Serial Contrast-Enhanced MR in Patients with Multiple Sclerosis and Varying Levels of Disability

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PURPOSE: To compare the rates of enhancement and changes in lesion burden in patients with multiple sclerosis (MS) and varying levels of disability. **METHODS:** Monthly enhanced MR images of the brain were obtained for 6 months from seven patients with mildly disabling relapsing-remitting MS and from seven patients with secondary progressive MS and severe disability. At entry and 1 year later, two unenhanced T2-weighted images of the brain were also obtained. **RESULTS:** Despite the fact that both groups had clinically active disease and had similar increases in unenhanced MR lesion load, the total number of enhancing lesions was 239 in patients with relapsing-remitting MS (42 on the baseline images, 151 new, and 46 persistent during follow-up) (average number of lesions per patient per year was 68) and 21 in those with secondary progressive MS (five on the baseline images, 13 new, and three persistent during follow-up) (average number of lesions per patient per year was seven). **CONCLUSION:** Our data indicate that the rate of enhancement significantly decreases in the more advanced phases of MS. This is important when planning clinical trials, and suggests that mechanisms underlying lesion formation might be dissimilar in different MS patient groups.

Index terms: Brain, magnetic resonance; Sclerosis, multiple

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Contrast enhancement on magnetic resonance (MR) images of patients with multiple sclerosis (MS) represents areas of blood-brain barrier damage or inflammation (1, 2). Contrast-enhanced MR imaging shows phases of disease activity five to 10 times more frequently than indicated by clinical relapses (3) and twice as frequently as does unenhanced MR imaging (4). This high sensitivity of enhanced MR imaging in showing active lesions in patients with MS is the reason that changes in the rate of enhancement on monthly MR images are used as the primary end point in phase II clinical trials (5). Indeed, statistical simulations (6, 7) have demonstrated that use of this MR end point, instead of the clinical relapse rate, allows the study of smaller patient cohorts with shorter follow-up periods.

The frequency of enhancement differs significantly among the different clinical forms of MS (8). It has been estimated that the average number of active lesions detectable on monthly MR images in a given patient per year is 20 for those with relapsing-remitting or secondary progressive MS, nine for those with benign MS, and three for those with primary progressive MS (8, 9).

Secondary progressive MS is considered a natural continuation of the relapsing-remitting phase of the disease (10), which is why these two subgroups of patients are usually considered together. It is known, however, from previous epidemiological studies (11, 12), that the frequency of relapses diminishes when a severe degree of disability is reached. In this study, we obtained monthly enhanced T1-weighted images for 6 months and yearly T2-weighted images in patients with relapsing-remitting MS and mild disability and from severely disabled patients with secondary progressive MS to com-

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pare the rates of enhancement and the changes in lesion burden between the two groups.

Patients and Methods

Patients

Fourteen patients with clinically definite MS (13) were studied prospectively as part of a long-term natural history study at our institution. Seven patients had a relapsing-remitting course, and seven had a secondary progressive course (10). To be included in the study, all patients had to have at least one relapse and/or at least a 1-point increase in score on the Expanded Disability Status Scale (EDSS) (14) in the year preceding the study. They also had to have no clinical relapses and/or to have not been treated with steroids or psychotropic drugs in the preceding 3 months. Every 3 months during the follow-up period, a full neurologic examination, with degree of disability scored according to the EDSS, was performed by one investigator, who was unaware of the MR results. An increase in EDSS score was considered to have occurred only when it was confirmed on two consecutive examinations.

In case of a relapse, a 5-day course of methylprednisolone (1 g IV) was allowed; however, no other immunomodulating or immunosuppressive treatment was permitted during the study period. We are aware that relapses and steroid treatment can significantly affect contrast enhancement (15, 16); however, since there is no better solution, we decided not to change the MR schedule in cases of relapses or steroid treatment. Written informed consent was obtained from all the patients before inclusion in the study.

MR Imaging

MR imaging of the brain was performed on a 1.5-T system. T1-weighted (768/14/2 [repetition time/echo time/excitations]) spin-echo images, with 5-mm contiguous axial sections, a 256 × 256 image matrix, and a 230-mm field of view, were obtained before and 5 to 7 minutes after injection of gadopentetate dimeglumine (0.1 mmol/kg) every month for the first 6 months of the study. At entry into the study and 1 year later, moderately T2-weighted (2000/50/1) spin-echo MR images of the brain were obtained, with 5-mm contiguous axial sections, a 256 × 256 image matrix, and a 230-mm field of view. Patients were carefully repositioned according to published guidelines (3). The patients were always placed in a comfortable position at the center of the head coil using a standardized landmark and the indicator light. Then, planning images (T1-weighted spin echo) were acquired in the following order: a single axial section was obtained; from this, a coronal section was planned using an oblique projection if necessary to compensate for patient misalignment; a sagittal section was prescribed from the coronal image, again compensating for any misalignment of patient position using the falx cerebri as a reference; and, finally, the main series of sections was prescribed from the sagittal image. These sections run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum.

Quantification of MR Abnormalities

The number of enhancing lesions was determined by agreement between two experienced observers who were unaware of the disease pattern. On the follow-up images, enhancing lesions were defined as new at their first appearance and as persistent when present on at least two consecutive scans. In previous studies (17, 18), we demonstrated that our interobserver variability in counting the number of enhancing lesions in MS patients is very low. Lesion volume was measured on the moderately T2-weighted entry and exit scans in a random order by a single observer, who was unaware of the patient's disease pattern, using a semiautomated segmentation technique based on local thresholding. We are aware that the moderately T2-weighted sequence we used may not have been as sensitive as more heavily T2-weighted sequences in detecting MS lesions; however, it resulted in good resolution of the MS lesions (particularly in the subcortical regions) and also had the advantage of suppressing the cerebrospinal fluid signal, which was necessary for the semiautomated segmentation technique to be applied properly. The software used for assessment of lesion volume was the "/usr/image" library (University of North Carolina, Chapel Hill) and Dispim image display software (David Plummer, University College, London, United Kingdom) running on a computer workstation (Sun Microsystems, Mountain View, Calif). The measurements were obtained by using a mouse-controlled cursor to click on the perimeter of the lesions on the computer display.

The computer program first examines the image in a region close to where the mouse was clicked to find the strongest local intensity gradient, which it considers to be the edge of the lesion. Then the lesion is outlined by following a contour of isointensity from this initial edge point, thus defining the lesion as a region of the image in which the signal intensity is locally above the signal intensity at the initial edge position. This sometimes gave poor results, because other structures (such as abutting gray matter) adjacent to the lesion were as bright, leading to the contour moving away from the lesion outline. When this happened, the lesions were outlined manually by the observer by moving the cursor to define the boundary of the lesion. Each outline was stored on computer disk before proceeding with automatic computation of the lesion volume. The lesion volume was calculated simply as the lesion area multiplied by the section thickness. This technique to segment MS lesions is characterized by high intrarater and interrater reproducibility (18–21).

Statistical Analysis

Differences in clinical and MR measures between the two groups of patients were calculated using Student's *t* test for nonpaired data in case the data were normally

TABLE 1: Main clinical and unenhanced MR characteristics in patients with relapsing-remitting and secondary progressive MS

	RRMS	SPMS	*P*
Mean age (SD), y	29 (5.8)	41 (9.2)	.01
Men/women	3/4	3/4	NS
Median disease duration (range), y	6 (2–10)	10 (7–18)	.03
Median EDSS score at entry (range)	1.5 (1.0–3.5)	6.0 (5.0–6.0)	.001
Median EDSS score at exit (range)	1.5 (1.0–3.5)	6.0 (6.0–6.5)	.001
Median lesion load at entry (range), mm^3	10 860 (1605–72 850)	13 435 (2410–41 640)	NS
Median lesion load at exit (range), mm^3	11 560 (4655–73 115)	13 810 (2975–44 310)	NS
Median change of lesion load (range), mm^3	920 (240–3050)	1010 (375–7400)	NS

Note.—RRMS indicates relapsing-remitting MS; SPMS, secondary progressive MS; and EDSS, Expanded Disability Status Scale.
* Statistical analysis: see the text for details; NS indicates not significant.

distributed or using the Mann-Whitney test in case the data were not normally distributed. Correlations between clinical and MR parameters were calculated using Spearman's rank correlation coefficient.

Results

Clinical Data

Seven patients with relapsing-remitting MS and seven patients with secondary progressive MS were studied. Table 1 lists the main clinical characteristics of the two groups of patients. Patients with secondary progressive MS were older, had longer disease duration, and were more disabled than patients with relapsing-remitting MS. In the prestudy period, 19 relapses were recorded in all the patients with relapsing-remitting MS and nine relapses occurred in three patients with secondary progressive MS; the EDSS score increased by 1 point or more in one patient with relapsing-remitting MS and in five patients with secondary progressive MS. Similarly, during the study period, 19 relapses were recorded in all the patients with relapsing-remitting MS, and eight relapses were recorded in four of the patients with secondary progressive MS; four patients with secondary progressive MS had an increased EDSS scores (one patient by 1 point and three patients by 0.5 points) and none with relapsing-remitting MS.

MR Imaging

Table 1 reports the lesion volume at entry and at the end of the study period, and shows the yearly change for the two groups of patients. None of these MR measures was different between the two groups.

The total number of enhancing lesions was 239 in patients with relapsing-remitting MS (42 were on the baseline images, 151 were new, and 46 were persistent on the follow-up images) and 21 in those with secondary progressive MS (five were on the baseline images, 13 were new, and three were persistent on the follow-up images) ($P = 0.001$) (Table 2). This gives a mean frequency of enhancing lesions of 68 per patient per year in the relapsing-remitting MS group (Fig 1) and of seven per patient per year in the secondary progressive MS group (Fig 2). Three patients with secondary progressive MS always had inactive contrast-enhanced lesions, whereas this was never found in patients with relapsing-remitting MS.

In total, 219 lesions enhanced on one of the follow-up scans, 36 lesions enhanced on two consecutive scans, four lesions enhanced on three consecutive scans, and one lesion, in a patient with relapsing-remitting MS (patient 10; see Table 2), enhanced on all the scans (Fig 3).

Correlations between Clinical and MR Data

No significant correlations were found between changes in EDSS score and lesion load over the study period (Spearman's rank correlation coefficient = 0.3). The number of relapses during the study period correlated significantly with the number of enhancing lesions (Spearman's rank correlation coefficient = 0.72, $P = .009$).

Discussion

We selected two groups of MS patients with marked disease activity (ie, frequent relapse rate and/or severe increase of disability), who are typically involved in clinical trials. Our results indicate that, despite clinical activity remaining severe during the study period and both groups showing a similar increase in lesion load, the rate of enhancement was markedly higher in less disabled patients who had relaps-

TABLE 2: Number of total and new enhancing lesions detected on monthly MR images in patients with relapsing-remitting and secondary progressive MS

Patient	Type of MS	No. of Total (and New) Enhancing Lesions						
		Entry	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
1	SPMS	0	0	1 (1)	1 (1)	0	2 (2)	0
2	SPMS	0	0	0	0	0	0	0
3	SPMS	1	0	0	0	0	0	0
4	SPMS	4	0	1 (1)	0	1 (1)	0	1 (1)
5	SPMS	0	3 (3)	3 (1)	0	1 (1)	2 (1)	0
6	SPMS	0	0	0	0	0	0	0
7	SPMS	0	0	0	0	0	0	0
8	RRMS	2	1 (1)	4 (4)	0	0	5 (5)	4 (2)
9	RRMS	4	2 (2)	0	7 (7)	2 (1)	6 (5)	0
10	RRMS	3	12 (11)	10 (5)	19 (17)	6 (0)	5 (3)	14 (11)
11	RRMS	27	3 (0)	0	9 (9)	13 (12)	12 (9)	16 (11)
12	RRMS	6	2 (0)	3 (3)	5 (4)	1 (0)	3 (3)	3 (1)
13	RRMS	0	4 (4)	2 (1)	1 (1)	0	1 (1)	3 (3)
14	RRMS	0	1 (1)	4 (4)	2 (2)	2 (1)	4 (2)	6 (5)

Note.—SPMS indicates secondary progressive MS; RRMS, relapsing-remitting MS.

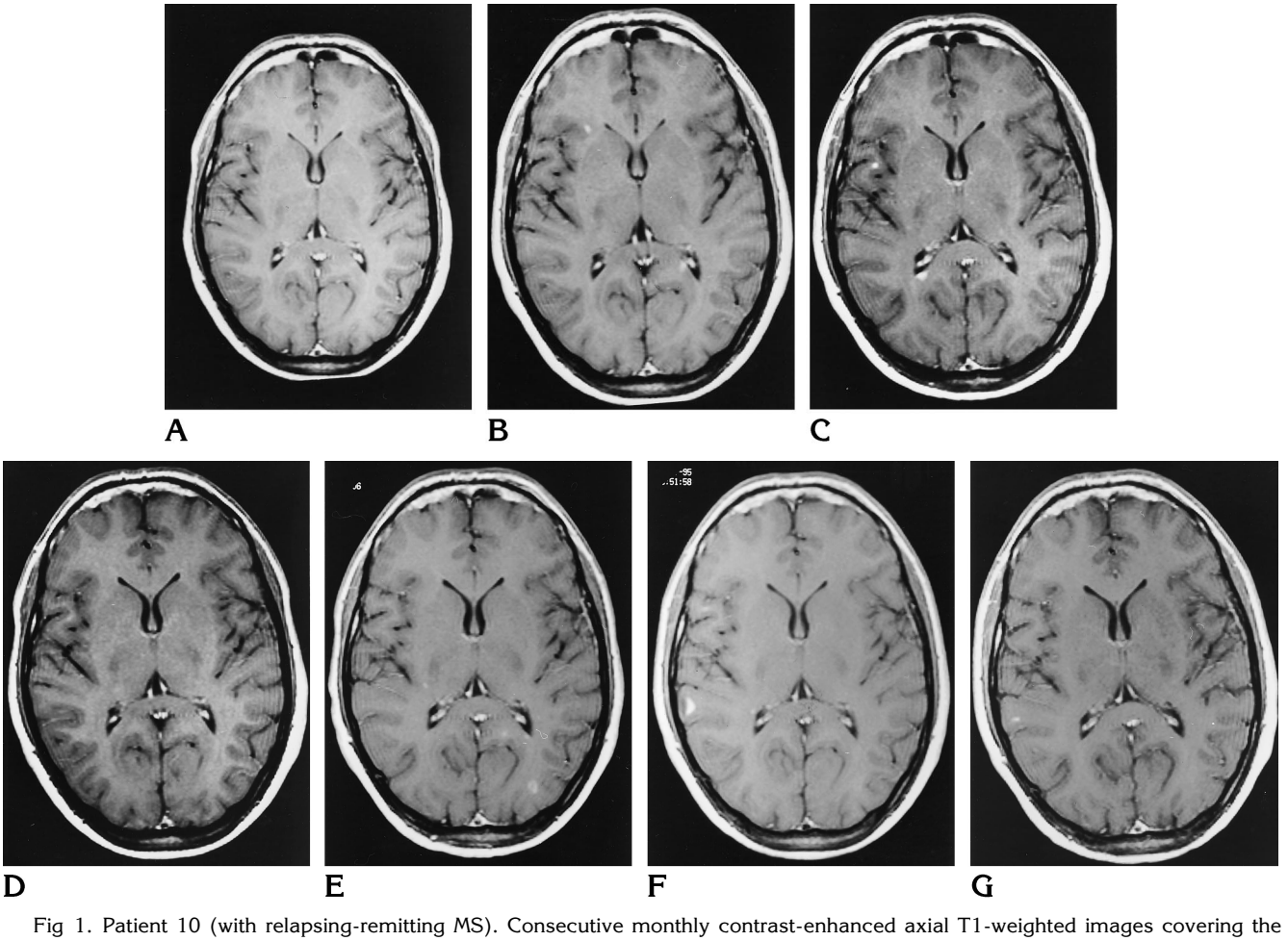

Fig 1. Patient 10 (with relapsing-remitting MS). Consecutive monthly contrast-enhanced axial T1-weighted images covering the entire follow-up period. Several enhancing lesions are visible in different brain regions on five of the seven images.

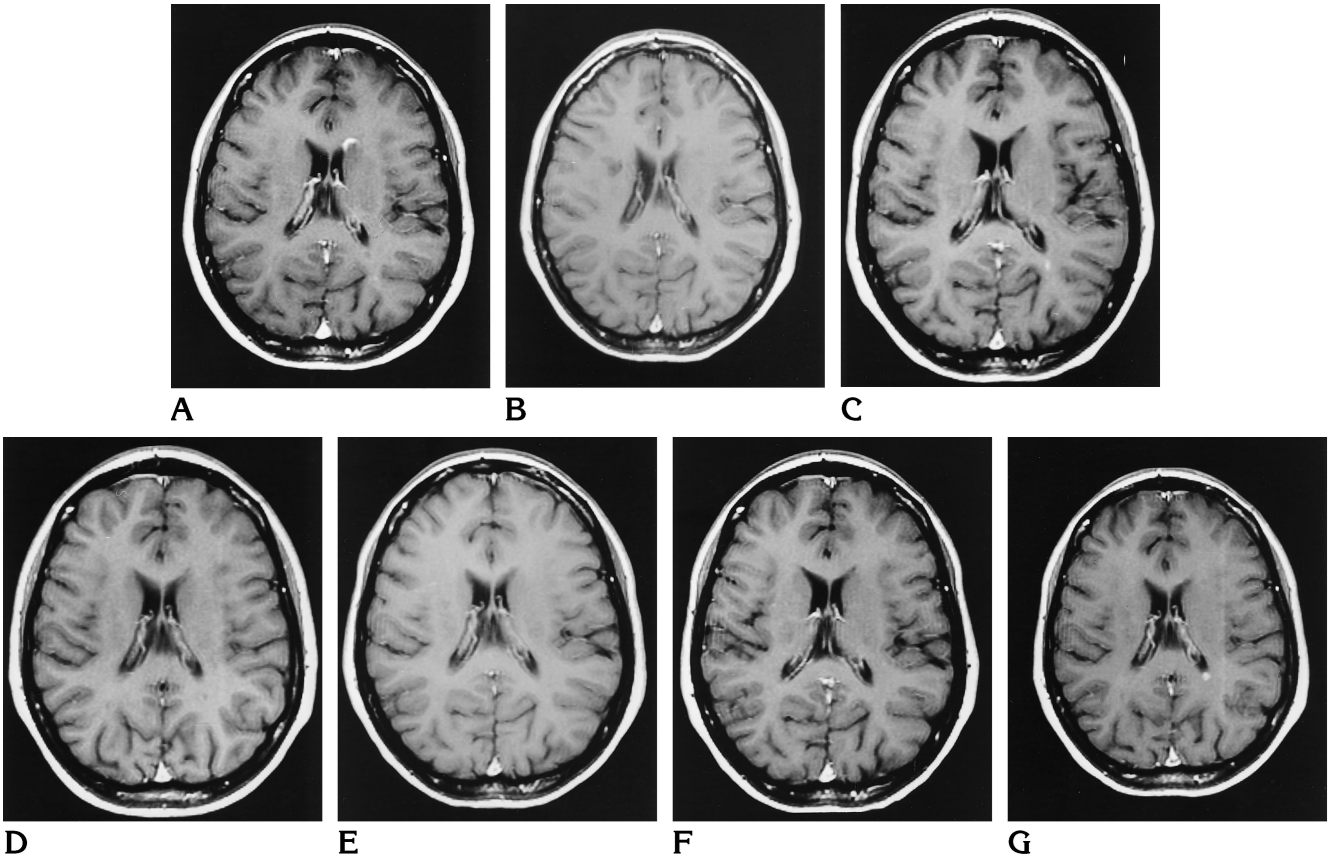

Fig 2. Patient 4 (with secondary progressive MS). Consecutive monthly contrast-enhanced axial T1-weighted images covering the entire follow-up period. Only three enhancing lesions are visible in different brain regions on three of the seven images.

ing-remitting MS. This observation has two major implications, one related to the nature of factors responsible for disease activity in these two clinical groups and the other to the definition of the most useful MR measures for clinical trials in which such patients are enrolled.

Although patients with relapsing-remitting MS have a pattern of disease evolution that is clearly distinct from that of patients with secondary progressive MS, it is also clear that secondary progressive MS is the continuation and worsening of a preexisting relapsing-remitting course, which occurs in a considerable proportion of patients with early relapsing-remitting MS (10). Thus, previous studies evaluating the rate of enhancement detectable in different clinical categories of MS always considered these two groups of patients together (3, 7, 8). From previous studies we have learned that in such patients the average number of active lesions detected with monthly MR imaging is around 20 lesions per year per patient, and that this figure is much higher than the number of detectable lesions in patients with other patterns of disease evolution (8). Epidemiological studies (11, 12), as well as our results, have shown, however, that the rate of clinical relapse diminishes when the secondary progressive phase of the disease is entered. It is, therefore, conceivable that the pathologic pattern of disease evolution changes accordingly.

A previous brain MR study (22) showed that there is a correlation between changes of disability and the total number of active lesions present on unenhanced MR images over a 2- to 3-year period. Similarly, another study (23) showed that frequency of enhancement is reduced in patients with secondary progressive MS without superimposed relapses compared with those in whom progression and relapses were associated. Our data show that the frequency of enhancement in less disabled patients with relapsing-remitting MS is about 10 times higher than that of more severely disabled patients with secondary progressive MS. We studied the two possible extremes of the pathologic process: none of the patients with relapsing-remitting MS had an EDSS score greater

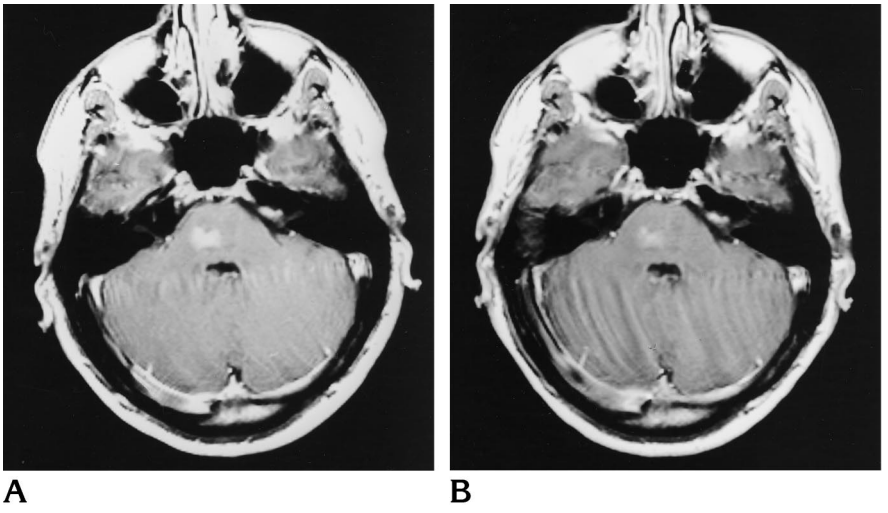

Fig 3. Patient 10 (with relapsing-remitting MS). Contrast-enhanced axial T1-weighted images obtained at baseline (*A*) and at the end of the follow-up period (ie, 6 months later) (*B*). A large enhancing lesion is visible in the brain stem in *A*. This lesion enhanced on all the images and was still present 6 months later (*B*), although reduced in size.

than 3.5, whereas five of the seven patients with secondary progressive MS had EDSS scores equal to or greater than 6.0. On the contrary, the relapse rate was higher in patients with relapsing-remitting MS. This might be the reason the rates of enhancement were so different in the two groups, with an extremely high rate of enhancing lesions in the relapsing-remitting MS group. All these data seem to indicate that the development of disability in secondary progressive MS is only partially related to the short-term disease activity, as happens for relapsing-remitting MS (24, 25). In our opinion, in patients with secondary progressive MS, other factors, such as progressive tissue destruction within preexisting lesions and/or spinal cord damage, are probably more important in determining disability.

Nevertheless, our patients with secondary progressive MS had a median increase of lesion load, which was similar to that of patients with relapsing-remitting MS and within the expected range for untreated MS patients (26). This observation further strengthens the hypothesis that different pathologic mechanisms might operate in the two disease subgroups. If a similar yearly increase in lesion load is detectable in patients with markedly different propensities to form new lesions, this means that formation of MS lesions can occur independently from blood-brain barrier damage, as shown by contrast enhancement, or that the degree of blood-brain barrier damage could be highly variable, or that in patients with relapsing-remitting MS, the inflammatory abnormalities associated with blood-brain barrier breakdown resolve better than they do in patients with secondary progressive MS, thus leaving few if any residual T2 lesions. The first explanation, which is not mutually exclusive with the others, is in agreement with previous studies involving proton MR spectroscopy (27) (J. Wolinsky, personal communication, May 1996), which showed that evidence of demyelination can occur in the absence of contrast enhancement and that blood-brain barrier dysfunction and demyelination do not have the same temporal evolution. In addition, it has been found that cuprizone-induced demyelination is unaccompanied by changes in blood-brain barrier permeability (28). The second explanation is supported by a previous pathologic study (29) showing that the degree of inflammation is different in lesions of MS patients with different patterns of disease evolution and by MR studies (30–32) showing that the use of a triple dose of contrast material enables detection of many more enhancing lesions in patients with MS but that the magnitude of this increased sensitivity is different for the different clinical subgroups. The third explanation is in agreement with the data by Stone et al (33), which showed marked fluctuations of lesion load on monthly T2-weighted MR images in mildly disabled patients with relapsing-remitting MS, indicating that many lesions seen on T2-weighted images can disappear or shrink over short periods of time. This might be due to the effectiveness of reparative mechanisms in these patients; such mechanisms might be less effective in the lesions of most disabled patients, in whom several repetitive damaging episodes might have occurred.

The vast majority (98%) of the enhancing lesions detected in the present study had a du-

ration of enhancement that ranged from 4 to 8 weeks. This finding is in agreement with previous observations indicating that it is unusual for enhancement in MS lesions to last more than 8 weeks (34). However, it is possible, as was also shown in the present study, that in MS lesions, enhancement can last longer and, in fact, one lesion in a patient with relapsing-remitting MS enhanced for the entire duration of the follow-up period (ie, 6 months), although its size was progressively reduced (Fig 3).

The high sensitivity of enhanced MR imaging in detecting MS activity, which was found to correlate with both short-term (24) and long-term (25, 35) clinical evolution, has led to the design of clinical trials with relatively few patients and short follow-up periods (7, 8). Our data indicate that this MR measure is particularly helpful for relapsing-remitting patients. On the other hand, the lower frequency of enhancement in severely disabled secondary progressive MS patients raises the question of whether this MR marker would be of use in clinical trials involving MS patients in the more advanced phases of their disease evolution, since more patients and longer follow-up periods would be necessary to detect treatment efficacy. Monthly enhanced MR imaging is time-consuming and expensive. Further studies are therefore needed to define the role of other MR markers of disease evolution in these patients—such as measures of spinal cord atrophy (36, 37), changes of magnetization transfer ratio (38), or hypointense lesion load on T1-weighted images (39)—that might show better the specific pathologic changes occurring in the more advanced phases of MS.

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