Using Gadolinium-enhanced Magnetic Resonance Imaging Lesions to Monitor Disease Activity in Multiple Sclerosis

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The highly variable clinical course and the lack of a direct measurement of disease activity have made evaluation of experimental therapies in multiple sclerosis (MS) difficult. Recent studies indicate that clinically silent lesions can be demonstrated by magnetic resonance imaging (MRI) in patients with mild relapsing-remitting MS. Thus, MRI may provide a means for monitoring therapeutic trials in the early phase of MS. We studied 12 patients longitudinally for 12 to 21 months with monthly gadolinium (Gd)-enhanced MRIs. The data have been used to identify the most effective design of a clinical trial using Gd-enhanced lesions as the outcome measure. Frequent (>1/mo) Gd-enhancing lesions were observed in 9 of the 12 patients, indicating that the disease is active even during the early phase of the illness. The frequency of the lesions was not constant; there was marked fluctuation in lesion number from month to month. However, the magnitude of the peak number of lesions and the frequency of the peaks varied among patients. Because of this variability, the most effective use of Gd-enhancing lesions as an outcome measure in a clinical trial was a crossover design with study arms of sufficient duration to allow accurate estimation of lesion frequency. Monitoring Gd-enhancing lesions may be an effective tool to assist in the assessment of experimental therapies in early MS.

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The clinical variability in multiple sclerosis (MS) has made design and assessment of clinical trials difficult [1]. Although there is increasing interest in treating patients before significant disability occurs, the inability to predict the future course of the disease has made assessment of the risk-benefit relationship difficult. Some patients will continue to have mild disease throughout the course of the illness. Treatment of these patients early in the course of the disease with potentially toxic treatments may pose greater risk than the disease. Further complicating clinical trials has been the difficulty in measuring disease activity, which is usually assessed indirectly by measuring disability. Magnetic resonance imaging (MRI) is well established as the optimal imaging technique for the diagnosis of MS [2–8], and the presence of disease activity in the absence of clinical changes has been confirmed by recent MRI studies [9, 10]. Areas of increased signal on T2-weighted images, which reflect demyelination, inflammation, or edema [11], have been shown to occur in the cerebrum in clinically stable patients [9, 10]. In addition, use of gadolinium (Gd) with T1-weighted imaging can identify areas of breakdown in the blood-brain barrier. These areas of enhancement seem to represent the initial stage of lesion development [12–15] and are probably associated with active inflammation [14, 16]. Recent studies, including an initial report on 6 of the patients from our present study, indicate that frequent, new Gd-enhancing lesions occur in patients without corresponding clinical changes [17–19]. These findings indicate that MRI parameters and, in particular, Gd-enhancing lesions, should be helpful in monitoring disease activity in patients with MS and may provide a suitable tool for assessing the effectiveness of clinical trials, particularly in patients with early, mild, relapsing-remitting MS [1, 20].

Our previous investigation of patients with MS using Gd-enhanced MRI suggested that the occurrence of enhancing lesions was not constant over time. Because the pattern of lesion occurrence affects the usefulness

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of MRI in monitoring clinical trials, the initial study has been expanded into an extended longitudinal examination of 10 patients with relapsing-remitting MS and 2 patients with chronic-progressive MS studied for 12 to 21 months. The data derived from this study have been used to evaluate the optimal design of a clinical trial using Gd-enhanced lesions as the primary outcome measure.

Materials and Methods

Patient Selection

This study was reviewed and approved by the Institute Clinical Research Subpanel and informed consent was obtained from each patient prior to beginning the study. Twelve patients with clinically definite MS were selected for this study. Disability was classified according to the Expanded Disability Status Scale (EDSS) [21]. Ten patients had relapsing-remitting MS and 9 of these had mild disability (EDSS $\leq$ 3.5). The tenth patient with relapsing-remitting disease had an EDSS score of 6.5 and required bilateral assistance to walk due to corticospinal tract involvement, but her other clinical findings were mild. Two patients had chronic-progressive disease; 1 started with a relapsing-remitting course, whereas the other (Patient 12) had a chronic-progressive course since the onset of his illness.

Patient Evaluation

Patients were imaged and examined monthly. Examination consisted of a standardized neurological examination. Patients were rated using the functional systems scale and EDSS. Exacerbations were defined using a modification of the Schumacker criteria [22] and consisted of any new symptom or worsening of previous symptoms associated with significant changes in signs lasting longer than 24 hours.

MRI Scans

Imaging was performed monthly for 12 to 21 months in the 12 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 to the lateral canthus of the eye. The canthal-meatal line between these capsules delineated the plane of each scan. A scout slice was performed at the start of each study to establish consistent head positioning. MRI scans were performed on a General Electric Signa 1.5T unit (General Electric, Milwaukee, WI) 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 $\times$ 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 approximately 5 minutes after Gd (Magnevist, 0.1 mmol/kg; Berlex Laboratories, Cedar Knolls, NJ) was administered, using 2 excitations, a 192 $\times$ 256 acquisition matrix, and 5 mm contiguous slices. All studies were performed with a field of view of 24 cm.

Image Evaluation

MRIs were evaluated by at least 2 neurologists, and questionable lesions were reviewed with a neuroradiologist. T1-weighted, Gd-enhanced images were visually compared to images taken prior to administration of contrast. Most enhancing lesions were 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. Lesions were numbered sequentially, and new enhancing lesions were defined as lesions that had not enhanced the previous month. Reenhancement of lesions was noted in patients studied for more than 12 months. Because reenhancing lesions may reflect areas of renewed breakdown of the blood-brain barrier, they have been considered new lesions.

Statistical Analysis

Inspection of the frequency of lesions indicated that the number of lesions varied from month to month in the same patient. Because there was a suggestion of a cyclical trend in lesion frequency, new and total enhanced lesion data were examined by fitting the data to Poisson regression models [23] with sinusoidal trends. The best fitting sinusoidal curve with a frequency between 2 and 14 months was obtained and compared using a chi-square test to the data fitted to a model employing a constant mean. Lesions occurring randomly would have a best fit with the model employing a constant mean. Such a comparison is particularly sensitive for detecting a pattern of fluctuations between high and low frequency. This analysis was done using Poisson regression in conjunction with an analytic technique [23] originally proposed for another application [24]. A p value of 0.01 was chosen as the cutoff for statistical significance to account for multiple comparisons inherent in fitting these models separately to each of the 10 patients.

The data from the 10 patients with relapsing-remitting MS were used to calculate sample sizes for various trial designs. The sample sizes required to detect a 50% reduction in lesion frequency due to treatment (alpha = 0.05, power = 0.8; two-tailed test) were computed for various parallel and crossover study designs using variance estimates obtained with repeated sampling techniques (the bootstrap analysis) [25, 26]. Sample sizes were computed using standard size calculations [27].

Results

Characteristics of Gd-enhancing Lesions

The clinical characteristics of the patients are shown in Table 1. These patients were studied with monthly MRIs, including Gd-enhanced images, for periods ranging from 12 to 21 months. A total of 197 MRIs were analyzed in this study.

With the exception of Patient 12, numerous Gd-enhancing lesions were observed in each of the patients (see Table 1). The total number of enhancing lesions was greater than the number of new enhancing lesions because some lesions persisted and were observed on more than one sequential examination (data not shown). In the majority (68%) of new lesions, enhancement was not detected at the next monthly examination, indicating that the duration of the enhancement was less than 2 months. This observation is

Table 1. Clinical Parameters of Patients Studied by Serial Gadolinium-enhanced MRI

Patient	Age (yr)	Years from Diagnosis	Course	Months Studied	EDSS		Exacerbations	Average No. Gd-enhancing Lesions	
					Start	End		Total	New
1	44	2	R/R	19	1.5	1.5	0	3.4	2.2
2	29	2	R/R	19	2.0	2.0	1	0.5	0.2
3	41	5	R/R	20	1.5	1.5	1	1.6	1.1
4	28	3	R/R	19	1.5	2.0	4	5.0	4.1
5	28	2.5	R/R	21	1.5	1.5	1	3.3	2.4
6	41	3.5	R/R	20	3.5	2.5	1	5.6	3.3
7	38	16	R/R-CP	14	5.5	6.0	0	1.8	1.1
8	31	10	R/R	14	1.5	1.5	2	5.6	3.5
9	38	2.5	R/R	13	2.0	2.5	3	0.9	0.7
10	28	6	R/R	12	6.5	6.5	1	8.0	5.9
11	43	9	R/R	14	2.0	2.0	1	3.2	2.1
12	60	17	CP	12	6.0	6.5	0	0.1	0.1

R/R = relapsing-remitting; CP = chronic-progressive.

consistent with previous reports [15, 18]. Twenty-eight percent of the lesions were seen on 2 concurrent examinations, whereas 5% persisted for 3 months. None of the lesions persisted for more than 4 months. In general, lesions persisting for 2 months or longer were observed in patients with a large number of new enhancing lesions (Patients 5, 6, 8, and 10). Reenhancement of lesions that were enhanced previously was observed in 5 patients. It is likely that reenhancement will be observed more frequently as patients are followed longer.

The mean number of Gd-enhancing lesions per month varied among the 12 patients. Although 3 of the patients with relapsing-remitting disease (Patients 2, 3, and 9) and both of the patients with chronic-progressive disease (Patients 7 and 12) had an average of 2 or fewer new lesions per month, 4 of the patients with relapsing-remitting disease (Patients 4, 6, 8, and 10) had an average of 3 or more new lesions per month.

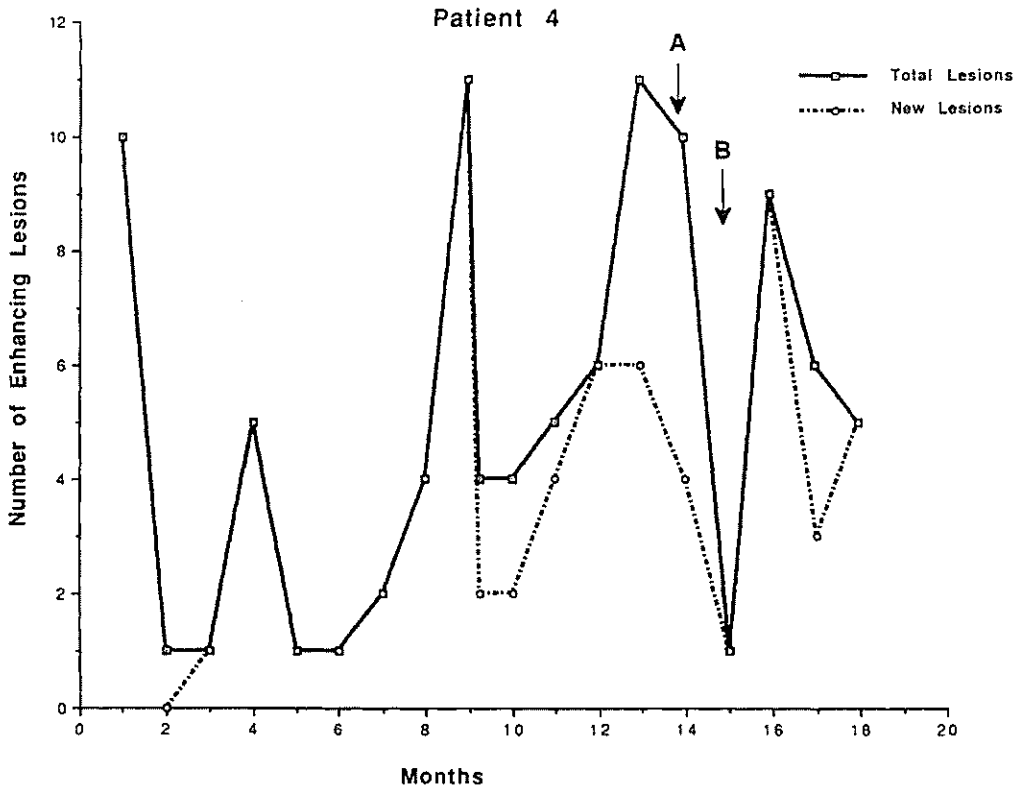
Pattern of Lesion Occurrence

As indicated, inspection of the frequencies of new enhancing lesions indicated that the lesions were not occurring at a constant rate but tended to occur in bursts of increased lesion frequency. Figure 1 illustrates the fluctuating number of Gd-enhancing lesions in Patient 4. By inspection, the pattern of lesion frequency in this patient had a cyclical trend. A suggestion of a similar cyclical pattern in lesion frequency was also observed in the other patients. Consequently, the likelihood that the pattern of lesion occurrence was not random was assessed using Poisson regression models as described in Materials and Methods. In 6 of the 10 patients with relapsing-remitting MS, the total and new lesion data fit a model employing a sinusoidal mean significantly better than a model using a constant mean ($p < 0.01$) (Fig 2). This finding indicates that the mean of the lesion frequency was not constant and that the lesions were not occurring with random frequency. Although not reaching statistical significance, a sinusoidal trend in lesion frequency was also observed in 3 of the remaining 4 patients ($p < 0.06, 0.12, 0.12$). The Poisson regression model with sinusoidal trends was used only as a means to describe the fluctuating nature of lesion frequency over short durations and to test for nonconstancy in lesion frequency. The model was not intended as a definitive description of lesion occurrence. Using the fitted curves, the period between the peaks in lesion frequency varied considerably and ranged from 2.1 to 12 months. The mean period between peaks in the patients showing a significant fit to a sinusoidal curve was 6.2 and 5.9 months for all 10 patients.

Correlations Between Clinical Changes and Gd-enhancing Lesions

As reported previously, the frequency of enhancing lesions seen on MRI did not necessarily parallel clinical changes. Most notable was Patient 12, who despite continued clinical progression had only 1 enhancing lesion during 10 months of study. Because the clinical course demonstrated by Patient 12 may represent a unique form of MS (i.e., primary chronic-progressive MS) [18, 28, 29], the findings from this patient were excluded from the subsequent analysis.

A dissociation between clinical change and enhancing lesions in the cerebrum was observed in the 11 remaining patients. All had new enhancing lesions, often numerous, that occurred without new symptoms or abnormalities on neurological examination.



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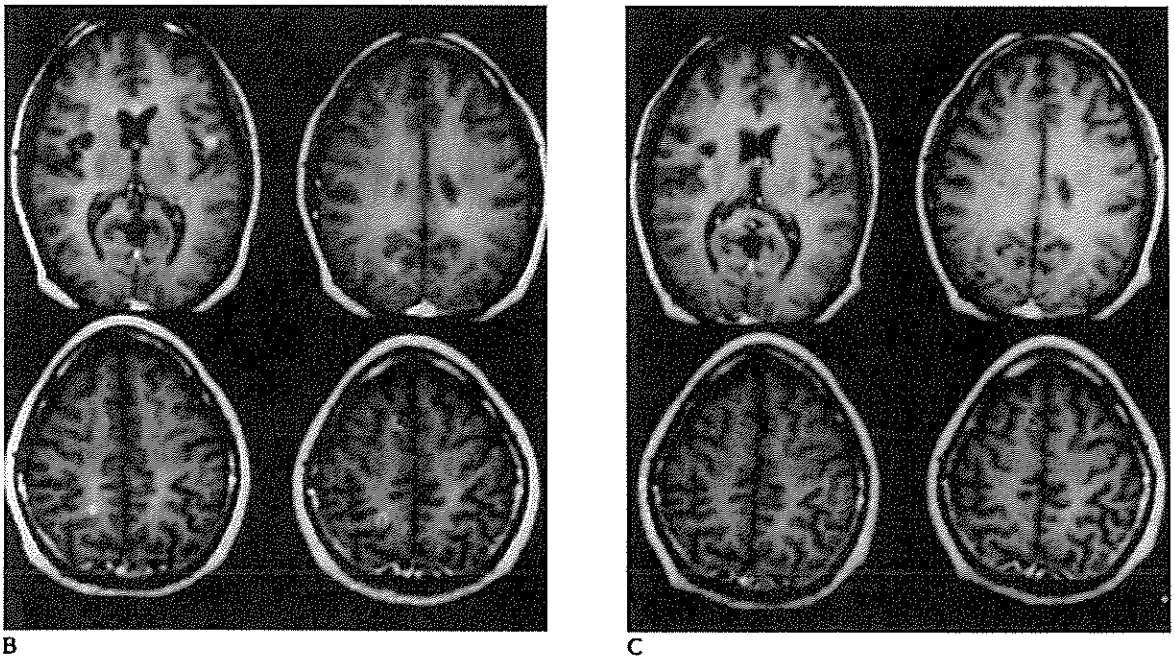

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Fig 1. (A) Fluctuations in number of total and new Gd-enhancing lesions in Patient 4. (B) T1-weighted postgadolinium MRI of Patient 4 at month 14. Four representative slices are shown demonstrating multiple enhancing lesions. (C) T1-weighted postgadolinium MRI at month 15. Four representative slices showing reduction in number of enhancing lesions.

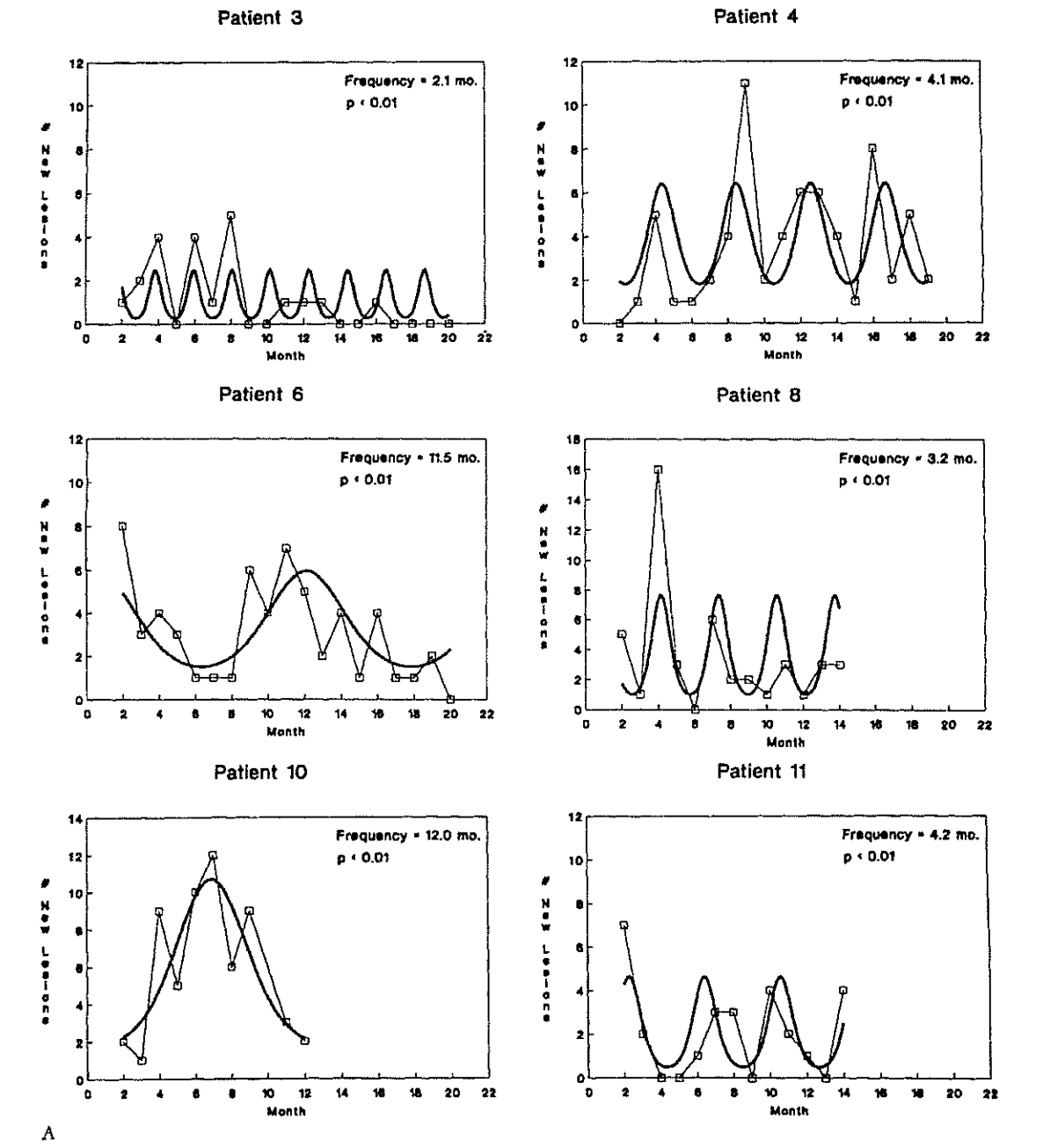

Fig 2. The observed number of new lesions and the frequency of lesions derived from the best fitting Poisson regression model with sinusoidal trends. (A) $p < 0.01$. *(B)* $p > 0.01$.

For example, Patient 1, who had a mean of 2.2 new Gd-enhancing lesions per month, was clinically stable throughout the 19-month study period. Each of the remaining 10 patients had one or more exacerbations (see Table 1). The clinical findings associated with these exacerbations could not be explained by the location of the new enhancing lesions in the cerebrum and, in most instances, were consistent with involvement of the spinal cord or the brainstem.

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