One year follow up study of primary and transitional progressive multiple sclerosis

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Abstract

Objective—To document clinical and magnetic resonance imaging (MRI) characteristics of a large cohort of primary and transitional progressive multiple sclerosis (PP and TP MS) patients over one year.

Introduction—Patients with PP or TP MS have been shown to have low brain T2 and T1 lesion loads and slow rates of new lesion formation with minimal gadolinium enhancement, despite their accumulating disability. Serial evaluation of these patients is needed to elucidate the pathological processes responsible for disease progression and to identify clinical and MRI measures which can monitor these processes in treatment trials.

Method—Patients, recruited from six European centres, underwent two assessments on the expanded disability status scale (EDSS) and MRI of the brain and spinal cord, 1 year apart.

Results—Of the 167 patients studied (137 with PP MS and 30 with TP MS), 41 (25%; 35 PP and six TP) showed a one step increase in the EDSS. The mean number of new brain lesions seen was 0.88 in the PP group and 0.47 in the TP MS group. Both groups demonstrated change in T2 lesion load over the year (p < 0.002), with median percentage changes of 7.3% in the PP group and 10.8% in the TP MS group. The PP group also showed a significant change in T1 load (p < 0.001, median change 12.6%). The number of new cord lesions seen was small (mean of 0.14 in the PP group and no new cord lesions in the TP group). Both groups demonstrated a decrease in cord cross sectional area (p < 0.001, median changes; PP 3.8%, TP 4.9%), but only the PP group showed evidence of significant brain atrophy (p < 0.001, 0.95%).

Conclusion—Although the monitoring of disease progression in this patient group is difficult, this study demonstrates changes in both lesion load and atrophy, which, if shown to correlate with clinical change over a longer time will facilitate therapeutic trial design.

Keywords: primary progressive; multiple sclerosis; magnetic resonance imaging

Ten per cent of patients with multiple sclerosis (MS) exhibit a progressive course from onset with no history of relapse or remission; so called primary progressive (PP) MS. Unlike patients with relapsing-remitting (RR) or secondary progressive (SP) MS their disability results solely from disease progression and not from the effect of relapses. There is also a similar group of patients whose course is essentially progressive with the important exception of a single relapse or remission at any time during disease progression or a relapse before the onset of progression, to whom the terms transitional progressive (TP) MS has been applied.6 Due to the relative rarity of both of these clinical subtypes and their unique clinical course, which excludes the use of relapse rate to assess disease activity, they have largely been excluded from therapeutic trials. Their further evaluation could, however, teach us much about the underlying mechanisms of disability resulting from disease progression as distinct from the effect of relapses, which may in turn facilitate appropriate trial design.

Through an EC funded initiative, MAGNIMS (magnetic resonance network in multiple sclerosis), we are studying a large number of such patients serially in a multicentre study involving six European centres (Amsterdam, Barcelona, Bordeaux, Lisbon, London, Milan). Recently reported cross sectional analysis of the baseline data7 was similar to previous studies and confirmed that patients with primary progressive MS have a relatively older age of onset, an equal sex ratio, and low mean T2 and T1 brain lesion loads.36 The MRI findings in TP MS were similar to those of PP MS.4 The number and volume of cord lesions differed little between the subgroups and there was no correlation with disability.5 There were weak correlations between disability (measured by the expanded disability status scale; EDSS) and MRI measures of spinal cord and brain atrophy. When this large cohort of PP and TP MS was separated into those presenting with a progressive spastic paraparesis compared with any other presentation (including progressive cerebellar, brainstem, visual, hemiplegic syndromes and progressive cognitive decline), the brain T2 and T1 lesion loads were significantly lower in the cord onset group than the others who demonstrated very large brain lesion loads, approaching those of a reference SP MS group. This showed that there is considerable overlap in the brain and spinal cord findings both between and within MS subtypes preventing clear cut distinction on radiological grounds.
The few serial studies carried out in primary progressive MS have demonstrated a low rate of development of new lesions and a rarity of enhancement with gadolinium-DTPA. These factors, combined with the difficulties of defining disease progression, have raised problems in the monitoring of treatment trials both clinically and by MRI in this patient group.

In this study we present 1 year follow up data of this large cohort, which provides an opportunity to assess whether there is change clinically or on MRI and to evaluate the relation between them.

Methods

Patients

All of the 191 patients previously studied throughout the six participating centres were approached for repeat assessment 1 year later including clinical examination and MRI. Clinical measures included the Kurtzke EDSS, 10 metre timed walk, and the nine hole peg test.

Imaging Protocol

Patients were imaged on the same scanner as the baseline studies, which were serviced regularly with no major upgrades. London and Lisbon scans were carried out using a Signa 1.5T system (General Electric, Milwaukee, Wisconsin, USA), the other four sites used Siemens Magnetom 1.5T systems.

Each patient underwent T1 and T2 weighted spin echo imaging of the brain, all sequences were acquired as contiguous, 3 mm thick, axial slices (44 images in total). In the spinal cord nine contiguous, 3 mm, sagittal T2 and proton density weighted slices were obtained. A volume acquired inversion prepared gradient echo acquisition of the cervical cord (60 1 mm slices) was also performed (Signa scanners; fast spoiled gradient echo: FSPGR, Magnetom scanners; magnetisation prepared rapid acquisition gradient echo: MPRAGE) and from the data set a series of five contiguous 3 mm axial slices (perpendicular to the spinal cord) were reformatted using the centre of the C2/3 disc as the caudal landmark. The imaging parameters for each site are detailed in the baseline data paper.

Analysis

The nine hole peg test was used as a measure of disability by averaging the times from both hands. When the patient was unable to perform the task or took longer than 5 minutes to complete it, the time for that hand was recorded as 300 seconds. A significant deterioration in either the nine hole peg test or 10 metre timed walk was defined as prolongation by 20% or more.

Baseline MRI analysis has been detailed previously. Brain lesions on year 1 scans were marked in a similar way with reference to the baseline images before lesion load measurement. The number of brain lesions at year 1 was recorded by two of us (VLS and SML) and the number and size of new spinal cord lesions were identified by DHM.

The measures of partial brain volume and cross sectional spinal cord area reflecting atrophy used in the baseline analysis were again acquired using the methods previously described.

Measurement reproducibility was assessed for brain lesion load, cerebral atrophy, and cross sectional cord area by repeating measurements on the baseline data set of 10 random subjects twice, at least 1 year apart. The coefficient of variation (COV) was calculated for each measure by dividing the SD by the mean. All of the statistical analysis employed non-parametric tests; the Mann-Whitney test was used to look for differences between the patient groups and the Wilcoxon signed ranks test to compare the baseline and year 1 results.

Correlations were assessed using the Spearman’s rank correlation coefficient. To reflect the large number of statistical comparisons a p value of 0.01 was considered significant and a value between 0.01 and 0.05 a trend. No mathematical correction of statistical significance was carried out to avoid inflating type II errors (the probability of accepting the null hypothesis when the alternative is true) and thus missing real differences.

Results

Of the 191 patients originally studied 167 (87%, range within centres 83%-94%) returned for repeat assessment, 137 patients with PP disease and 30 with TP MS. The mean time to follow up was 12.1 months (range 8-17 months). On review two patients had experienced a relapse in the preceding 12 months, one initially classified as TP became SP MS and was excluded from the analysis, the other, classified initially as PP, became TP MS for the follow up analysis.

Intrarater reproducibility was assessed for the MRI measures; the mean coefficient of variation (CV) for brain lesion load analysis was 2.48% (SD 1.55), the more automated measures of brain atrophy and cord cross sectional area measurement produced CVs of 0.51% (SD 0.38) and 0.65% (SD 0.54) respectively.

Forty one of the 167 patients (25%) had a one (or more) step deterioration in the EDSS, (an increase of 1.0 if the EDSS was ≤5 or an increase of 0.5 if it was >5); 13 (8%) had improved by one step. Thirty (18%) of 163 patients able to perform the nine hole peg test had a significant deterioration, six patients (4%) had improved. Of the 120 patients able to walk 10 metres 36 (30%) had deteriorated and 18 patients (15%) had improved. All three clinical measures changed significantly in the PP group but in the TP group only the timed 10 metre walk changed significantly (p<0.01, table 1).

On MRI 41.6% of the patients with PP MS demonstrated one or more new brain lesions and 25.5% one or more new cord lesions; when these were combined, 43.6% of the patients with PP had a new lesion in either brain or cord over the 1 year study period. Within the TP group 40.0% of patients demonstrated a new brain lesion but no new cord lesions were seen.
The brain MRI measure of T2 lesion load showed an increase over 1 year in both patient groups (PP: 7.3% median change, p<0.001, TP: 10.8% median change, p=0.002) and the T1 hypointensity lesion load increased significantly in the PP group (12.6% median change, p<0.001). There were no significant differences between the patient groups in either absolute change in lesion loads or in the percentage change. In the spinal cord, lesion load increased over the year in the PP MS group (p=0.001) but not in the TP MS group.

The six slice measure of brain volume reflecting atrophy only showed a significant change between baseline and 1 year in the PP MS patient group (median change 0.95%, p<0.001). Both groups showed a significant reduction in spinal cord area over the year, no differences in the degree or rate of change were seen between the two groups (median change PP: 3.75%, TP: 4.91%). Seventy four per cent of patients demonstrated a significant degree of cord atrophy (reduction by more than twice the COV); there was no difference in either clinical or other MR measures between those with atrophy and those without.

When the patients with PP were divided into those who presented with a progressive cord syndrome (112 patients) and those with any “other presentation” (25 patients), the former showed a significant change in EDSS from baseline to 1 year. The number of patients with a one step change in EDSS was not significantly different between the two groups (table 2). Both groups showed changes in T2 lesion load over the year, with no difference in the absolute or percentage change. However, only the cord presentation group showed a significant change in T1 hypointensity load (p=0.007). There was no difference in the number of new brain lesions identified. The cord presentation group showed increased cord lesion number (p=0.001) and volume (p=0.002) over the year but no difference in absolute or percentage change compared with the other group. Both groups showed measurable brain and spinal cord atrophy over the year but again no differences in the rates of change were found.

Of the 137 patients with PP MS 16 were receiving some kind of disease modifying treatment (eight methotrexate, five azathioprine, three cyclophosphamide) and five were partici-
Of the 13 patients who showed an improvement in their EDSS over the year, only one of these was in the treated group (placebo controlled trial of interferon β-1a). If patients on treatment were excluded from the PP MS patient group there was no difference in the absolute or percentage changes of MRI or clinical measures between the untreated group and the whole PP MS group, nor was there any difference in the number of new brain or cord lesions identified.

Correlations between the absolute or percentage change in clinical (EDSS, nine hole peg test, and 10 metre timed walk) and MRI measures in PP MS were poor. A one step change in EDSS correlated with the percentage increase in the number and volume of spinal cord lesions (r = 0.29, p = 0.019, 0.017 respectively) but not with brain lesions. None of the baseline MR measures were predictive of clinical change. There were, however, weak correlations between baseline clinical measures and changes in MR measures. The baseline EDSS correlated with the percentage change in T2 (r = 0.19, p = 0.03) and T1 hypointensity lesion loads (r = 0.27, p = 0.003).

### Discussion

This study aims to characterise the changes in clinical and MR parameters in both PP and TP MS over 1 year with a view to gaining insights into the pathological processes which result in disease progression and disability and guiding appropriate trial design, particularly in the selection of outcome measures. Obviously if large therapeutic trials are to be set up for PP MS there must be agreement on definitions. This study looked at two progressive groups in detail; purely PP MS and TP MS. However, throughout the literature there has been disagreement on defining patients with a history of a single relapse (before or during the progressive phase), some groups using the term single attack progressive MS (SAP MS) if the relapse preceded progression and progressive relapsing if superimposed on progression. The recently published London Ontario study included under the title of PP MS, patients with pure PP MS and those with so-called progressive-relapsing MS; however, they...
One year follow up study of primary and transitional progressive multiple sclerosis

717

both TP and PP MS by Gayou et al, 13% of PP and 17% of TP MS were stated to have “bouts” (relapses) during the progression phase.¹ This study, by using strict subtype definitions, hopes to clarify whether such phenotypic subdivisions are relevant, and by studying purely progressive patients aims to characterise the natural history of progressive disease distinct from any effect of relapses.

The limited serial studies carried out to date have shown fewer new lesions developing over time than patients with secondary progressive or relapsing-remitting disease and a lower rate of enhancement.⁹ ¹⁰ This has raised problems in monitoring such patients with MRI in therapeutic trials. Most trials rely on measures of disease activity in the short term (new lesions, gadolinium enhancement) and on levels of disease burden or lesion load for long term monitoring.¹¹ ¹² In PP MS it has been thought that these measures would be unlikely to change significantly over the usual time period associated with clinical trials. The results of this study suggest that this is not necessarily the case as measurable changes in several MR parameters have been demonstrated in this large cohort over the relatively short period of 1 year.

Clinical change remains the primary outcome measure in all definitive therapeutic trials.¹³ To date the EDSS has been relied on for this although it is known to have poor sensitivity to change.¹⁴ Twenty five per cent of the patients in this study showed a one step change in EDSS over the year, this was unconfirmed but in a cohort of purely progressive patients this is relatively reliable. Whereas the PP patient group showed significant change in all three clinical measures between baseline and 1 year, change in the TP group was restricted to the 10 metre walk although this may be a consequence of the smaller sample size. The difficulties in measuring clinical change over short time periods were also demonstrated in the recently published London, Ontario natural history cohort of PP MS which by their definition included patients with both pure PP MS and the progressive-relapsing MS subgroup.¹⁵ Progression probabilities (the probability of progression to the next DSS level in 1 year) were calculated for patients at each DSS level. Even when patients were at the DSS level of 4 or 5 the progression probability was only 40% and 33% respectively. At DSS 6 and 8 the probabilities of progression in 1 year fell to 4% and 2%.

In this study the rate of new lesion formation was extremely low with less than one new brain lesion a year in both patient groups. Despite this there was a measurable change in the T2 lesion load in both the PP and TP patient groups over 1 year. It is however, important to note the disparity in the mean and median values, indicating that the data is not normally distributed. This is important in comparing these data with previously published mean percentage change in lesion loads. Also as the primary progressive patients have considerably smaller lesion loads, greater percentage changes are seen with only small increases in absolute lesion volume.²⁴

As in previous studies of cerebral atrophy there was a significant difference between baseline and 1 year in the PP group, although no definite change in the TP group.¹² ²⁵ However, measures of spinal cord cross sectional area seemed more sensitive to change and was reduced in both groups.²⁶

The correlations between change in the clinical and MRI measures are poor. Change in the EDSS correlated only with change in cord lesion load; this is probably accounted for by the mobility bias of the EDSS. Despite encouraging correlations with measures of cord atrophy in cross sectional data, the degree of ongoing atrophy did not correlate with changes in any of the clinical measures. This is probably due to the high sensitivity of the cord area measurement, which showed significant atrophy in 74% of patients whereas the EDSS only detected clinical deterioration in 25% of patients.

When evaluating the PP patients according to presentation only the cord onset group showed a significant change in the EDSS between baseline and 1 year. This may again reflect the mobility bias of the EDSS in a patient group where the majority have a spastic paraparesis; alternatively the lack of change in the other group may be a consequence of the smaller sample size. Although the cord onset group had considerably lower T2 and T1 hypointensity brain lesion loads, both groups showed a definite increase in T2 lesion loads over the year with less absolute change (but higher percentage change) in the cord onset group. However, only the cord group showed a definite increase in T1 hypointensity load. Again this may be a consequence of the different sample sizes, as the rate and degree of change of T1 hypointensity lesion load were similar in the “other presentation” group. Both groups exhibited measurable degrees of cord atrophy but no difference in the rate of change.

The results from this large cohort of patients with PP MS suggest for the first time that there are measurable changes in several MR parameters over a time period of only 1 year. However, these changes have not been shown to correspond with definite clinical change, particularly with the EDSS, over 12 months in this patient group. This may be due to the relatively short study time; most clinical trials evaluating disease progression in MS are for a minimum time of 2 years. It is well known that MRI changes are much more sensitive than clinical changes.²⁷ Comparing these data with several recent therapeutic trials the median percentage change in T2 lesion load (7.3% in PP MS) is at the lower end of the range, which is in the order of 5%-12%.²¹ ²⁴ ²⁷-²⁹ The recent European multicentre study of interferon β-1b in SP MS reported a median increase in T2
lesion load of only 1.64% in the placebo group over the first year, this lower rate probably reflects the larger baseline lesion loads of these patients. The median absolute change in the placebo arm of that SP MS study was 0.30 cm³ (median 12.6% change) at 1 year compared with 0.33 cm³ in the PP patients in this study and 0.46 cm³ in the interferon β-1a RR MS study. These data show that annual lesion load measurements could be a more useful secondary outcome measure than previously anticipated in clinical trials in PP MS. The measurements of both brain and spinal cord atrophy correlate well with the EDSS in cross sectional studies and also demonstrate change over 1 year. Longer studies are needed to assess their clinical correlations but considering the extremely high reproducibility and level of automation compared with the measurements of brain lesion loads, they have considerable potential in future therapeutic trials.

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