SHORT REPORT

A preliminary study into the sensitivity of disease activity detection by serial weekly magnetic resonance imaging in multiple sclerosis

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Abstract

Long TR and gadolinium enhanced spin echo brain MRI was performed weekly for three months in three patients with relapsing-remitting or secondary progressive multiple sclerosis. During the study, 38 new enhancing lesions were seen; 11 showed enhancement for less than four weeks, and two enhanced on only one scan. All 16 new lesions seen on long TR scans showed initial enhancement. When only every fourth (monthly) scan was analysed, a total of 33 new enhancing lesions were seen. Subject to confirmation in a larger cohort, the results suggest: (a) that blood brain barrier leakage is an invariable event in new lesion development in relapsing-remitting and secondary progressive multiple sclerosis; (b) the small increase in sensitivity of weekly scanning does not justify its use in preference to monthly scanning when monitoring treatments.

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Serial brain MRI at monthly intervals has provided valuable insights into the natural history of multiple sclerosis, and is now often used to monitor the efficacy of experimental treatments.^{1,2} Scanning at this interval often shows asymptomatic new lesions in relapsing-remitting or secondary progressive multiple sclerosis, on average five to 10 times more often than clinical relapse.^{3–10} About 80% of new lesions on unenhanced conventional long TR spin echo scans show gadolinium enhancement (on T1 weighted spin echo sequences),^{5,6,11} indicating a breach of the blood-brain barrier. Gadolinium enhancement correlates with pathological features of activity—namely, perivascular lymphocyte and macrophage infiltration and myelin breakdown,^{3,12,13} and has usually ceased at the next monthly follow up although the associated long TR abnormality persists. Foci of enhancement are also often found in the absence of a definite corresponding change on the long TR images.¹¹ Thus the power of MRI in monitoring the effect of

lesion activity is increased by acquiring enhanced images in addition to standard long TR scans.

Two important questions arising are: (1) does increasing the frequency of MRI detect more active lesions, thus improving the sensitivity of the technique for therapeutic monitoring; (2) do new lesions appearing on monthly long TR scans without showing gadolinium enhancement display enhancement at shorter intervals—evidence that they do would suggest that impairment of the blood-brain barrier is an obligatory early event in the development of lesions in multiple sclerosis. To consider these questions, we have performed weekly MRI for three months in three patients, one with relapsing-remitting and two with secondary progressive multiple sclerosis.

Patients and methods

PATIENT SELECTION

The patients chosen had to have clinically definite multiple sclerosis¹⁴ of the relapsing-remitting or secondary progressive type^{5,6} and had to have gadolinium enhancement on their first scan. These criteria were to increase the possibility of a high yield of new gadolinium enhancing lesions during the study.¹¹ Of 11 patients screened only three had enhancing lesions. Thus eight patients did not continue after their first scan.

MRI PROTOCOL

Informed consent for gadolinium enhanced MRI was obtained from each patient before the commencement of the study.

Each patient was given 0.1 mmol/kg gadolinium-DTPA intravenously. The MRI protocol was then performed as follows:

Firstly, three sets of pilot scans were performed for the purposes of repositioning. These were a T1 weighted sagittal scan, an axial scan, and a coronal scan. After this an axial fast spin echo sequence was used to acquire long TR scans through the cerebral hemispheres (TR = 1500 ms, TE_f = 32/80 ms, slice number 16, slice thickness 5 mm, field of view 24 cm, matrix 256 × 128). Gadolinium enhanced T1 weighted images were then obtained (TR = 500 ms, TE = 14 ms, slice number 16, slice thickness 5 mm, field of view 24 cm, matrix 256 × 128).

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Top row: T1 weighted gadolinium enhanced MRIs. Bottom row: equivalent long TR scan acquired in the same study. The sequences show the development of two lesions (A and B). Lesion A enhances for one scan only with changes on the long TR scan one week later. Lesion B continued to enhance on six scans. A new lesion appeared on the long TR scan simultaneously with the enhancement.

Thirteen weekly studies were performed with the above protocol on each patient. Lesion activity was reported from hard copies by two radiologists (TH, MG-C).

Results

CLINICAL DATA

Patient 1 (aged 38 years) had relapsing-remitting multiple sclerosis. At the start of the study her expanded disability status scale (EDSS)¹⁵ score was 6. She had one mild relapse in the fourth week of the study. At the end of the study her EDSS score was still 6.

Patient 2 (aged 35 years) had secondary progressive multiple sclerosis. The initial

EDSS was 6. Further decline was observed during the study and the final EDSS was 7.

Patient 3 (aged 40 years) had secondary progressive multiple sclerosis. The initial EDSS was 7. She had no further decline during the study.

MRI DATA

The weekly gadolinium enhanced scans were reviewed first. During follow up, 38 new enhancing lesions appeared. Thirteen were still enhancing on the final scan. Of these 13, enhancement was present on six scans in one lesion, five scans in two, four scans in three, three scans in one, two scans in three, and the final scan only in three.

Of the 25 new enhancing lesions which could be followed up from the beginning to the end of enhancement, 11 (44%) enhanced for less than one month (on three scans or less). Two lesions enhanced on just one scan (figure).

To compare the sensitivity of weekly and monthly scanning, the first, fifth, ninth, and 13th scans were considered to be the monthly scans for this study. These scans showed 33 new enhancing lesions. Thus monthly scanning would have missed only five of 38 (13%) new enhancing lesions detected on weekly scans (see table: lesions 6, 12, 14, 24, and 25).

The weekly proton density and T2 weighted (long TR) scans were then reviewed without reference to the enhanced images. A total of 16 new lesions was seen. The images were then compared with the weekly enhanced scans, and it was apparent that all the new lesions on long TR scans displayed gadolinium enhancement at their first appearance. However, two of the new lesions on long TR were no longer enhancing on the next "monthly" scan. Thus monthly scanning showed 35 new lesions, 33 enhancing and two not (see table: lesions 12 and 24), whereas

Duration of enhancement of the 25 lesions in which enhancement could be followed from the beginning to the end

Lesion number	Week of study												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1		x	x	x	x	x	x						
2				x	x	x	x	x					
3				x	x	x	x	x					
4				x	x	x	x	x					
5				x	x	x	x	x					
6					x	x	x	x					
7					x	x	x	x					
8					x	x	x	x					
9									x	x	x		
10				x	x	x	x	x	x	x			
11					x	x	x	x	x	x			
12						x	x	x					
13							x	x	x	x			
14							x	x					
15									x	x			
16		x	x	x	x								
17		x	x	x	x	x							
18			x	x	x	x	x	x	x	x	x	x	
19				x	x	x	x	x	x	x			
20					x								
21					x	x	x						
22								x	x		x		
23								x	x	x			
24								x					
25									x	x	x		

Weeks 1, 5, 9, and 13 are shaded and simulate the analysis points of the "monthly" scans. An "x" indicates the presence of enhancement of a lesion. Thus at the monthly time points the enhancement of lesions 6, 12, 14, 24, and 25 would have been missed. However, lesions 12 and 24 could be clearly seen as new lesions on the long TR scan.

weekly scanning showed 38 new lesions, all enhancing.

Discussion

This study of three patients with relapsing-remitting (one patient) or secondary progressive (two patients) multiple sclerosis was intended to compare the sensitivity of weekly versus monthly brain MRI in detecting active lesions in multiple sclerosis, and to elucidate the consistency with which leakage of the blood-brain barrier occurs in the initial stages of new lesion formation. We are aware of only one other study in which weekly gadolinium enhanced scanning was performed, but in this the sensitivity of weekly versus monthly scans and the duration of enhancement were not described.¹⁶

As in a previous study of serial monthly scans,¹¹ we found that gadolinium enhancement markedly increased the yield of newly active lesions compared with unenhanced long TR SE images alone. The reasons for the greater sensitivity of enhanced scans have been discussed in detail elsewhere.¹¹ However, there was only a slight drop in the number of enhancing lesions comparing monthly with weekly enhanced scans. The slightly lower sensitivity of monthly scans should not appreciably alter the power of MRI to monitor disease activity in natural history or treatment trial studies, and if confirmed in a further study of a larger cohort, it would seem that the major additional burden to the patient and cost of weekly examinations will not be justified in such a setting.

On weekly scanning, every new lesion on long TR images showed an initial phase of gadolinium enhancement. The study establishes that enhancement sometimes lasts for less than two weeks, and it seems likely that new non-enhancing long TR lesions seen on monthly scans do have a brief phase of enhancement (as indeed seen in two lesions in the present study). Although we have only studied three patients, the consistency of this finding suggests that breakdown of the blood-brain barrier is an invariable and perhaps obligatory event in the development of new lesions in relapsing-remitting or secondary progressive multiple sclerosis. Such a conclusion supports earlier work in which enhancement has been found to precede the appearance of the long TR lesions in four instances, and clinical relapse in one.¹⁷

Unlike the relapsing forms of the disease, gadolinium enhancement is infrequently seen in new long TR lesions on monthly scans of patients with primary progressive multiple sclerosis, a relatively uncommon subgroup of patients in whom there is progressive deterioration in symptoms from onset without relapses.⁵ We wondered whether such lesions might enhance but for a shorter duration than those in patients with relapsing disease, and we performed weekly scans in four primary progressive patients to explore this possibility (unpublished data). There were, however, no new lesions during that study, reflecting the low frequency with which they appear in this group.

An alternative explanation is that there is a low grade leak to the blood-brain barrier which is not detectable using standard doses of contrast. Pathologically, low grade inflammation is indeed seen in primary progressive multiple sclerosis¹⁷ and a recent study using a higher dose of contrast agent (0.3 mmol/kg Gd-DTPA) has disclosed a substantial increase in the number of enhancing lesions.¹⁹

The role of the blood-brain barrier in the development of new lesions and its relation to the patient's clinical state are important issues which need to be considered. In this regard techniques are needed which maximise the sensitivity of MRI to impairment of the blood-brain barrier. These include the use of higher doses of gadolinium chelates, magnetisation transfer T1 weighted sequences,²⁰ and 3D volume T1 weighted gradient echo sequences.

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