used for linear measurements on film copies. The predominant head position on monthly scans was identified, and scans with nonconforming head positions were not included in the analysis. Third ventricular width was determined, and diameters of the left and right lateral ventricles were measured at the level of the interventricular foramen. The percentage of ventricular enlargement was calculated with equal weighing of measurements for the third ventricle and the mean of the lateral ventricles as follows: percentage of ventricular enlargement = [(V1/Vt1) + (Vr/Vt2) + (Vl/Vt2)] × 0.5] × 100 – 100, with Vt being the measurement for the third ventricle; V1, month of study; 0, baseline; and Vr and Vl, the width of the right and left lateral ventricles at the level of the interventricular foramen, respectively.

Linear regression of the values obtained for linear and volume measurements yielded R²=0.84 and P=.000. Good correlation between the 2 measures could also be seen for longitudinal data in 4 individuals (Figure 3).

For regression analysis, the t test, and nonparametric analysis, statistical software (StatView 4.5, Macintosh version; SAS Institute Inc, Cary, NC) was used.

Characteristics of enhancing lesions were analyzed on the initial MRI scans. Enhancing lesions on at least 3 monthly MRI scans (a minimum of 23 consecutive lesions) were studied. Patients were grouped according to the percentage of concentric ring–enhancing lesions exhibiting central contrast pallor.

The cumulative number of enhancing lesions and enlargement of the ventricles were compared longitudinally based on the mean monthly changes between patients (Figure 2) and among individual patients (Figure 3). To elucidate an association between the number of enhancing lesions and atrophy, the numbers of mean monthly lesions and mean monthly changes in ventricular measures were studied. A correlation analysis was performed on data from a natural history follow-up of at least 16 months (Figure 2) (linear regression, R²=0.65, P=.007). The correlation between enhancing lesions and atrophy was also maintained when patients were stratified according to corticosteroid use.

Because of differences in size, a low percentage loss of brain volume may be leveraged into a large percentage increase of ventricular and other fluid-filled spaces. For 2 patients (patients 1 and 2) (Figure 3), fractional brain volumes were available and were compared with ventricular changes. These 2 patients had reductions of 1.7% and 1.9% of the fractional brain volumes per year, respectively. When expressed based on the nonparenchymal volume, the total fluid-filled volume increased by 1.1% and 1.3% per months during the study period, respectively.

Lesion characteristics vary between patients, with some individuals exhibiting more concentric ring–enhancing lesions with central contrast pallor. These latter areas are thought to arise in zones of fulminate tissue destruction or glial scars. Seven of the 16 patients in the study cohort had greater than 1 in 7 lesions with central pallor. In the other 9 individuals, less than 1 in 10 lesions had this characteristic. Patients with high num-
bers of lesions with central contrast pallor had the strongest correlation between atrophy and cumulative lesion load (Figure 3). The presence of concentric ring-enhancing lesions with central pallor in itself strongly correlated with ensuing ventricular enlargement and loss of brain parenchyma (Figure 4). However, this group of patients had received the most corticosteroid treatments (Figure 2).

**COMMENT**

Focal inflammatory events leading to demyelination and repair are hallmark characteristics of multiple sclerosis. Serial MRI studies have added much to our understand-

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**Figure 2.** Correlation of mean ventricular diameter increase per month with mean monthly gadolinium-enhancing lesions on monthly magnetic resonance imaging scans. The mean monthly number of new lesions was calculated by dividing the cumulative number of new monthly lesions by the length of follow-up. The mean monthly increase of ventricular diameter was calculated as the difference between the mean diameter measured on the last 3 scans and the mean diameter measured on the first 3 scans, divided by the length of follow-up. Shaded symbols indicate values for patients with a high percentage of concentric ring-enhancing lesions; and unshaded symbols, values for patients with a low percentage of concentric ring-enhancing lesions. Patients had 0 (squares), 1 (diamonds), 2 (triangles), or 3 (circles) courses of methylprednisolone sodium succinate per year during follow-up. The shaded left-pointing triangles indicate normal volunteers. A correlation analysis was performed (linear regression, $R^2=0.65$ [95% confidence interval, 0.20-0.87], $z=2.68$, $P=.007$).

**Figure 3.** Correlation of ventricular volume and diameter increase with cumulative number of new contrast-enhancing lesions (found by magnetic resonance imaging [MRI]) on monthly scans for 4 patients (A, patient 1; B, patient 2; C, patient 3; and D, patient 4). Upper panel, Correlation of ventricular volumes calculated on coregistered MRI scans with a slice thickness of 3 mm, as described in the “Patients and Methods” section (shaded squares), with cumulative number of new enhancing lesions (unshaded squares) on monthly MRI scans. Lower panel, Correlation between measurements for ventricular diameters (percentage enlargement [caliper]) and volumes (percentage enlargement coregistration).

**Figure 4.** Comparison of atrophy in patients with a low ($\leq 15\%$) or a high ($> 15\%$) proportion of concentric ring-enhancing lesions with central pallor. The 2 groups were significantly ($P = .004$) different. Shaded diamonds indicate mean of measurements; unshaded diamonds, individual measurements.
ing of the natural history and pathophysiological features of this disease. Many short-term MRI changes are readily reversible, but several MRI variables, such as a reduced N-acetylaspartate level, low magnetization transfer ratios, and T1 hypointensity, are more persistent. To gain further insight into whether short-term inflammatory events lead to irreversible damage and associated loss of brain parenchyma, we studied the correlation between atrophy, cumulative number, and the characteristics of gadolinium-enhancing lesions. To control for the variability of atrophy rate as a function of disease duration, only patients with a long-term natural history of MRI follow-up, starting within 2 years of the clinical diagnosis, were included in this analysis. Ventricular enlargement was assessed using image processing software or measurement of ventricular diameters.

In patients with ongoing inflammatory activity and blood-brain barrier breakdown, the results presented in this study favor a strong relation between cumulative lesion load and atrophy (Figures 2 and 3). Since month to month ventricular changes are incremental, it is not possible to temporally link enhancing lesions, regional edema in the area of inflammatory lesions with resulting ventricular changes, and ensuing atrophy. The cumulative number of enhancing lesions varies greatly between patients. Similarly, individual patients exhibit varying degrees of cerebral atrophy. The correlation between ventricular enlargement and cumulative enhancing lesion load was particularly strong for patients with more concentric ring–enhancing lesions with central pallor (Figures 1 and 4). This group of patients also had the highest rate of clinical relapses and, therefore, the greatest number of corticosteroid treatments (Figure 2). Concentric ring–enhancing lesions with central contrast pallor are thought to arise either in previously damaged areas with avascular glial scars and peripheral neovascularization or from a fulminate local inflammation with destruction of parenchyma and passing microvasculature and peripheral angiogenesis. Rapid ventricular enlargement in this high-risk group of patients is probably multifactorial, especially in view of the high corticosteroid use.

The results of this study also indicate that enhancing lesions and atrophy can have predictive value, especially in patients with early disease. Patients with recurring enhancing disease activity on an MRI scan are at high risk for the development of cerebral atrophy, and may profit from early immunomodulatory intervention with medications such as interferon. The presence of many concentric ring–enhancing lesions seems to correlate with a more aggressive course of the disease.

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REFERENCES