Secondary progressive multiple sclerosis: the relationship between short-term MRI activity and clinical features


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Summary
We report the findings in 60 patients with secondary progressive multiple sclerosis who had monthly brain MRI studies for 4 months (one baseline and three follow-up scans). The purpose was to define the short-term MRI natural history in a large cohort with secondary progressive disease and to ascertain its relationship with other clinical and MRI features. The patients were participating in either a natural history study or the placebo arm or non-treatment phase of a therapeutic trial. The cohort had clinical features typical of secondary progressive disease: thus, all had moderate or severe locomotor disabilities [Expanded Disability Status Scale (EDSS), score 3.5–8], with a median disease duration of 12 years. There was equal representation of males and females. During the 3 months of follow-up there was a total of 362 new enhancing lesions seen in 42 patients, and there were 24 relapses in 20 patients. There was no correlation between new enhancing lesions and age at study entry, age of disease onset, gender, disease duration or EDSS, but there was a strong correlation with the number of enhancing lesions on the baseline scan ($r = 0.65$, $P < 0.0001$) and subsequent activity. There was a non-significant trend for higher numbers of new enhancing lesions in those having relapses during the 3 months of scanning ($P = 0.14$) or in the preceding 6 months ($P = 0.06$). The 34 patients who did not relapse in either period had significantly fewer new active lesions ($P = 0.02$) than those who relapsed at some stage during the 9 months. Nevertheless, considerable activity was seen in the non-relapsing cohorts: there was a mean of 3.5 (median 2) new enhancing lesions in those not relapsing during the 3 month study, and 5.5 (median 2) in those not relapsing in the previous 6 months. We conclude that short-term MRI activity is generally high in secondary progressive disease, confirming a useful role for the technique in exploratory trials. Further work should concentrate on elucidating the mechanisms of secondary progression by longer term follow-up studies of larger cohorts using multiple MRI and clinical measurements.

Keywords: multiple sclerosis; secondary progressive; MRI; exploratory treatment trials

Abbreviation: EDSS = Expanded Disability Status Scale

Introduction
In 90% of patients with multiple sclerosis, the early clinical course is characterized by acute relapses and remissions. In about one-third of the patients this relapsing–remitting phase persists over many years, often with minimal disability. However, after a variable interval the remainder begin to accumulate disabilities in a slow but steady fashion. This secondary progressive phase may develop with or without superimposed relapses. Entry to the secondary progressive phase has consistently been reported to portend a poorer prognosis (Confavreux et al., 1980; Weinshenker et al., 1989). Serial MRI has provided important new insights into the natural history of both relapsing–remitting and secondary progressive disease, and has become a widely used tool for monitoring therapy in these subgroups (Miller et al., 1996). Small cohort studies have reported similar and generally high levels of asymptomatic MRI activity in both groups, although...

Small cohort studies afford little opportunity to correlate MRI and clinical features reliably, although one consistent finding has been a higher frequency of enhancing lesions during relapses in both relapse-remitting and secondary progressive phases. A more detailed analysis was possible in a larger cohort of 68 relapse-remitting patients who had three consecutive monthly scans (Stone et al., 1995); MRI activity was found to correlate significantly with age and disability status. No secondary progressive cohort of this size has previously been analysed. Such a study is valuable in order to optimize strategies for therapeutic monitoring in secondary progressive disease and to gain further insight into the pathophysiological mechanisms of secondary progression, which at present are poorly understood. The present study reports on 60 patients with secondary progressive multiple sclerosis who had four serial MRI and clinical evaluations over 3 months.

Methods
We identified 60 patients from our centres with secondary progressive multiple sclerosis who had undergone at least four consecutive monthly enhanced MRI scans. Seventeen of the patients had been involved in previous natural history studies (Thompson et al., 1991; Kidd et al., 1996), 10 had been in the placebo arm of a parallel groups therapeutic trial of anti-CD4 monoclonal antibody (van Oosten et al., 1997), and 33 patients were enrolled in a single crossover study of the humanized anti-CD52 antibody Campath-IH, which required four consecutive months of enhanced MRI before treatment (protocol as used by Moreau et al., 1994). None of the patients had received any potential disease-modifying therapies during the 3 month period, although acute relapses, defined according to the criteria of Poser et al. (1983), were sometimes treated with a short course of intravenous methylprednisolone.

Secondary progressive multiple sclerosis was defined as having a slowly progressive increase in disability for at least 6 months, with or without superimposed relapses, after an initial relapsing-remitting phase (Lublin and Reingold, 1996). Disability was measured with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) at entry (month 0) and at exit (month 3). The MRI scans were all performed using similar protocols. Proton density and T2-weighted images (TR 2000–3500, TE 18–120 ms) were performed initially. Following the intravenous injection of 0.1 mmol/kg of gadolinium-diethylenetriaminepenta-acetic acid, a T1-weighted image was obtained (TR 360–640, TE 13–40 ms). The scans were carried out at 1.5, 0.6 and 0.5 T in 48, three and nine patients, respectively. The patients were repositioned using techniques described elsewhere (Gallagher et al., 1997). The MRIs were all reviewed by experienced neuroradiologists in our centres. All enhancing lesions on the baseline scan and the new enhancing lesions on each of the three follow-up scans were counted.

The number of new enhancing lesions on the follow-up scans was correlated with the following parameters: age at scanning, age of onset of disease, sex, disease duration (i.e. from the time of first symptom), EDSS at study entry, clinical relapses during the study period or in the preceding 6 months, duration of the initial relapse-remitting and of the current secondary progressive phases, the progression index for each patient (i.e. the EDSS/disease duration in years), and enhancement on the baseline scan.

Statistical analysis was performed using descriptive statistics such as the mean, median, range and standard deviation to describe the average frequency of new enhancing lesions over the 3 month follow-up period in the entire cohort, as well as for comparing the frequency of new lesion activity in various subgroups.

Non-parametric testing using the Mann–Whitney U-test statistic was used to compare differences in lesion frequency between patients who had relapsed either during the 3 months of the study or in the preceding 6 months, and those who had not relapsed. It was also used to compare the differences in lesion frequency in patients aged >40 years and those <40 years at the time of the study. Spearman rank correlation coefficients were used to examine for association between the number of new enhancing lesions during the study and enhancing lesions on the baseline scan, the patient’s age of disease onset, disease duration, the duration of the relapse-remitting and secondary progressive phases of disease, the EDSS at entry and the progression index.

Results
There were 29 males and 31 females. Their mean age at the time of the study was 40 years (median 39; range 24–57; SD 8). The mean age of disease onset was 28 years (median 27; range 13–47; SD 8). There was wide variation in the duration of the initial relapse-remitting phase (mean 8 years; median 8; range 1–23). Wide variation was also seen in the duration of the secondary progressive phase (mean 3 years; median 2; range 1–12). The mean EDSS at the start of the scanning period was 5.5 (median 6; range 3.5–8; SD 1), and at exit from the study it was 6 (median 6; range 4–8.5; SD 0.8).

Thirty-two patients (53%) displayed a total of 282 enhancing lesions on the baseline scan. During follow-up, a total of 362 new enhancing lesions was seen (mean 6 per patient, range 0–75) (Fig. 1). Forty-two patients (70%) displayed one or more new enhancing lesions (Fig. 1). Fourteen patients showed no enhancing lesions either at baseline or follow-up. During the study period there was a total of 24 clinical relapses in 20 patients. In the 6 months prior to scanning, 19 patients had a clinical relapse.

There were no significant correlations between the number of new enhancing lesions during the study and age at study,
age at onset of disease, total disease duration, or of the relapse-remitting and secondary progressive phases, gender, EDSS at entry or progression index (Table 1). There was a non-significant trend for older patients to show less MRI activity: for those aged less than 40 years \((n = 32)\), there was a mean of 8 new enhancing lesions per patient (median 4, range 0–75, SD 15); for those aged 40 years or more \((n = 28)\) the mean was 4, median 2, range 0–24, SD 12 \((P = 0.08, \text{Mann–Whitney } U\)-test) .

Although not significant, there was a trend for the group having relapses during the 3 months of scanning to develop more new enhancing lesions than those who did not (Tables 1 and 2); a similar non-significant trend was noticed for those having a relapse in the previous 6 months when compared with those who did not (Tables 1 and 2).

Thirty-four patients (16 males and 18 females) did not relapse either in the 3 months of scanning or in the previous 6 months. This group had significantly fewer new enhancing lesions over the 3 months of scanning than the 26 patients who relapsed at some stage during the 9 month period (non-

### Table 1  Correlation of the number of new enhancing lesions during the study with other clinical and MRI variables

<table>
<thead>
<tr>
<th></th>
<th>( r ) value</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>Enhancing lesions on baseline scan</td>
<td>0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at study</td>
<td>-0.22</td>
<td>0.09</td>
</tr>
<tr>
<td>Age of disease onset</td>
<td>-0.10</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.003</td>
<td>0.98</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.09</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of relapse-remitting phase</td>
<td>-0.14</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of secondary progressive phase</td>
<td>-0.11</td>
<td>0.39</td>
</tr>
<tr>
<td>EDSS at entry</td>
<td>-0.08</td>
<td>0.56</td>
</tr>
<tr>
<td>Progression index</td>
<td>0.08</td>
<td>0.54</td>
</tr>
<tr>
<td>Relapses during 3 months of scanning</td>
<td>0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>Relapses during previous 6 months</td>
<td>0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Relapses during whole 9 months</td>
<td>0.62</td>
<td>0.02</td>
</tr>
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</table>

The number of enhancing lesions on the entry scan correlated strongly with the number of new enhancing lesions in the next 3 months \((r = 0.65, \ P < 0.0001)\). Patients with enhancement on the entry scan had a mean of 9 new enhancing lesions (median 6, range 0–75, SD 13); those without enhancing lesions had a mean of 3 new enhancing lesions (median 1, range 0–43, SD 8) \((P = 0.02, \text{Mann–Whitney } U\)-test) (Tables 1 and 2).

The potential effect of scanning patients at different magnetic field strengths was also examined. The 48 patients scanned at 1.5 T had a mean of 2.9 enhancing lesions on the baseline scan (median 1, range 0–30, SD 6.23) and 6.5 new enhancing lesions on follow-up (median 4, range 0–75, SD 11.3). The 12 patients scanned at 0.5 or 0.6 T had a mean of 0.33 enhancing lesions on baseline (median 0, range 0–2, SD 0.65) and 4.08 new enhancing lesions on follow-up (median 0, range 0–43, SD 12.3). These differences were statistically significant \((P = 0.01\) for the baseline scans and \(P = 0.004\) for the follow-up scans, Mann–Whitney \(U\)-test).

There were no significant differences between the two groups...
when age, disease duration, disease onset, EDSS and progression index were compared. Also, a similar proportion of patients in each group had relapses during the whole 9 month period (five of 12 patients scanned at 0.5 or 0.6 T and 21 of 48 patients scanned at 1.5 T had a relapse at some stage). The correlation between baseline scan enhancement and subsequent MRI activity was even stronger when only the results of the patients scanned at higher field strength were analysed ($r = 0.78$, $P < 0.0001$).

**Discussion**

Secondary progression is defined in the recent Lublin and Reingold (1996) criteria as having developed when there has been a period of steadily increasing disability for at least 6 months, with or without superimposed relapses, following an initial relapse–remitting phase. In practice it is often difficult to make a firm distinction between relapsing–remitting and secondary progressive phases. Confident detection of steady neurological deterioration requires regular and accurate neurological observation. It can be especially difficult to determine when there are superimposed acute relapses followed by partial remissions, the key issue being whether the baseline is stable or progressing between relapses. Undoubtedly errors of classification are made, and it is likely that there are pathophysiological mechanisms common to the relapsing–remitting and secondary progressive phases. The major stimulus for making the distinction is the large body of evidence which indicates a poorer prognosis once patients enter a progressive phase of the disease, whether from onset (primary progressive multiple sclerosis, which occurs in ~10% of patients) or after an initial relapsing–remitting phase. The secondary progressive phase of multiple sclerosis is the one most often associated with the development of severe and irreversible locomotor disabilities.

In our series, the secondary progressive cohort had demographic features typical of those already described. Thus, the length of the preceding relapsing–remitting phase was highly variable, their median disease duration at the time of study was substantial (median 12 years), and they all had moderate or severe locomotor disabilities (EDSS range 3.5–8). We therefore feel confident that the patients were appropriately classified.

We have confirmed the observation in smaller cohorts that, although there are marked variations between individuals, as a group secondary progressive multiple sclerosis patients exhibit a considerable amount of MRI activity. The overall rate of new enhancing lesions was 15 times the clinical relapse rate during the study (362 new enhancing lesions versus 24 relapses).

We found very few correlations between short-term MRI activity and clinical features. There was at most a weak and non-significant trend for less activity in older patients with a longer disease duration. Unlike one previous report in relapse-remitting multiple sclerosis (Stone et al., 1995), neither EDSS level nor age was related to MRI activity. It is, however, of interest that the male : female ratio was 1 : 1, whereas that reported in multiple sclerosis overall is 1 : 2 (apart from primary progressive multiple sclerosis (Thompson et al., 1997). The observation of a higher proportion of males with the progressive forms of the disease is consistent with a number of natural history studies that have indicated a poorer long-term prognosis in males (Weinshenker et al., 1991; Runmarker and Anderson, 1993). The results nevertheless suggest that restrictions concerning age, gender, disease duration or EDSS are not necessary when recruiting secondary progressive patients into short-term trials using MRI as the primary outcome.

There was a non-significant trend for those with a relapse during the 3 months of scanning or in the previous 6 months to exhibit higher levels of new enhancing lesions (a significant difference was found when comparing relapsing and non-relapsing groups for the whole 9 month period). We had expected the effect of recent relapses to be more striking, one previous small cohort study having found a much greater difference between those having and those not having superimposed relapses (Kidd et al., 1996). It is possible that the difference between relapsing and non-relapsing patients is reduced by the use of high-dose corticosteroids to treat acute relapses; uncontrolled studies suggest that these cause a temporary reduction in the number of enhancing lesions for periods ranging from 1 week to 2 months (Miller et al., 1992; Barkhof et al., 1994; J. A. Frank, personal communication). However, in one of these studies there was a total of 53 new enhancing lesions amongst 10 patients 1 month after a course of 1 g methyl prednisolone per day for 3 days (our standard regime for treating relapses) (Miller et al., 1992). This suggests that the effect of this particular regime on new lesion formation is likely to be modest and transient.

Perhaps more striking was the substantial amount of MRI activity seen in the non-relapsing patients. There was a total of 139 new enhancing lesions in the 40 patients not relapsing during the 3 months of scanning (mean 3.5 per patient), and 226 new enhancing lesions in the 41 patients who did not relapse during the previous 6 months (mean 5.5 per patient) (Table 2). This suggests that for short-term MRI outcome studies it is not mandatory to confine recruitment to those who have relapsed in the last 6 months. We are not able to comment on the influence of relapses during longer periods, such as the previous 12–24 months, as we did not feel that the retrospective review of hospital and other available records was reliable beyond the most recent 6 months. Needless to say, almost all new trials require some level of recent clinical activity as part of the entry criteria to clinical trials, e.g. two relapses in the last 12–24 months (IFNB Multiple Sclerosis Study Group, 1993; van Oosten et al., 1997).

We found significantly less MRI lesion activity in the patients studied at 0.5 or 0.6 T compared with those studied at 1.5 T. Although this comparison involves different patients, the two groups exhibited a similar clinical profile; in
particular, similar proportions had relapses during the 9 month study period, this being the one clinical feature to significantly correlate with MRI activity. There is thus a real possibility that the ability to detect enhancing lesions is significantly lower at lower field strengths. A study of enhancing activity in the same cohort at 0.5 and 1.5 T would be required to clarify this issue, which has practical implications for the choice of scanner in multicentre studies.

There has been considerable debate as to whether there is a change in MRI activity as patients move from relapse-remitting to secondary progressive phases. Published series of small cohorts have given conflicting answers. Some have reported similar amounts of activity (Thompson et al., 1991, 1992; Kidd et al., 1996), others that there is less activity in secondary progressive multiple sclerosis (Fillipi et al., 1997; Molyneux et al., 1997), and one report describes higher levels of activity on T2-weighted scans in chronic progressive multiple sclerosis (the majority of patients in that study had secondary progressive disease) (Koopmans et al., 1989).

In a larger study of 68 patients who had three consecutive monthly scans at 1.5 T, a mean of 4.5 enhancing (new and persistent enhancement combined) lesions per scan was reported (Stone et al., 1995). This compares with a mean of 2.2 new enhancing lesions per scan in the 48 secondary progressive patients that we studied at 1.5 T. On monthly scans about three-quarters of the total of enhancing lesions are new and one-quarter persistent (i.e. they had enhanced the previous month) (Harris et al., 1991; Kidd et al., 1996). This will undoubtedly contribute to the lower mean and median activity rates shown in our secondary progressive group. If the numbers are increased by one-third in the secondary progressive group to allow for the (estimated) persistent enhancing lesions, the active lesion rate in our secondary progressive multiple sclerosis cohort is about two-thirds that of the early relapsing–remitting group studied by Stone et al (1995).

In an earlier study, Thorpe et al. (1993) studied a single enhanced scan of 53 relapse-remitting and 52 secondary progressive patients and reported a gadolinium score (which took note of the number and size of enhancing lesions) of 3.9 (SD 6.4) in the former group and 4.6 (SD 9.1) in the latter. Taken in conjunction with the present study, it seems that, if there is a lower level of MRI activity in secondary progressive versus early relapsing–remitting disease, it is of only a modest degree.

Our conclusion that the lesion activity differences between relapse-remitting and secondary progressive multiple sclerosis are modest is supported by another study we recently performed in 28 of our secondary progressive cohort who had been scanned for 6 months (Tubridy et al., 1997). They were compared with 31 relapsing–remitting patients who had undergone an identical scanning and activity analysis protocol at our centres in order to calculate sample size requirements for therapeutic trials using new lesion activity as the primary outcome measure. We found similar numbers of active scans in each cohort; the median number of new lesions per scan in the secondary progressive group was half that of the relapse-remitting group, although the mean number was 35% higher. This reflected the tendency of the majority of secondary progressive patients to exhibit lower amounts of activity while a minority exhibited especially high levels. These moderate differences were reflected in the sample size calculation; to show a 70% reduction of new active lesions over 6 months in a placebo-controlled, parallel groups trial required 2 × 30 relapsing–remitting or 2 × 50 secondary progressive patients (Tubridy et al., 1997).

The one strong predictor of new MRI activity over the 3 months of the current study was the presence of enhancing lesions on the entry scan. This has implications for exploratory phase I/II trials in secondary progressive multiple sclerosis which have a primary MRI outcome. Because of the considerable variation between patients in their amount of MRI activity, substantial numbers are still required in order to demonstrate treatment effects (see above). The present results suggest that it should be possible to reduce the numbers by selecting only those patients with enhancing lesions at screening.

An important question, both for understanding the pathophysiology and for monitoring the treatment of secondary progressive disease, is the relationship between gadolinium enhancing lesions and the long-term clinical prognosis. Gadolinium enhancement, which indicates impairment of the blood–brain barrier, is a consistent feature of new lesions in relapse-remitting and secondary progressive disease and has been associated with signs of pathological activity such as perivascular lymphocyte cuffs, macrophage infiltrates and active demyelination (Katz et al., 1993; Rodriguez et al., 1993). In a 5 year follow-up of a cohort of 11 secondary progressive patients who had undergone monthly gadolinium-enhanced scanning for 6 months, Losseff et al. (1996a) found a greater degree of clinical progression in those exhibiting higher levels of MRI activity. While this suggests that an important relationship may emerge, follow-up of much larger cohorts is needed and should soon become available from the placebo arm data of several large secondary progressive multiple sclerosis trials currently in progress.

Other lines of evidence suggest that the pathophysiology of progression is complex and not solely related to focal blood–brain barrier changes seen using gadolinium. First, one recent serial study identified some secondary progressive patients with clinical disease progression in association with increasing cerebral atrophy (implying ongoing tissue loss) but no enhancing lesions (Losseff et al., 1996b). Secondly, studies in primary progressive multiple sclerosis have consistently reported a minimal amount of enhancement in the face of clinical progression (Thompson et al., 1991; Kidd et al., 1996; Silver et al., 1997).

It is, however, likely that some enhancement has been missed in studies to date which have used single-dose gadolinium chelates (0.1 mmol/kg). The combination of triple dose, delayed scanning and magnetisation transfer contrast more than doubles the number of enhancing lesions seen in
secondary progressive multiple sclerosis (Silver et al., 1997) (although there is no increase in primary progressive disease). A serial study in a secondary progressive cohort using these new techniques is needed in order to determine their potential role in therapeutic monitoring. Such studies should also help to elucidate the pathophysiology of secondary progression, especially if combined with other magnetic resonance parameters such as magnetisation transfer imaging and the quantitation of atrophy and T1 hypointense lesions, all of which have a greater potential to define axonal loss and demyelination (Gass et al., 1994; Losseff et al., 1996b, Truyen et al., 1996), the pathological substrates of disability in multiple sclerosis.

Acknowledgements
The authors would like to acknowledge Professor C. H. Polman and Dr D. Kidd for supplying clinical and MRI data on some of their patients. The MRI scanner is sponsored by a generous grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland. N.T. is supported by a grant from Athena Neurosciences. The studies involving CAMPATH-1H (A.J.C. and D.A.S.C.) are supported by the Medical Research Council and by MuSTER.

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