Gadolinium enhanced MRI predicts clinical and MRI disease activity in relapsing-remitting multiple sclerosis

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Abstract

The aim of the study was to evaluate the predictive power of baseline gadolinium (Gd) enhanced MRI in relation to subsequent clinical and MRI activity.

Sixty eight patients with clinically definite relapsing-remitting multiple sclerosis had a baseline Gd enhanced MRI and were followed up clinically and by monthly Gd enhanced MRI for six months.

The occurrence of relapses during the follow up period was predicted by the presence of at least one enhancing lesion on the baseline MRI ($P < 0.05$). The number and volume of enhancing lesions at baseline were significantly associated with both enhancing lesions observed during the follow up period ($P < 0.0001$) and the accumulation of abnormality on T2 weighted images ($P < 0.0001$). Moreover, the presence of three or more enhancing lesions at baseline scan was consistently associated with the development of permanent abnormalities on T2 weighted images six months later.

The study suggests that the number and volume of Gd enhancing lesions at a single examination are strong short term predictors of subsequent clinical and MRI activity.

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There is a general agreement that an abnormal MRI in patients presenting with a clinically isolated syndrome suggestive of multiple sclerosis is predictive of the development of clinically definite multiple sclerosis.[1–6] The value of MRI in predicting disease progression is less clear in clinically definite multiple sclerosis. A serial MRI study over a two to three year period in nine patients with relapsing-remitting multiple sclerosis suggested that lesion enhancement may be related to subsequent clinical worsening.[7] Another study showed that the number of enhancing lesions during the six month serial MRI study was weakly predictive of disability at five years in secondary progressive multiple sclerosis.[8] By contrast other authors reported that the change in number of new lesions on T2 weighted images or number of enhancing lesions on T1 weighted images did not predict the changes in disability two weeks later.[9]

The aim of this study was to identify whether baseline gadolinium (Gd) enhanced MRI predicts six month clinical and MRI activity in relapsing-remitting multiple sclerosis.

Materials and methods

As part of an open cross over recombinant human interferon β-1a study, 68 patients with relapsing-remitting multiple sclerosis were studied clinically and with monthly enhanced MRI over a six month observation period before the treatment phase.[10] Neurological examination was also performed at the time of clinical exacerbations. In case of relapse the patients were treated with intravenous methylprednisolone (1 g daily for six days).

Brain MRI was performed on a Toshiba 50 S superconductive 0·5 unit using a T2 weighted spin echo pulse sequence with echo times (TE) of 30 and 90 ms, a repetition time (TR) of 2500 ms, two excitations, 256 × 160 matrix, and 5 mm slices with a 1 mm gap between sections in a field of view of 25 cm. T1 weighted spin echo (TR 400/TE 18) images were obtained 15 minutes after injection of Gd-DTPA at 0·1 mmol/kg.

The presence and number of enhancing lesions on T1 weighted postcontrast images were identified directly from the computer screen with a multislice view. The volume of enhancing lesions was estimated with a semiautomated local thresholding technique by analysing each slice in turn (Sun Microsystem, Mountain View, CA, USA).[11]

T2 weighted images were analysed at the baseline and the seventh scan with a semiautomated thresholding technique.[11] The number of new lesions and the change in total lesion volume from baseline to the seventh scan were compared.

DATA ANALYSIS

The presence of at least one enhancing lesion (enhancing scan), the number and volume of

total enhancing lesions and total lesion volume on T2 weighted images on the baseline scan were considered as the baseline MRI parameters.

The occurrence of relapses over the six month follow up period was defined as the indicator of clinical activity.

Activity on MRI included the mean number and volume of monthly enhancing lesions (total and new) over the follow up, the number of new lesions, and the change in total lesion volume on T2 weighted images from baseline to seventh scan.

The relations between all baseline MRI parameters considered as being potential determinants and indicators of disease activity were evaluated by linear regression analysis and logistic regression analysis. Unpaired t tests and χ^2 tests were also used.

Results

BASELINE CLINICAL/MRI FEATURES

We studied 68 patients with relapsing-remitting multiple sclerosis (21 men and 47 women). Mean (SD) age was 30·5 (7·3) years, disease duration was 5·0 (2·9) years, and expanded disability status scale (EDSS) score was 2·15 (0·9). The number of relapses in the previous 12 months was 1·5 (0·8) and the time between the last relapse and study entry was 5·1 (3·2) months.

The mean (SD) number and volume of enhancing lesions on baseline scan were 1·8 (3·6) (range 0 to 23, median 1) and 231 (403) mm³ (range 0 to 2335, median 75) respectively. The mean total lesion volume on T2 weighted images was 13 201 (11 548) mm³ (range 1135 to 48 890, median 8975). An enhancing baseline scan was seen in 35 (51%) of the 68 patients. The number of relapses in the year before study did not predict the presence of enhancement on the baseline scan, whereas the time between the last relapse and baseline scan did so (P = 0·02, unpaired t test).

CLINICAL AND MRI FINDINGS OVER THE SIX MONTH PERIOD

Thirty six patients (53%) had a total of 58 clinical exacerbations, 43 of which required treatment with corticosteroids.

Enhancing lesions were detected on 238 (58%) of 407 scans. The mean (SD) number of monthly total and new Gd enhancing lesions per patient were 3·0 (4·3) (range 0 to 23·5, median 1·5) and 2·6 (3·8) (range 0 to 21·7, median 1·3) respectively, and the volume of total enhancing lesions was 471 (693) mm³ (range 0 to 3708, median 193). The presence of at least one enhancing scan over the six month period was noted in 33 of the 35 patients (94%) with enhancing baseline scan and in 28 of 33 patients (85%) with unenhancing baseline scan.

RELATIONS BETWEEN BASELINE MRI CHARACTERISTICS AND INDICATORS OF DISEASE ACTIVITY

Twenty three of the 35 patients (66%) with an enhancing baseline scan and 13 of the 33 patients (39%) with a non-enhancing scan had a relapse. At logistic regression analysis, a baseline enhancing scan significantly predicted the occurrence of relapses (odds ratio 3·2, 95% confidence interval 1·2–8·9, P < 0·05). At linear regression analysis the number of enhancing lesions on the baseline scan was predictive of the number of monthly total and new enhancing lesions (P < 0·0001) whereas enhancing volume predicted the volume of monthly total enhancing lesions (P < 0·0001; table 1). Similar results were found when the first scans after each methylprednisolone treatment were excluded (43 of 407 scans; data not shown).

The number of enhancing lesions on the baseline scan also predicted the number of new lesions on T2 weighted images from baseline to seventh scan (P < 0·0001). Finally, the total lesion volume on T2 weighted images and the volume of enhancing lesions on the baseline scan predicted the change in total lesion volume on T2 weighted images (P < 0·001 and P < 0·05 respectively; table 1).

The patients with three or more Gd enhancing lesions on baseline scan had a significantly higher rate (100% probability) of occurrence of new lesions and of an increase in total lesion volume on T2 weighted images at follow up compared with those with two, one, or no enhancing lesions (P = 0·03 and P = 0·01, χ^2 test respectively). However, the probability of having a clinical relapse in the patients with three or more enhancing lesions on the baseline scan was not significantly different from that of the others (P = 0·4, χ^2 test; table 2).

Table 1 Association of baseline MRI parameters with indicators of MRI disease activity during a six month follow up

Predictive baseline MRI parameters	*Indicators of MRI activity during follow up*	*β (SEM)*	*P value*
No of enhancing lesions	Mean No of monthly enhancing lesions	1·02 (0·08)	< 0·0001
	Mean No of monthly new enhancing lesions	0·92 (0·07)	< 0·0001
	No of new lesions on T2	0·58 (0·17)	< 0·0001
Volume of enhancing lesions (mm³)	Mean volume of monthly enhancing lesions (mm³)	1·09 (0·17)	< 0·0001
	Change in total lesion volume on T2 (mm³)	2·13 (1·05)	< 0·05
Total lesion volume on T2 (mm³)	Change in total lesion volume on T2 (mm³)	0·12 (0·04)	< 0·001

β = linear regression coefficient.

Table 2 Relation between Gd enhancing lesions on baseline MRI and disease activity over a six month period

	No of Gd enhancing lesions on baseline MRI				
	0	*1*	*2*	*3*	*⩾ 4*
No of patients	33	11	10	5	9
No of patients with increased total lesion volume on T2	22 (68)	7 (64)	6 (60)	5 (100)	9 (100)
No of patients with new lesions on T2	20 (61)	10 (91)	8 (80)	5 (100)	9 (100)
No of patients with relapses	13 (39)	7 (64)	7 (70)	3 (60)	6 (67)
No of new enhancing lesions/month/patient:					
Mean	1	1·9	1·9	5·1	9·1
Median	0·5	1·3	1·8	6·8	6·3
Range	0–7·3	0–5·3	0·2–3·7	0·5–8·3	3–21·7

Values in parentheses are %.

Discussion

The type of clinical course or the phase of disease are poor predictors of subsequent worsening in multiple sclerosis and there is some evidence that MRI may be superior in this respect.[7 8 12 13]

This study demonstrates that the presence of a single enhancing scan is predictive of subsequent relapse. Because patients with an enhancing scan will develop more enhancing lesions during follow up, it is likely that one of these lesions could be located in a clinically relevant brain area.

We found that the number of enhancing lesions on the baseline scan predicts the mean number of total and new enhancing lesions during the follow up period. Miller *et al* have similarly reported that a single enhancing MRI can be quite strongly predictive of the amount of enhancing activity in the next three months.[13] Furthermore, the number of new lesions and the increase in total lesion volume on T2 weighted images from baseline to seventh scan were predicted by the number and volume of enhancing lesions at baseline respectively. These data strongly suggest that the more active the disease, the greater the accumulation of permanent abnormalities even over a brief follow up period. This is not surprising since longitudinal MRI studies have previously shown that most enhancing lesions are followed by permanent T2 abnormalities.[14]

The change in total lesion volume on T2 weighted images is also predicted by the total lesion volume on the baseline scan. This finding complements previous MRI studies, which demonstrated that in patients with a clinically isolated syndrome suggestive of multiple sclerosis the lesion load at presentation correlates with increase in lesion load at five year follow up.[5 6]

Our study supports the role of Gd enhanced brain MRI as a possible surrogate marker for exploratory or preliminary phase II trials. In this respect, the term "surrogate" seems to be appropriate as it indicates a non-clinical assessment which may predict short term disease activity. Furthermore, the highly predictive value of three or more enhancing lesions on baseline scan for subsequent MRI activity emphasises the importance of including MRI in relatively short term trials.

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