Serial Gadolinium-enhanced Magnetic Resonance Imaging Scans in Patients with Early, Relapsing-Remitting Multiple Sclerosis: Implications for Clinical Trials and Natural History

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Six patients with early, mild, relapsing-remitting multiple sclerosis were studied with monthly gadolinium-enhanced magnetic resonance imaging scans for 8 to 11 months. Numerous enhancing lesions were observed irrespective of clinical activity. Four of the 6 patients had one or more enhancing lesions present on each examination. The other 2 patients had enhancing lesions noted in 7 and 9 of 11 months. In contrast, only two clinical exacerbations were observed during the study period. Neither the exacerbations nor other changes in symptoms or signs correlated with occurrence of the enhancing lesions. Enhancement generally persisted for less than 1 month. The opening of the blood-brain barrier as reflected by gadolinium enhancement on magnetic resonance imaging may represent ongoing disease activity in patients with mild, relapsing-remitting multiple sclerosis who are clinically stable. The frequency of these lesions appears to be sufficient to use as an outcome measure in clinical trials testing clinical efficacy in patients with early, relapsing-remitting multiple sclerosis.

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In spite of extensive investigations, multiple sclerosis (MS) remains a disease of uncertain cause and without an effective treatment. An immunopathological process is generally postulated to contribute to the pathogenesis, and various forms of immunosuppressive therapy have been attempted. Unfortunately, therapeutic trials in patients with MS are accompanied by many difficulties, including unpredictable changes in disability. Additionally, measurements of efficacy are limited to assessing disability that may not adequately reflect disease activity. Therapeutic trials have usually involved patients with chronic, progressive disease and with moderate to severe disability. It has been argued that the course in the chronic, progressive phase of the disease is more predictable and the relationship between the risk and the benefit of treatment more acceptable. Increasingly, however, investigators are coming to the conclusion that treatment of the disease in the earlier stages may be necessary to have significant impact on its course.

Recent studies in patients with MS, with magnetic resonance imaging (MRI), suggest the presence of disease activity as measured by new abnormalities on T2-weighted images or by gadolinium-enhancing lesions in patients who are clinically stable [1–7]. This provides further rationale for treating patients with early, relapsing-remitting disease. The major obstacle has been the lack of reliable means of assessing efficacy, particularly at this stage of the disease.

A study of serial gadopentetate dimeglumine (GdDTPA)-enhanced MRI was initiated to determine if the technique can be used to establish an outcome measurement in the treatment of patients with early, relapsing-remitting disease. These studies were also undertaken to further define the natural history of the disease in this early phase. To date, 6 patients with early, relapsing-remitting disease have been studied at monthly intervals for 8 to 11 months. These patients had only mild disability and were generally clinically stable during the period of the study. Substantial num-

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Table 1. Clinical Characteristics of Patients at Onset of Study

	Age (yr)	Sex	Duration of MS (mo)	Month after Last Exacerbation	EDSS at First Month	EDSS at Last Month	WBC (CSF)	IgG Index	Presence of OCB
Patient No.									
1	43	F	5	3	1.5	1.5	0	0.65	−
2	29	F	10	5	1.5	1.5	0	1.70	+
3	40	F	32	8	2.0	2.0	1	1.06	+
4	25	M	8	2	1.5	1.5	4	0.69	+
5	26	F	13	4	1.5	1.5	25	2.30	+
6	39	F	35	4	3.5	2.5	2	1.93	+
Mean	34	. . .	17.2	4.3	1.9	1.8	. . .	. . .	. . .

MS = multiple sclerosis; EDSS = Expanded Disability Status Score; WBC = white blood cell count; CSF = cerebrospinal fluid; OCB = oligoclonal bands.

bers of enhancing lesions have been observed in these patients, indicating that disease activity is occurring in the early phases of the disease even during clinically stable periods. These findings have implications for both the pathogenesis and experimental treatment of patients with MS.

Methods

Patient Selection

Six patients with MS, referred by local physicians to be considered for ongoing clinical studies, were selected for this Intramural Research Board–approved protocol. Individuals were chosen who filled the criteria of clinically definite MS as defined by Poser and colleagues [8], were judged to have mild, early, relapsing-remitting diseases (i.e., an Expanded Disability Status Score [EDSS] of 3.5 or less) [9], and would be able to complete monthly MRI scans. Informed consent was obtained from each patient before starting the study.

Patient Evaluation

Patients were admitted to the Clinical Center, National Institutes of Health (Bethesda, MD), for complete physical and neurological examination, lumbar puncture, and the initial MRI scan. Subsequently, patients were examined and imaged monthly (every 4 weeks) at the same time of day. The examining physician (H. M.) was blinded to the results of all MRI scans. An exacerbation was defined by using a modification of the criteria of Schumacher and co-workers [10] and consisted of a new symptom or worsening of previous symptoms associated with significant changes in signs and lasting more than 24 hours. Histories of increased symptoms that represented either mild changes in preexisting symptoms or were not associated with new or changed signs were judged insufficient to classify as an exacerbation. During the study, some patients were also noted to have changed or new neurological signs; these were usually mild, not associated with new symptoms, and classified as changed signs, not exacerbations.

MRI Scans

Imaging was performed monthly for 8 to 11 months in 6 patients. Reproducible head positioning from month to month was assured by placing one vitamin E capsule in the external ear canal and taping a second at the lateral canthus of the eye. The canthal meatal line between these capsules delineated the plane of each scan. MRI scans were performed on a General Electric Signa 1.5 T (General Electric, Milwaukee, WI) by using a T2-weighted spin echo pulse sequence with an echo time (TE) of 80 msec, a repetition time (TR) of 2,000 msec, 2 excitations, a 128 × 256 acquisition matrix, and 5-mm contiguous interleaved slices. T1-weighted spin echo (TR 600/TE 20) images of the brain were performed before and after GdDTPA (Magnevist 0.1 mmole/kg, Berlex Laboratories, Cedar Knolls, NJ) was administered using 2 excitations, a 192 × 256 acquisition matrix, and 5-mm contiguous interleaved slices. All studies were performed with a field of view of 24 cm.

Image Evaluation

T1-weighted images after contrast were visually compared with T1-weighted images before contrast. Most enhancing lesions are easily recognized as areas of increased signal intensity in the white matter. Questionable small areas of enhancement near the cortical surface were excluded from the analysis. Moreover, possible small areas of enhancement in the white matter were not included unless a corresponding area of abnormality was identified on the T2-weighted images. New enhancing lesions were defined as lesions that were not present on the T1-weighted enhanced MRI performed 1 month previously.

Results

Clinical Characteristics of Patients

The 6 patients examined in this study had early, mild MS of the relapsing-remitting form. Their clinical characteristics at the onset of this study are shown in Table 1. The mean duration of disease, dated from the first clinical sign or symptom, was 17.2 months; and the mean level of disability, measured by using the EDSS, was 1.9. One of the 6 patients (Patient 6) was recovering from a period of worsening before entry into this study. All of the patients had experienced an exacerbation within 8 months before entry. Cerebrospinal fluid findings consistent with the diagnosis of MS (an elevated immunoglobulin IgG index and oligoclonal bands) were found in all but 1 patient.

Table 2. Clinical Course of Patients

	Scans (n)	Exacerbations (n)	Change in Signs (n)[a]	Change in Symptoms (n)[a]	Fatigue (n)[a]	T2 Lesions on Initial Scan (n)	GdDTPA+ Lesions Per Scan (mean, n)
Patient No.							
1	8	0	1	6	5	41	3.6
2	11	0	0	0	4	22	0.7
3	11	0	2	2	2	46	1.6
4	8	1	2[b]	2[b]	1	64	3.0
5	11	1	2[b]	3[b]	0	75	2.6
6	11	0	1	4	4	74	6.2
Total	60	2	8	17	16	. . .	. . .

[a]Number of occasions.
[b]One occasion was associated with an exacerbation.

The patients were clinically evaluated monthly at the time of MRI examination for a total of 60 occasions. Table 2 summarizes the clinical course of patients during the study. There was no permanent worsening in the patients' level of disability. Two patients had clinical exacerbations during the study. The exacerbation in 1 patient (Patient 5) occurred during the third month in the study and was characterized by decreased sensation in the lower extremities. This resulted in an 0.5 increase in EDSS that persisted for 1 month. One exacerbation occurred in 1 patient (Patient 4). It occurred in the seventh month and was characterized by decreased temperature sensation in the right foot that resulted in a 0.5 increase in the EDSS, which returned to baseline the next month. A third patient (Patient 6) entered the study with an EDSS score of 3.5 and subsequently improved to a score of 2.5, predominantly due to improvement of strength in the lower extremities. The EDSS score did not change in the remaining 3 patients.

MRI Findings

The initial MRI scans of the 6 patients were consistent with early, mild MS. T2-weighted images showed discrete lesions that were generally periventricular. This pattern did not change significantly by the end of the study period. After administration of GdDTPA, numerous enhancing lesions (n = 29) were noted on T1-weighted studies. All of these enhancing lesions exhibited corresponding areas of increased signal intensity on T2-weighted images. Representative images for 1 patient done at the beginning and end of the study are shown in Figure 1.

LONGITUDINAL STUDIES. The frequent occurrence of enhancing lesions was confirmed by analysis of the serial studies. New enhancing lesions (n = 113) occurred in all patients during the course of the study. The number and time course of enhancing lesions in individual patients are shown in Figure 2. Each patient appeared unique with respect to the number of new lesions and differences from month to month. The maximum number of enhancing lesions varied among the patients, with some patients having as many as 10 lesions at one time, whereas other patients, such as Patient 2, never had more than two lesions. In each patient, the number of lesions varied from month to month, however, a striking observation was that one or more enhancing lesions were visible in most patients on all occasions. The average number of enhancing lesions seen on MRI scans is noted in Table 2.

CLINICAL CORRELATIONS. There was almost total lack of clinical correlation with numbers or locations of the enhancing lesions. Patients who had exacerbations or had changed signs or symptoms insufficient to be classified as an exacerbation did not have enhancing lesions that could explain those findings. It is possible that some of the clinical changes were related to active lesions in the spinal cord, which was not studied. Exacerbations and changed signs or symptoms are noted on individual graphs (see Fig 2). In addition to the lack of correlation with specific signs and symptoms, there was also no correlation between the frequency of lesions and general clinical changes, including subjective aspects of fatigue (see Table 2). Patients with a higher mean number of lesions per scan, however, tended to complain more frequently of symptoms (r^2 = 0.47).

EVOLUTION OF ENHANCING LESIONS. Most new enhancing lesions did not enhance on the next scan 1 month later. Excluding lesions enhancing on the first and last scan, for which the total duration of enhancement cannot be calculated, 94 new enhancing lesions were observed. Sixty-nine of these did not enhance 4 weeks later. Twenty lesions continued to enhance for greater than 4 weeks but less than 8 weeks. Three lesions persisted longer than 8 weeks but less than 12 weeks,

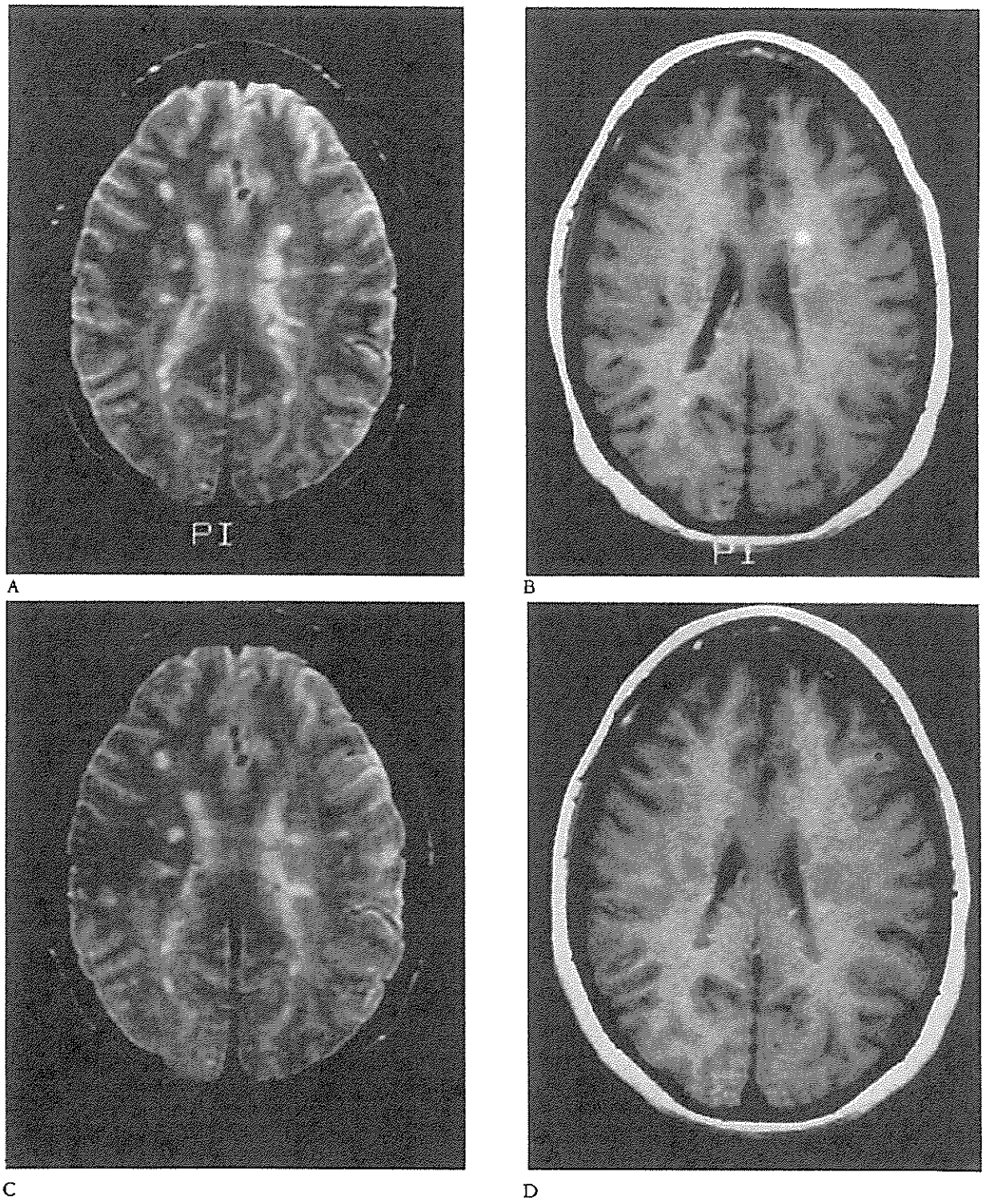

Fig 1. Representative magnetic resonance images from 1 patient (Patient 6) at the beginning (A, B) and end of our study (C, D). Panels A and C are T2-weighted images. Panels B and D are T1-weighted images after administration of gadopentetate dimeglumine (GdDTPA). Enhancing lesions appear as regions of increased signal intensity (white) on T1-weighted images after administration of GdDTPA. Note the size and relative brightness (signal intensity) of the T2 lesions that correspond to the enhancing lesions.

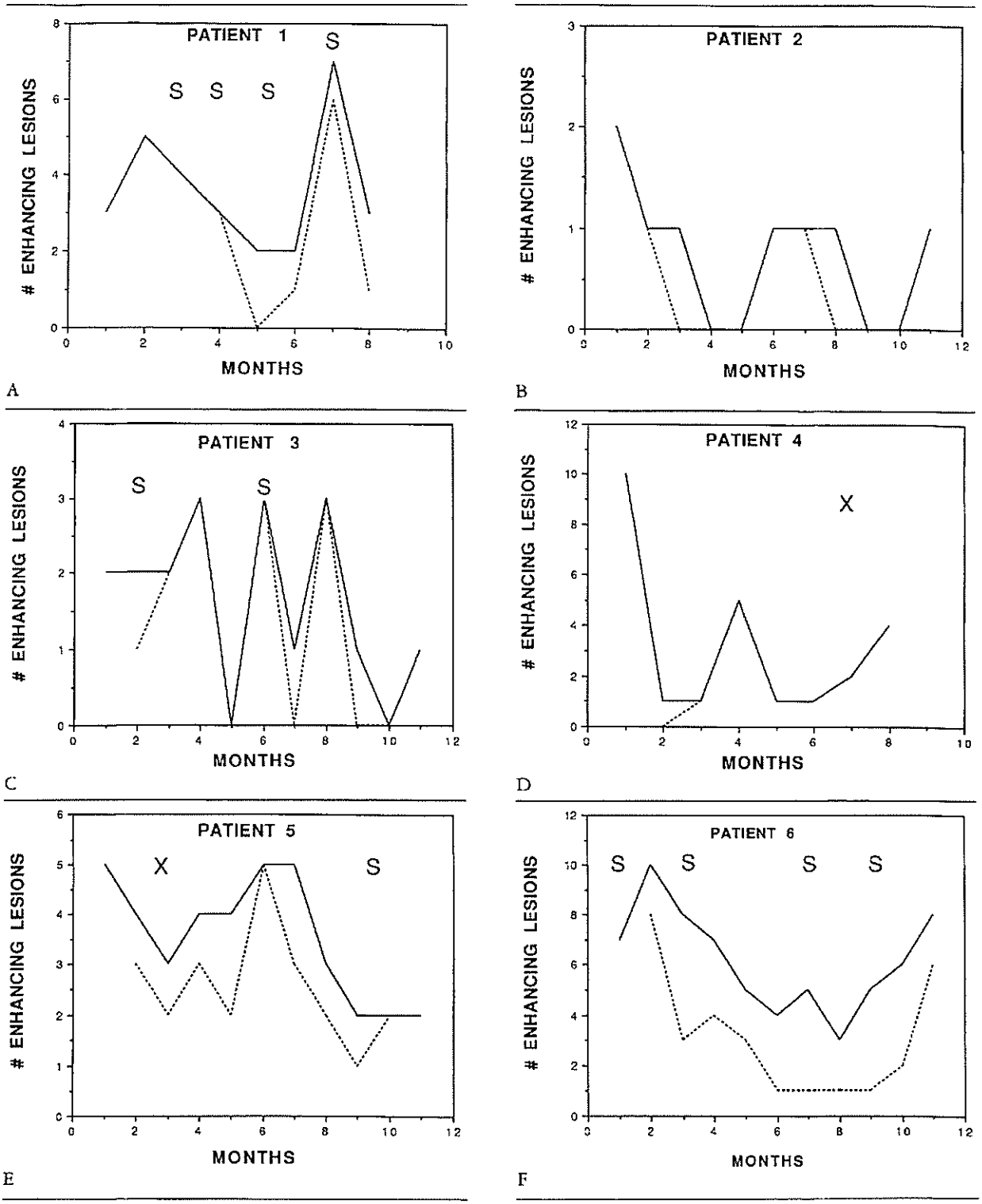

Fig 2. Graphs A–F show patterns of enhancement in individual patients (Patients 1–6, respectively). The solid upper trace shows the total number of enhancing lesions from each month. The lower, dashed line reveals the total number of new enhancing lesions each month. An "X" marks the time of exacerbation. An "S" signifies mild signs or symptoms that did not meet the criteria for an exacerbation (see Methods).

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