PAPER

Cord atrophy separates early primary progressive and relapsing remitting multiple sclerosis

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Background and objective: The onset of multiple sclerosis is relapsing remitting or primary progressive. An improved understanding of the causes of early progressive disability in primary progressive multiple sclerosis (PPMS) could provide mechanistic targets for therapeutic intervention.

Methods: Five magnetic resonance imaging (MRI) parameters that could potentially cause progressive disability were investigated in 43 patients with early PPMS and in 37 patients with early relapsing remitting multiple sclerosis (RRMS): atrophy in brain, both grey matter and white matter; intrinsic abnormality in brain, both grey matter and white matter (measured by the magnetisation transfer ratio (MTR)); and atrophy of the upper cervical spinal cord. Both groups were also compared with controls.

Results: Patients with PPMS were older and more likely to be men. Both patient groups had atrophy of brain grey matter and white matter, and intrinsic abnormality in MTR of normal-appearing grey matter and white matter. Cord atrophy was present only in the PPMS (mean cord area: PPMS, 67.8 mm²; RRMS, 72.7 mm²; controls, 73.4 mm²; $p=0.007$). This was confirmed by multivariate analysis of all five MRI parameters, age and sex.

Conclusion: Grey matter and white matter of the brain are abnormal in both early RRMS and PPMS, but cord atrophy is present only in PPMS. This is concordant with myelopathy being the usual clinical presentation of PPMS. Measurement of cord atrophy seems to be clinically relevant in PPMS treatment trials.

About 15% of patients with multiple sclerosis present with a steadily accumulating neurological deficit—usually a spastic paraplegia that indicates spinal cord dysfunction—known as primary progressive multiple sclerosis (PPMS). These patients are older at onset (mean age 40 v 30 years) and the proportion of male patients is higher than in those with an onset of relapsing remitting multiple sclerosis (RRMS).¹ The mechanisms of disability in patients with PPMS are not well understood. Patients with PPMS become disabled at an earlier stage despite having no greater load of lesions visible on magnetic resonance imaging (MRI) of the brain,² nor have differences been noted between patients with RRMS and those with PPMS in terms of the number of focal spinal cord lesions that are visible on T2-weighted MRI scans.^{3,4} One study reported a higher frequency of diffuse hyperintensity on proton-density-weighted scans of the spinal cord in patients with PPMS.⁵

In recent years, we have recruited two cohorts of patients in the early stages of RRMS and PPMS to investigate—using serial multimodal MRI and clinical follow-up—potential prognostic markers and pathogenic mechanisms in the two types of multiple sclerosis. The present study directly compares quantitative MRI measures in these patients with early RRMS, those with early PPMS, and controls using identical analysis methods applied to anonymised scans by a blinded investigator (MB) to identify imaging features that might associate with the more disabling clinical course seen in PPMS. Five MRI parameters were pre-selected for investigation because each could—if more severely abnormal—help explain disability in PPMS: (a) brain grey matter volume; (b) brain white matter volume; (c) normal-appearing brain grey matter magnetisation transfer ratio (MTR); (d) normal-appearing brain white matter MTR; and (e) upper cervical cord cross-sectional area. We hypothesised that

patients with early PPMS have a more disabling course of their multiple sclerosis, because one or more of the five MRI parameters is abnormal when compared with patients with early RRMS.

PARTICIPANTS AND METHODS

Patients

We studied 43 patients with PPMS, 37 with RRMS and 58 controls. All the patients had clinically definite multiple sclerosis⁶ and also fulfilled established criteria for PPMS or RRMS.⁷ None had previously received disease-modifying drugs. Controls were healthy volunteers. The study had approval of the Joint Medical Ethics Committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, and written informed consent was obtained from all participants. The patients are being followed serially with clinical and MRI examinations; for the present study, baseline MRI data (ie, when first acquired) have been used. Details of the MRI acquisition and analysis protocols are provided elsewhere.^{8–11}

Statistical analysis

Comparisons within the patient group between PPMS and RRMS used logistic regression of the binary group indicator on the MRI parameters as predictors; these models give the relative odds of being in a group depending on the predictor value. Univariate analyses included each of the five MRI parameters of interest separately, whereas multivariate regressions included all five parameters, with backward

Abbreviations: MRI, magnetic resonance imaging; MTR, magnetisation transfer ratio; NAGM, normal-appearing grey matter; NAWM, normal-appearing white matter; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis

Table 1 Clinical features and lesion findings on magnetic resonance imaging

	PPMS	RRMS	Controls
Sex, M:F	26:17	9:28	28:30
Mean (SD) age (years)	43.3 (10.7)	36.73 (7.3)	40.15 (10.8)
Range	19.5–65.8*	24.1–55.6*	23.2–67.5*
Mean (SD) disease duration (years)	3.26 (0.75)	1.81 (0.68)	NA
Range	1.54–5.68*	0.54–3.11*	
Median EDSS	4.5	1.5	NA
Range	1.5–7.0	0–3.0	
Median PD lesion load (ml)	14.76†	11.75†	NA
Range	0.24–130.5	0.75–50.1	
Median T1-hypointense lesion load (ml)	4.63‡	4.96‡	NA
Range	0.06–44.73	0.31–25.69	
Number of patients with gadolinium-enhanced lesions (%)	21/43 (49%)	30/37 (81%)	

EDSS, Expanded Disability Status Scale; F, female; M, male; NA, not applicable; PD, proton density; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis.

*In cases when scans were not carried out on the same day, age and disease duration were calculated at the earliest of scans in every patient.

†PPMS versus RRMS, $p=0.082$ using univariate logistic modelling; $p=0.009$ after adjusting for age and sex.

‡PPMS versus RRMS, $p=0.296$ using univariate logistic modelling; $p=0.051$ after adjusting for age and sex.

elimination of those not significant at $p<0.05$; age and sex covariates were added to all models to adjust for these covariates. Comparisons between patients and controls on MRI parameters used linear regression of the measures on diagnostic group indicators with age and sex covariates. However, these linear regressions also give age-adjusted and sex-adjusted comparisons between the two patient groups for each MRI parameter separately, in terms of differences in means, and these are also reported. Significance is reported at $p<0.05$. Analyses were implemented in Stata 8.2 and SPSS V.11.0 for Windows.

RESULTS

Table 1 shows demographic features of all participants and MRI lesion findings.

Table 2 shows the univariate comparisons between the two multiple sclerosis groups and controls of the five non-lesion MRI measures of interest.

Univariate comparison of MRI parameters among PPMS, RRMS and controls

MTR data were available for 39 patients with PPMS, 37 with RRMS and 38 controls. Scans for brain volume measures were available for 42 patients with PPMS, 36 with RRMS and 46 controls. Scans for cord atrophy measures were available in 37 patients with PPMS, 36 with RRMS and 24 controls.

Multivariate comparison of MRI parameters between PPMS and RRMS

The variables included in the multivariate model were grey matter fraction, white matter fraction, mean normal-appearing grey matter (NAGM) MTR, mean normal-appearing

white matter (NAWM) MTR, upper cervical cord area, age and sex. In all, 69 patients (35 with RRMS and 34 with PPMS) had valid data on all these variables. Table 3 summarises the model.

DISCUSSION

As expected, the PPMS cohort had an older age at onset, with a greater proportion of women in the RRMS group. Age and sex were included as covariates in the comparative analysis of MRI measures between groups. Atrophy of the cervical cord emerged as a consistent finding only in the PPMS group, and was the only MRI parameter that was markedly different between the PPMS and RRMS groups (age and sex were also considerably different in the multivariate analysis).

Cord atrophy findings

The decrease in mean cord area in PPMS was about 7% compared with controls, but this figure may be an underestimate, as cord areas are generally larger in men than in women¹² and there was a higher proportion of men in the PPMS cohort. Multivariate analysis showed that among the five MRI measures, upper cervical cord area alone could differentiate PPMS and RRMS. The most common manifestation in PPMS is progressive spastic paraplegia (and was the presentation for 33/43 of the presently reported PPMS cohort).

There is evidence for extensive axonal loss in postmortem examination of the spinal cord in multiple sclerosis.¹³ Axonal loss is a likely substrate of irreversible disability and loss of spinal cord axons, and could account for the progressive myelopathy and cord atrophy seen in most patients with PPMS. A more detailed MRI investigation of intrinsic cord

Table 2 Univariate comparison of magnetic resonance imaging parameters of multiple sclerosis among patients and controls

	Mean (SD) values			Mean estimated difference (p value)*		
	PPMS	RRMS	Controls	PPMS v RRMS	PPMS v controls	RRMS v controls
Grey matter fraction (%)	52.89 (2.38)	54.78 (2.26)	55.54 (2.59)	−0.008 (0.145)	−0.020 (<0.001)	−0.013 (0.011)
White matter fraction (%)	26.53 (2.43)	26.75 (1.59)	28.06 (1.82)	−0.007 (0.163)	−0.017 (<0.001)	−0.010 (0.022)
NAGM MTR (pu)	31.53 (0.77)	31.94 (0.63)	32.25 (0.47)	−2.182 (0.161)	−6.193 (<0.001)	−4.011 (0.006)
NAWM MTR (pu)	37.82 (0.71)	37.89 (0.56)	38.32 (0.6)	−1.066 (0.462)	−5.268 (<0.001)	−4.202 (0.002)
upper cervical cord area (mm ²)	67.82 (8.54)	72.65 (8.47)	73.43 (7.63)	−5.980 (0.007)	−6.281 (0.010)	−0.300 (0.892)

MTR, magnetisation transfer ratio; NAGM, normal-appearing grey matter; NAWM, normal-appearing white matter; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis.

*Age and sex adjusted difference in means and p value.

Table 3 Multivariate model predicting primary progressive multiple sclerosis and relapsing remitting multiple sclerosis

Variable in model	Odds ratio (PPMS v RRMS)*	95% CI (p Value)
GMF (%)	0.97	0.67 to 1.42 (0.890)
WMF (%)	1.15	0.65 to 2.02 (0.634)
Mean NAGM MTR (pu)	0.75	0.15 to 3.76 (0.724)
Mean NAWM MTR (pu)	0.48	0.14 to 1.58 (0.226)
Cord area (mm ²)	0.90	0.82 to 0.99 (0.031)
Age (years)	1.14	1.04 to 1.25 (0.005)
Female patient	0.13†	0.02 to 0.67 (0.014)

GMF, grey matter fraction; MTR, magnetisation transfer ratio; NAGM, normal-appearing grey matter; NAWM, normal-appearing white matter; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; WMF, white matter fraction.

*Odds ratio per 1 unit higher of row variable, unless otherwise indicated.

†In females compared with males.

abnormality has been enabled by measurement of MTR and diffusion, both of which are abnormal in the cervical cord in PPMS.^{14, 15} These measures may not, however, be specific for axonal loss. Spinal N-acetyl aspartate measured by spectroscopy might give more specific information regarding axonal integrity, but is difficult to measure reliably in the cord on 1.5-T scanners, although it may be feasible at higher fields.

MRI findings of brain grey matter and white matter

The abnormal volume of grey matter and white matter of the brain and MTR in both early RRMS and PPMS confirms previous investigation of both cohorts separately using similar but not always identical approaches.^{8–11} In the present study, an identical analysis was applied to all scans by a single investigator who was blinded to the clinical details and group assignment of the MRI scans. It was thus possible, we consider to be for the first time, to compare in a standardised and unbiased manner the findings in the two patient groups, and none of the four brain measures differed between them.

Atrophy in brain white matter and grey matter probably reflects neuroaxonal loss, but other factors may also contribute—for example, demyelination. The intrinsic MTR changes seen in NAWM and NAGM were quantitatively small, whereas large reductions of MTR in focal multiple sclerosis lesions show patterns that differentiate demyelinated from remyelinated lesions.¹⁶ The much smaller changes seen in normal-appearing tissues are less specific and might indicate subtle disruption of myelin or axonal loss, inflammation or glial proliferation, all of which occur in macroscopically NAWM. Grey matter abnormalities may be due to cortical demyelinating lesions, which are rarely seen on MRI. The lack of distinction between the two cohorts suggests that pathological changes in NAWM and NAGM may not directly cause the relapse or progressive paraplegia that characterise one or other group. Such globally measured abnormalities in brain grey matter and white matter nevertheless have the potential to influence future prognosis.

The reason that we prioritised MTR to investigate NAWM and NAGM in this study is that it has—in our experience—proved to be a particularly stable and reproducible measure, and has also been sensitive in detecting abnormalities and their progression over time. Additional MRI measures from NAWM or NAGM—for example, magnetic resonance spectroscopy, diffusion and T1 relaxation—may provide different information on the underlying pathology and hence prognosis.

MRI lesion measures

Patients with RRMS had a higher likelihood of exhibiting gadolinium-enhanced lesions (table 1), whose presence

suggests active inflammation. The frequency of gadolinium-enhanced lesions in the early PPMS group, although less than that seen in the RRMS cohort, was higher than previously reported in other PPMS cohorts¹⁷: this may reflect the earlier stage of the disease and use of triple-dose contrast. The presence of more inflammatory lesions at an early stage of the disease may also have contributed to the slightly higher T2 and T1 lesion volumes observed in this cohort than another large PPMS cohort of longer disease duration previously reported from our and other European centres.¹⁸

CONCLUSION

In an investigator-blinded study comparing cohorts of patients with PPMS and RRMS of short clinical disease duration, we found that in addition to (expected) differences in age and sex between the groups, considerable cervical cord atrophy was seen only in patients with PPMS. The finding suggests the potential of cord atrophy to reflect ambulatory disability better than other MRI measures of brain pathology. Measurement of cord atrophy may be particularly relevant in experimental treatment trials in PPMS. In future, longitudinal studies might usefully evaluate the rates of change in spinal cord size in this and other cohorts with early RRMS and PPMS.

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NEUROLOGICAL PICTURE

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Fast-growing adenoid cystic carcinoma: a neurotropic malignancy

An 81-year-old man presented to the neurology department with a 2-month history of diplopia and recent onset of left-sided ptosis. He had also had pain in the left eye and left nasal congestion for the past month.

Two years ago, he had presented to a different department with a 6-month history of left upper lip and cheek paraesthesia, which was still present. At that time, a small (1×0.5 cm) mobile lump was found in the left upper lip and excised. Histological examination confirmed a benign muco-coele retained in the salivary gland. This was insufficient to explain the continuing symptoms of paraesthesia and therefore the brain and orbits were subjected to magnetic resonance imaging (MRI). No abnormality was found (fig 1).

On presentation to the neurology department, fullness of the left orbit and left ptosis and restriction of left eye movements in all directions were observed. In addition, pinprick sensation was reduced in the maxillary division of the left trigeminal nerve. An urgent MRI scan was repeated 12 months after the first (fig 2A,B). This showed an advanced soft-tissue mass filling the left maxillary sinus, with tumour margins beyond the medial and lateral borders and extension from the hard palate to the cavernous sinus. Biopsy results showed proliferating epithelial cells with "honeycomb" spaces, consistent with adenoid cystic carcinoma.

Adenoid cystic carcinoma is a rare malignant neoplasm arising from the epithelial cells of secretory glands, most commonly the salivary glands.¹ This is of interest to neurologists, as contiguous perineural invasion is a hallmark of adenoid cystic carcinoma and partly explains its tendency to spread. It surrounds and invades nerve sheaths, causing cranial or peripheral neuropathy, a feature possibly mediated via expression of surface cell adhesion molecules.² Presentation is late as growth is often slow, but it can occasionally be rapid. It was so in this case, potentially with an indolent initial phase that was not apparent on MRI. Treatment focuses on surgical excision with concomitant radiotherapy, but mortality is high from multiple tumour recurrence and late distant metastases.

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Figure 1 T2 axial scan showing minor inflammatory changes in the left antrum (arrow).

Figure 2 T1 axial (A) precontrast and (B) postcontrast scans, showing mixed-signal mass in and extending beyond the left antrum (arrow).

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