MRI dynamics of brain and spinal cord in progressive multiple sclerosis

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Abstract

Objective—To assess the usefulness of serial cord MRI in patients with progressive multiple sclerosis.

Methods—Monthly MRI of the brain and spinal cord with and without gadolinium enhancement was carried out in 19 patients with progressive multiple sclerosis (10 primary progressive, nine secondary progressive) over the course of one year.

Results—During this period there were 132 active lesions in the brain and only six in the cord. One hundred and twelve (85%) active brain lesions occurred in the secondary progressive group; three new cord lesions occurred in each group. In the secondary progressive group MRI activity was high in patients who had superimposed relapses, whereas in those who progressed without relapse and in the primary progressive group it was low. Cross sectional areas of the cord decreased at the C5 level in both groups, implying progressive atrophy of fibre tracts. There was no relation between either brain or cord MRI activity and change in disability over the study period.

Conclusions—Although the detection of new lesions by frequent cord imaging using current technology has little role in the monitoring of disease activity in progressive multiple sclerosis, the serial measurement of cord cross sectional area may be important. There is also evidence to suggest that the mechanism underlying irreversible disability in patients with progressive multiple sclerosis may be different in patients who continue to relapse than in those who do not.

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Keywords: magnetic resonance imaging; spinal cord; progressive multiple sclerosis; disability

The application of serial brain MRI in multiple sclerosis has provided profound insights into the evolution of the pathological process over time. The relation between the extent and development of abnormalities on MRI and the clinical status and course of the patients is unclear. As many of the clinical effects of multiple sclerosis are associated with spinal cord disease, particularly in the progressive phase, it is essential to investigate spinal cord involvement in such patients to gain a greater understanding of the nature of disability. With the advent of new imaging techniques and the multarray receiver coil system it is now possible to more clearly define the extent of this involvement in vivo. A recent study of 80 patients scanned using these techniques showed that spinal cord lesions were equally prevalent in disabled and non-disabled patients, and benign and progressive subgroups alike; this study also showed that spinal cord atrophy was common, and that there was an association between cord atrophy and disability. It is possible that the nature of the change in spinal cord lesions over time might give a better understanding of the nature of progressive disability in multiple sclerosis. Furthermore, after the recent and successful application of brain MRI to monitor therapeutic efficacy as judged by lesion activity and area, it is important to determine whether serial spinal cord imaging might have a useful role in this context. With these considerations in mind we have performed a serial MRI study of the brain and spinal cord in a group of patients with progressive multiple sclerosis.

Methods

Twenty patients were recruited from the population of patients with multiple sclerosis attending the outpatient department of the National Hospital for Neurology and Neurosurgery; 10 had primary progressive multiple sclerosis, defined as a clear history of progressive neurological deterioration from the onset of the disease, without relapse or remission, and 10 had secondary progressive disease, defined as clear history of progressive neurological deterioration for at least six months, following an initial relapsing/remitting course. All had oligoclonal bands in the CSF, and all conformed to the criteria of Poser et al for clinically definite multiple sclerosis. All patients gave written informed consent to participate in the study which had been approved by the ethics committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

A full history was taken from each patient, which was followed by a complete neurological examination. Disability was scored with the functional score (FS) and expanded disability status scale (EDSS) and the motor component of the functional independence measure (FIM), a scale which measures ability to perform activities of daily living (score range 0–100). Patients were seen at monthly intervals.
for 12 months, at which times they were questioned about new or recurring symptoms, were re-examined, and the disability was scored by a single observer (DK).

**MRI PROTOCOL**

All scans were carried out with a Signa 1.5 T superconducting system (GE Medical Systems, Milwaukee) at the time of each clinical assessment.

**Brain MRI**

T2 and proton density weighted images of the brain were acquired using a fast variable echo sequence (TR 3500 ms, TE 18 and 90 ms with an echo train length of eight and a 192 x 256 image matrix). The brain was surveyed in 34 4 mm contiguous interleaved axial slices. T1 weighted images (TR 570 ms, TE 13 ms) were acquired 5–10 minutes after injection of gadolinium-DTPA (0.1 mmol/kg).

**Sagittal spinal cord MRI**

Two sets of 3 mm thick contiguous interleaved sagittal T2 weighted FSE images were obtained with a multiaxial spinal coil (GE Medical Systems, Milwaukee) with a 48 cm field of view, which enabled the entire cord to be visualised on a single image. Sequence variables were: TR 2500 ms, TE 51 and 102 ms, echo train length 16, 512 x 512 image matrix, two excitations, phase encoding superior-inferior. T1 weighted sagittal images (TR 500 ms, TE 19 ms) were acquired 15–20 minutes after injection of gadolinium-DTPA.

Brain and sagittal spinal cord scans were analysed by a neuroradiologist (BK), who was blinded to clinical details. Intrinsic brain lesions were documented and a total lesion load derived after weighting lesion size according to their largest in plane diameter: 1, <5 mm; 2, 5 to 10 mm; 3, >10 mm; an extra point was added for lesions with a confluent appearance—that is, extensive lesions with a smooth outline which tended to be seen around the ventricles. In the spinal cord lesions were identified only if areas of high signal intensity were seen on both proton density and T2 weighted scans. Lesion size was scored according to its maximum length along the cord in the sagittal image: 1, ≤5 mm; 2, 5 to 10 mm; 3, ≥10 mm. At serial assessment the appearance of new and enlarging lesions on proton density and T2 weighted images, and the appearance of enhancement on T2 weighted images was recorded. Active lesions were defined as any new enhancing lesion or any lesion which, although not enhancing, was either new or enlarging on the proton density and T2 weighted images. Lesions which showed persistent enhancement were only counted once.

**Axial spinal cord MRI**

Axial 5 mm thick slices of the cord were acquired using a gradient echo sequence: TR 300 ms, TE 15 ms, flip angle 15°. A single slice was acquired at each of four vertebral levels—C5, T2, T7, and T11. The images were renamed and placed in a random order so that the observer (DK) was blinded both to the identity of the patient and also to the time at which the image was acquired. The cross sectional area of the cord at each level was calculated by manually tracing the circumference of the cord images with Disipage software (Dr DL Plummer, Department of Medical Physics, University College London) on a Sun workstation. Measurements were carried out at two separate times to assess the reliability of the observer, and the mean of the two measurements taken. Change in cord area was calculated by subtracting the mean area at the beginning of the study from that at the end. Atrophy was considered to be present when the measured area was more than 2 SDs below that of the mean areas obtained for healthy controls at the appropriate level.

**STATISTICAL ANALYSIS**

Group data comparisons were made using Student's t, Mann-Whitney, and Kruskal-Wallis tests as appropriate, paired observations were contrasted with the Wilcoxon matched pairs signed rank test, and correlations were made by Spearman's rank correlation method.

**Results**

**CLINICAL ACTIVITY**

One patient in the secondary progressive group had to withdraw from the study after a severe relapse; frequent flexor spasms rendered her scans uninterpretable owing to motion artifacts. These were excluded from the analysis. Table 1 shows the clinical characteristics and MRI lesion loads of the 19 remaining patients. The median number of visits per patient was 12 (range 10 to 13).

In the primary progressive group eight patients (80%) deteriorated neurologically on examination resulting in a change in EDSS. In the secondary progressive group seven patients (78%) worsened on the EDSS, of whom four had had a total of seven superimposed relapses. Overall the median change in EDSS was 1.0 (SD 0.97) (range 0–3). The median change in FIM was 11.4 (SD 9.0) (0–27). Change in FIM correlated with change in EDSS (r = 0.808, P < 0.002).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics and MRI lesion loads in the two patient groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (y)</td>
<td>Duration of progression (y)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>Age (y)</td>
</tr>
<tr>
<td>40-1 (5-6)</td>
<td>9 (0-9)</td>
</tr>
<tr>
<td>32-4 (3-20)</td>
<td>3-20</td>
</tr>
<tr>
<td>29-52 (3-22)</td>
<td>1 (1-7)</td>
</tr>
</tbody>
</table>

Values are mean (SD) with range below.
MRI activity
Over the study period a total of 231 scans of the brain and cord were carried out. There was a total of 132 active brain lesions, 112 (85%) of which occurred in the secondary progressive patient group; 107 (95%) of these enhanced. There were 20 active brain lesions in three primary progressive patients, of which 14 (70%) enhanced (13 in one patient). The median number of active brain lesions was significantly greater in the secondary progressive group (P = 0.02) (table 2). Median brain lesion activity was 19-0 (SD 27-0) (4-63) in the four secondary progressive patients who had had superimposed relapses, 2-0 (SD 1-3) (0-3) in the five who had progressed without relapse (P < 0.02) and 2-2(SD 5-6) (0-18) in the 10 primary progressive patients (table 2).

There was a total of six active lesions in the spinal cord (four new and two enlarging), of which only one was seen to enhance (in a secondary progressive patient); three of the lesions were in the primary progressive group, three in the secondary progressive group. All six patients with cord activity showed new activity on brain MRI.

The median combined number of active brain and cord lesions was greater in the secondary progressive than the primary progressive group (P = 0.02). In the secondary progressive group MRI activity was significantly greater in those who had had superimposed relapses compared with those without (P < 0.05).

Cross sectional areas of the cord

Intrarater reliability was 2-0%. There was a reduction in cord area in which was most pronounced at the C5 level (median change in area = −2-62 mm², range −20-45 to +6-70 mm²) (P < 0.05; figure), and was greater in the primary progressive group (median change −5-39 mm², range −20-45 to +5-15 mm²) than the secondary progressive group (median change −2-62 mm², range −17-10 to +6-70 mm²; P < 0.05 for both groups). The reduction in cord area was significant at C5 both for the entire group and the individual subgroups (P < 0.05).

Relation between MRI findings and clinical change
Eight patients (six primary progressive, two secondary progressive), four of whom had deteriorated on the EDSS, had no active MRI lesions. There was no significant correlation between brain or total CNS activity and change in EDSS or FIM in the 19 patients as a whole, nor in the two subgroups, although total CNS activity did correlate with change in both EDSS and FIM (r = 0.83, P < 0.05) in the four secondary progressive patients who relapsed.

There was no significant difference in MRI brain activity in those who changed by ≥1-0 on the EDSS compared with those who changed less (median activity 2-0 (SD 10-3) (0-30) v 0-0 (SD 19-8) (0-63) (P = 0-3). There was no correlation between change in cord area at any of the four levels and change in EDSS or FIM, nor between MRI activity in the brain or cord; there was, however, a trend towards a significant difference between change in cord area in those who changed <1-0 on EDSS and those whose change was greater, this trend was most noticeable at C5 (median change in area −1-7 (−8-2 to +5-9 mm²) v −5-2 (−20-45 to +5-15 mm²), P = 0-8). There was no significant difference between change in cord area of patients who had had active lesions (median −3-68 (range −7-1 to +6-70 mm²)) and those who had not (median −1-25 (range −20-45 to +5-15 mm²)) (P > 0.5).

Discussion
The use of multiarray coils with fast spin echo has greatly increased the resolution of spinal cord imaging. In the present study patients with progressive multiple sclerosis had much

Table 3 Cross sectional cord areas at onset and end of study

<table>
<thead>
<tr>
<th>C5</th>
<th>T2</th>
<th>T7</th>
<th>T11</th>
</tr>
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<tbody>
<tr>
<td>100-70 (10-82)</td>
<td>60-10 (7-44)</td>
<td>50-35 (6-36)</td>
<td>64-20 (8-18)</td>
</tr>
<tr>
<td>73-85 (11-4)</td>
<td>43-35 (7-20)</td>
<td>34-60 (6-10)</td>
<td>39-70 (7-20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary progressive</th>
<th>101-47 (9-96)</th>
<th>50-30 (6-99)</th>
<th>50-20 (6-71)</th>
<th>63-15 (6-56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary progressive</td>
<td>98-25 (12-32)</td>
<td>61-03 (9-86)</td>
<td>51-25 (6-35)</td>
<td>64-82 (8-91)</td>
</tr>
</tbody>
</table>

Values are median (SD) with range below.
Axial slice of cord
(gravitational echo) of patient
with primary progressive
multiple sclerosis at the
beginning (A) and end
(B) of 12 month study
period showing a reduction
in cross sectional area from
88 mm² to 83 mm². The
patient deteriorated
clinically with EDSS going
from 3-5 to 5-5 and had
no new lesions of brain or
cord during the study.

A

B

less detectable activity in the spinal cord than
in the brain. Only six active cord lesions were
seen over a 12 month period compared with
132 active lesions in the brain. No patient had
cord activity in the absence of brain activity. A
failure to detect more cord activity in a patient
population which showed quite pronounced
clinical change over the study period is per-
haps surprising. This may in part relate to our
inability to detect small lesions within the cord
which, although capable of producing
detectable clinical deficit, may be beyond the
resolution of existing techniques. The location
of the lesion within the cord may also be
important and this would be better appreci-
ated on systematic axial imaging of the whole
cord which was not performed in this study.
Nevertheless, these results suggest that in its
present state serial imaging of the cord
to detect new disease activity would not make
useful a contribution in therapeutic trials of
progressive multiple sclerosis.

Another aspect of spinal cord pathology
which may be important to monitor is that of
atrophy. It has recently been shown that
patients with multiple sclerosis have on aver-
age a smaller cord area that normal controls.5
In the same study patients who had cord atro-
phy (defined as an area more than 2 SDs
below the mean for normal controls) were
more disabled than those who did not have
atrophy. In the present study atrophy was
measured serially by a single blinded observer.
There was good intrarater reliability of the
measurement technique used (2%), and a
reduction in cord area was seen in 15 patients
over a 12 month period. This was most pro-
nounced at the C5 level, which has a higher
proportion of pyramidal tract fibres that at any
other level of the cord. There was also a non-
significant trend suggesting that patients with
progressive atrophy were more likely to
develop increasing disability. It seems likely
that axonal loss makes an important contribu-
tion to such progressive atrophy thus giving
further evidence that this pathological process
plays a significant part in the development of
progressive functional deterioration. Further
data are required to determine the usefulness
of measuring cord atrophy in therapeutic tri-
als. A larger number of patients will need to be
studied over a longer period of time.

The results of this study raise interesting
questions with regard to the development of
disability in multiple sclerosis. One of the
main findings is that a number of patients
developed disability in the absence of any
obvious new MRI activity. There is already
evidence to suggest that patients with primary
progressive multiple sclerosis have a different
pattern of MRI activity than those in the
relapsing and remitting and secondary pro-
gressive groups.8 Patients in this group tend
to have fewer lesions on brain MR and develop
fewer new or enhancing lesions over time. The
hypothesis that this may be a less inflamma-
tory form of multiple sclerosis is supported by a
recent pathological study.10 The mechanism
by which such patients develop disability is not
clear but again may be explained by progres-
sive axonal loss in pre-existing lesions rather
than obvious new demyelinating lesions. In
the present study five of the nine patients
with secondary progressive multiple sclerosis
deteriorated without any superimposed relapses
and these patients also showed few, if any, new
lesions in the brain or spinal cord, their MRI
activity being very similar to that of the
patients in the primary progressive group.
Similar findings have been made by our group
in a larger serial study of the brain which did
not involve the use of gadolinium DTPA.4

These findings may have important implica-
tions both for our understanding of the nature
of disability and for the role of MRI in moni-
toring that activity. They suggest that there
may be more than one mechanism for the
development of disability. On the one hand,
in relapsing and remitting patients and in sec-
ondary progressive patients who continue to
relapse, disability may relate directly to the
formation of new lesions. On the other hand
there is a group of patients in whom develop-
ment of progressive disability may relate to
mechanisms not as clearly demonstrated
through conventional MRI, including progres-
sive axonal loss. This emphasises the impor-
tance of the development of new MR
techniques which will allow clearer identifica-
tion of axonal loss.12

In summary this study shows that whereas
at present the detection of new lesions in the
spinal cord does not make a useful contribution to monitoring of disease activity in progressive multiple sclerosis the measurement of cord atrophy may be important. There may be different mechanisms in the development of disability and the results emphasise the need to develop MR techniques which will allow them to be measured (particularly axonal loss). This will allow a better understanding of the nature of disability and result in more accurate monitoring of disease activity in therapeutic trials.13

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