Grey matter involvement by focal cervical spinal cord lesions is associated with progressive multiple sclerosis

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Abstract

Background: The *in vivo* relationship of spinal cord lesion features with clinical course and function in MS is poorly defined.

Objective: To investigate the associations of spinal cord lesion features on MRI with MS subgroup and disability.

Methods: We recruited 120 people: 25 clinically isolated syndrome, 35 relapsing-remitting (RR), 30 secondary progressive (SP), 30 primary progressive (PP) MS. Disability was measured using the expanded disability status scale. We performed 3T axial cervical cord MRI, using 3D-fast-field-echo and phase-sensitive-inversion-recovery sequences. Both focal lesions and diffuse abnormalities were recorded. Focal lesions were classified according to the number of white matter (WM) columns involved and whether they extended to grey matter (GM).

Results: The proportion of patients with focal lesions involving at least two WM columns and extending to GM was higher in SPMS than in RRMS ($p=0.03$) and PPMS ($p=0.015$). Diffuse abnormalities were more common in both PPMS and SPMS, compared with RRMS (OR 6.1 [$p=0.002$] and 5.7 [$p=0.003$] respectively). The number of lesions per patient involving both the lateral column and extending to GM was independently associated with disability ($p<0.001$).

Conclusions: More extensive focal cord lesions, extension of lesions to GM, and diffuse abnormalities are associated with progressive MS and disability.

Introduction

Two long disease duration imaging studies in MS have shown that spinal cord atrophy is associated with disability, independently from brain atrophy or lesion load[1, 2]. However, neither study investigated the contribution of focal spinal cord lesions or diffuse abnormalities[3-7] to disease progression.

Focal spinal cord lesions are typically seen on MRI as hyper-intense abnormalities on sagittal T2-weighted images[3]. However, this approach underestimates the number of lesions[8] and axial acquisitions improve detection[9]. A further advantage of axial imaging is that involvement of central grey matter (GM) and white matter (WM) columns by lesions is more clearly determined[10-12].

In a previous pilot study we used a combination of: axial 3D-fast-field-echo (FFE) and 3D-phase-sensitive-inversion-recovery (PSIR) scans, on 3T MRI, to record the anatomical location of lesions within the cervical cord[13]. These two sequences combined may therefore be useful to investigate spinal cord imaging abnormalities (both focal and diffuse) that are associated with progression and disability.

In this present study of a moderately large clinical cohort, we investigate the following hypotheses:

(i) More extensive focal lesions, i.e., involving two or more WM columns, occur more frequently in progressive than non-progressive MS.

(ii) Extension of focal lesions to GM is more common in progressive MS.

(iii) Diffuse abnormalities occur more frequently in progressive MS.

(iv) The location of focal cord lesions will affect the association seen with disability - with motor disability being particularly related to lateral column involvement.

Methods

Subjects

We recruited people with CIS, or MS[14], subgroups were classified using published criteria[15]. Recruitment was performed without reference to earlier spinal cord imaging findings. None of the subjects had a relapse or received corticosteroids within a month prior to participation. Disability was recorded using the expanded disability status scale (EDSS)[16]. This study was approved by the national research ethics service committee and informed written consent was obtained from all participants.

MRI protocol

The 3T MRI protocol for this study was as previously described[13] (provided in full in a supplementary file). Briefly, two 3D-axial sequences were acquired in the upper cervical cord centred at C2/C3: FFE and PSIR, with 0.5 x 0.5 mm^2 in plane resolution, as well as a sagittal PD/T2 scan of the cervical cord for orientation of the axial slices. In addition a PD/T2 brain scan was acquired for identification of brain lesions.

Image analysis

Using the sagittal image for orientation of axial slices, lesions were first recorded on the slice-matched 3D-FFE and 3D-PSIR images by an experienced reader (HK) using the classification system described below, with subsequent and final confirmation of the presence and classification of all lesions being made be a second reader, who was an experienced

neuroradiologist (KM)[13]. Lesions were analysed on all ten 5mm thick axial slices. Both readers were blinded to the clinical status of the cases being reviewed. Images degraded by artefacts were excluded from analysis.

Focal lesions

We defined focal lesions as abnormal areas of clearly increased signal intensity on the 3D-FFE image and decreased signal intensity on 3D-PSIR image and a clearly demarcated border from the surrounding tissue. Focal lesions were only recorded when they were clearly visible on both scans. Focal lesions were always evident in WM, i.e., they had higher signal on 3D-FFE and lower signal on 3D-PSIR with respect to adjacent WM. While it was possible to identify lesions that extended to the GM, it was not possible to determine their extent or location within GM as lesion signal intensity was generally similar to that of normal cord GM on both sequences.

Focal lesions were classified based on the number of WM columns involved. The column that was maximally covered (in many cases entirely) by a lesion was recorded (in comparison to partial coverage of other columns) and if extension into one or more additional columns was seen (e.g. a lateral column lesion extending into the posterior column) this was also noted.

The classification system devised for lesions is shown in Table 1. Lesions involving a single column were either confined to WM only (type I – demonstrated in Figure 1; in these lesions normal appearing cord WM was visible between the lesion and GM), or extended to the GM (type II – Figure 2). When focal lesions involved two (type III –Figure 3) or more (type IV –

Figure 4) columns, they invariably extended to the GM adjacent to the affected columns, i.e., no lesions involved two or more columns without extending to GM. For lesions that covered multiple slices of the image, their extent was classified from the slice with maximal involvement.

Diffuse abnormalities

These were defined as abnormal areas of intermediate signal intensity, between that of focal lesions and normal appearing spinal cord (Figure 5). Diffuse abnormalities also lacked a well demarcated border from adjacent normal appearing cord. These were recorded on the 3D-FFE scan, where they were visible as an intermediate hyper-intense abnormality relative to the normal appearing cord. Diffuse abnormalities were often not seen on the 3D-PSIR scan, or if they were, they were poorly defined areas of subtle hypo-intensity relative to normal appearing cord.

Diffuse abnormalities were recorded, when seen, as present or absent. An anatomical classification system based on spinal cord columnar involvement – as undertaken for focal lesions - could not be implemented due to the absence of a clearly defined border demarcating their termination.

Statistical analysis

Stata 13 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis. Statistics given at lesion level are descriptive only: tests were all conducted at subject level. A summary of all the statistical tests performed is provided in table format in a supplementary file.

(i) Focal lesion features and diffuse abnormalities: comparison between clinical subgroups

To investigate for differences in the number of focal lesions between clinical subgroups, we performed a single test for 'linear trend'[17] by regressing the lesion variable (i.e. number of lesions) on a group variable coded numerically in the order: 0=CIS, 1=relapsing-remitting (RR), 2=primary progressive (PP), 3=secondary progressive (SP) MS.

To test whether more extensive (types III and IV) focal lesions, extension to GM, and diffuse abnormalities would be seen more frequently in progressive MS, we compared these lesion characteristics between groups using logistic regression, with the lesional element being compared (lesion extent, extension to GM, and diffuse abnormalities) as the binary dependent variable. Clinical subgroup indicators were entered as predictors in each model and adjustment was made for age, gender and disease duration. Separate adjustment was performed so that age and disease duration were not in the model simultaneously, since across subject groups disease duration will necessarily vary substantially in patients of the same age. Where patients did not have a particular lesion characteristic (e.g. diffuse abnormalities) an exact chi-square test was used. To minimise the number of comparisons, only the following four were performed: RRMS vs. each of the three other groups (CIS, PPMS and SPMS), and PPMS vs. SPMS.

Due to the exploratory nature of the study, no adjustment for multiple comparisons was performed[18].

(ii) Lesion features: investigation for independent associations with physical disability

A multiple linear regression model was constructed with EDSS as response variable on the lesion predictors listed in the supplementary material. A standard manual forward stepwise procedure was used as follows: (i) age, gender and disease duration were retained in the model throughout; the first MRI variable entered was the subject classification according to their most extensive lesion; (ii) each MRI variable entered was retained if $p<0.05$, while any MRI variables with $p>0.05$ were removed; with each new variable combination thus constructed, the procedure was repeated, until all MRI variables in the model were $p<0.05$ and no other variable improved the model at $p<0.05$. There was no marked deviation from normality or homoscedascity of regression residuals; the regression estimates were confirmed using non-parametric bias-corrected and accelerated bootstrap[19].

Results

(i) Demographics of clinical subgroups (Table 2)

We recruited 120 people: 25 CIS, 35 RRMS, 30 SPMS and 30 PPMS. Three subjects' scans were excluded due to motion: CIS (n=1), RRMS (n=1) and SPMS (n=1).

Using the T2-weighted brain scan, criteria for dissemination in space was fulfilled in 15 cases of the CIS cohort; it was not possible to investigate for dissemination in time, with a single time point non-contrast enhanced scan[14].

(ii) Number of focal spinal cord lesions by type (I-IV) and location (Table 3)

Lesion numbers in each category (type I-IV) are summarised in Table 3. We identified 354 focal spinal cord lesions in total. Although similar numbers of type I lesions (involving a single WM column) were seen in all subgroups of MS, a higher number of focal lesions that involved two columns (type III) were seen in SPMS (n=22) compared to either RRMS (n=16) or CIS (n=2). There were also a higher number of type IV lesions (involving three or more WM columns) in progressive MS: SPMS (n=8), PPMS (n=5), RRMS (n=1) and CIS (n=0).

Focal lesions involved the lateral and posterior columns (75% and 38% of lesions respectively) more frequently than the anterior column (6%). Extension to the GM was seen in 67% of the lesions.

(iii) Lesion characteristics by MS subgroup (Table 4)

The proportion of people with one or more focal spinal cord lesions increased in the order: CIS (42%), RRMS (85%), PPMS (97%) and SPMS (100%). The mean of the total number of lesions per patient similarly increased in the order: CIS (mean 0.8), RRMS (2.8), PPMS (3.5) and SPMS (4.7). This increase was approximately linear with a significant increase of 1.2 (95% CI 0.9, 1.6; $p<0.001$) lesions per MS subgroup. Adjustment for age, gender and disease duration did not affect the results. The mean, median and range per subject of the number of cord lesions in each subgroup are shown in Table 5.

The proportion of subjects with more extensive lesions (type III or IV), was significantly higher in RRMS vs. CIS (OR 6.8, 95% CI 1.4, 33.9; p=0.019), SPMS vs. RRMS (OR 3.1, 95% CI 1.1, 8.7; p=0.033) and in SPMS vs. PPMS (OR 3.8, 95% CI 1.3, 11.2; p=0.015). No differences were seen between PPMS vs. RRMS (OR 3.2, 95% CI 0.79, 13.3; p=0.104). These significant group differences remained after adjusting for age, gender or disease duration.

The proportion of subjects with lesions extending to the GM (type II-IV) was also greater in RRMS vs. CIS (OR 8.3, 95% CI 2.5, 27.6; p=0.001) and SPMS vs. RRMS (OR 10.1, 95% CI 1.2, 85.3; p=0.034) but not significantly greater in SPMS vs. PPMS (OR 3.1, 95% CI 0.3, 31.8; p=0.338). No difference was seen between PPMS and RRMS (OR 0.8, 95% CI 0.29, 2.26; p=0.684).

Diffuse abnormalities were present in over half of PPMS (57%) and SPMS (55%) patients but only in 18% of RRMS and none of CIS (p=0.037 for RRMS vs. CIS, exact chi-square test). The OR for having diffuse abnormalities was higher in PPMS vs. RRMS was 6.1 (CI 2.0, 19.1; p=0.002) and for SPMS vs.

RRMS, 5.7 (95% CI 1.8, 18.1; p=0.003). These significant differences remained after adjustment for age, gender or disease duration.

(iv) Independent associations between EDSS and spinal cord lesion characteristics

The best independent predictors of EDSS were found to be the number of a subject's lesions which involved a lateral column and extended to GM (p=0.0007), and the subject's most extensive lesion (i.e. the lesion that covered the greatest number of columns in that subject, entered as a single term rather than as a categorical variable, p=0.045), in a model also containing age at scan (predicted 0.06 increase in mean EDSS per year of age, p<0.001), gender (predicted 0.60 higher mean EDSS in men compared to women, p=0.032) and disease duration (predicted 0.07 increase in mean EDSS per year duration, p=0.001).

In this model, compared to subjects with no lesions that involved a lateral column and extended to GM, having one, two and three or more such lesions predicted respectively 0.8 (95% CI -0.26,1.77; p=0.143)), 0.7 (-0.46, 1.81; p=0.239) and 2.1 (0.94, 3.32; p=0.001) higher mean EDSS (with p=0.0007 for the overall contribution of the categorical variable); and in the same model mean EDSS was predicted with borderline significance to be higher by 0.4 (95% CI 0.01, 0.78; p=0.045) per category of the subject's most extensive lesion. In total 30 patients had three or more lesions that involved a lateral column and extended to the GM: RRMS n=6, PPMS n=10; and SPMS n=14.

None of the other MRI variables entered additionally into this model (see supplementary Table 2) was significant, but in particular neither (i) the total number of lesions, nor (ii) the number of lesions involving a lateral column but not extending to GM, nor (iii) the number of lesions extending to GM but not involving a lateral column, contributed significantly to the above model, confirming the importance of the more specific predictor of lesions that both involved a lateral column and extended to GM.

The proportion of explained variance (R^2) was 66%, compared to 46% for a model with only age, gender and disease duration, and with 44% for a model with just the two lesion variables.

Discussion

In this study we demonstrate two new associations of spinal cord lesion characteristics with clinical status and disability in MS. Firstly, focal lesions involving at least two spinal cord WM columns and extending to the GM (Type II and IV lesions) are more frequent in SPMS. Secondly, focal lesions that involve lateral columns and extend to GM are independently associated with disability. We also confirmed previous observations in finding a significant association between diffuse abnormalities and progressive MS[4-7].

Post mortem spinal cord studies have demonstrated extensive focal lesions involving several WM columns and GM[20, 21]. However, due to inherent limitations of spinal cord imaging[22], there has been little information on the anatomical location of focal lesions seen on axial *in vivo* images in progressive MS, and how those features compare with findings in the earlier relapsing remitting phase of the disease.

Although some previous imaging studies demonstrated a greater number of focal lesions in SP than RRMS[4, 5, 9, 23], our study extends these findings. Firstly, this was the first study to document a greater number of spinal cord columns covered by individual focal lesions in SPMS. This observation was in comparison to RRMS and CIS, where focal lesions, were more often restricted to a single column.

Secondly we invariably detected extension to the GM when focal lesions were themselves more extensive (i.e. they involved at least two WM columns). Although we could not directly determine the how much of the GM was

affected by the lesions, our findings are consistent with spinal cord GM involvement being extensive in SPMS, and are in line with pathology reports, where 56% and 67% of focal lesions involved the GM [24, 25].

Although the total number of lesions detected was greater in PPMS than RRMS, neither the number of lesions involving two or more WM columns, nor extension to the GM, differed significantly from RRMS. These results are in agreement with previous studies demonstrating similar focal spinal cord lesion abnormalities in both RRMS and PPMS[3, 5, 23].

The mechanisms that account for the greater number of lesions covering two or more WM columns in SPMS cannot be determined from this current study. However, this subgroup had disease duration of two decades, which may result in a more prolonged exposure to pathogenic processes that underlie the formation of new focal lesions, accounting in turn for the greater number of extensive lesions seen.

A question arising from this observation is whether lesions restricted to a single column of the cord evolve to encompass multiple columns. Extensive inflammation and demyelination[26] seen pathologically, may provide a milieu conducive to the formation of new extensive lesions and/or coalescence of existing lesions. Longitudinal studies are required to elucidate the processes involved.

Diffuse abnormalities may be seen on sagittal PD-weighted images in MS and are more commonly seen in PPMS[4-8]. In this present study, people with progressive MS were almost six times more likely to have diffuse

abnormalities, compared to RRMS. Diffuse abnormalities may reflect demyelination and/or axonal loss as reported at *post mortem*[5, 8].

This current study demonstrates an independent association of disability with focal lesions that involve *both* the lateral column and extend to GM, which may reflect damage in the corticospinal tract, and/or GM inter-neuronal loss[27]. Recent studies have shown that both atrophy and microstructural abnormalities in cord GM are associated with disease progression in MS[28, 29]. The sequences used in our study could not differentiate lesional from non-lesional cord GM and future studies are needed to identify image contrast modalities that enable depiction and quantitation of lesions *within* cord GM.

The independent association of the most extensive focal lesions with disability was only of borderline significance. This probably reflect several factors including limited pathological specificity of the imaging sequences employed, variable functional effects according to lesion location within the cord, and effects of remote lesions outside of the cord region studied. In a recent report of a cohort with long disease duration MS, several MRI measures including lesions in the cervical cord and infratentorial regions were associated with disability[30].

A number of limitations should be considered in the interpretation of the results of this study. Firstly, the images were restricted to the upper cervical cord. This approach minimised physiological motion and likely provided the greatest yield of lesions[20, 21]. A future study would be of interest that employs axial sequences with greater coverage[9], measures of cord atrophy[30] and quantitative MRI[31]. Although an association of cord atrophy and disability is

well recognised, the sequences we used to detect lesions were not suited to investigate atrophy of the whole cord or grey or white matter. Secondly, the extent of lesions within the cord GM could not be quantified[24], nor was it possible to visualise subpial lesions[20, 21], therefore neither of these features could be incorporated into the classification system used. This may be improved in future studies using higher image resolution, modified spinal cord coil designs, and higher field strength imaging[32]. Finally this cross-sectional study did not facilitate investigation of the progression of abnormalities, which could be addressed longitudinally.

Through the use of high resolution axial cervical cord MRI, we have demonstrated significant associations of progressive MS and disability with focal cord lesion location and extent and with diffuse abnormalities. Future longitudinal studies are warranted to investigate the potential of cord lesion imaging to help understand and monitor MS disease progression.

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Type I	Spinal cord lesion involving a single column and confined to the white matter
Type II	Spinal cord lesion involving a single column and grey matter
Type III	Spinal cord lesion involving two columns and grey matter
Type IV	Spinal cord lesion involving three or four spinal cord columns and grey matter

Table 1. Classification system used for focal spinal cord lesions identified on axial scans

	CIS* n = 25	RRMS n = 35	PPMS n = 30	SPMS n = 30
Age (years)	36.5 ± 9.0	38.7 ± 9.7	50.6 ± 9.9	51.1 ± 9.2
Gender Female:Male	14:11	23:12	13:17	18:12
Disease duration (years)	0.4 ± 0.4	6.5 ± 5.2	10.4 ± 7.5	19.9 ± 11.5
Median EDSS (range)	1 (0 – 3.5)	2.5 (0 – 6)	6 (2 – 7.5)	6.5 (4 - 8)
Disease modifying drugs (%)	0 (0)	19† (54)	0 (0)	5‡ (17)

Table 2. Demographics of all people with a clinically isolated syndrome or MS recruited for this study. Data represents mean ± standard deviation. The CIS cohort*: optic neuritis (n=21), partial myelitis (n=2), multifocal CIS (n=1; optic neuritis with a brainstem syndrome) and hemispheric presentation (n=1; unilateral hand weakness due to a motor cortex lesion). †Disease modifying drugs in RRMS cohort: β-interferon (n=13), natalizumab (n=5), and glatiramer acetate (n=1). ‡SPMS cohort: β-interferon (n=5).

Total number of lesions	Type I	Type II	Type III	Type IV	Grey matter involvement	Anterior column	Posterior column	Lateral column
CIS n = 18	8 (44.5%)	8 (44.5%)	2 (11%)	0 (0%)	10 (56%)	2 (11%)	5 (28%)	13 (72%)
RRMS n = 94	36 (38%)	41 (44%)	16 (17%)	1 (1%)	58 (62%)	5 (5%)	38 (40%)	67 (71%)
PPMS n = 106	36 (34%)	55 (52%)	10 (9%)	5 (5%)	70 (66%)	7 (7%)	37 (35%)	79 (75%)
SPMS n = 136	37 (27%)	69 (51%)	22 (16%)	8 (6%)	99 (73%)	6 (4%)	54 (40%)	107 (79%)
All subjects n = 354	117 (33%)	173 (49%)	50 (14%)	14 (4%)	237 (67%)	20 (6%)	134 (38%)	266 (75%)

Table 3. The number (percentage) of focal lesion types (I-IV) and also the number of focal lesions involving the spinal cord grey matter and each column of the spinal cord in each clinical subgroup. Note: the cumulative numbers of lesions with specified white matter column involvement exceeds the total number of lesions, since some lesions seen involved more than one column e.g. extension into the lateral and posterior column by the same lesion.

Total number of people	Number of people with focal spinal cord lesions	Number of people with Type I lesions	Number of people with Type II lesions	Number of people with Type III lesions	Number of people with Type IV lesions	Number of people with lesions involving the grey matter	Number of people with diffuse abnormalities
CIS n = 24	10 (42%)	8 (33%)	5 (21%)	2 (8%)	0 (0%)	6 (25%)	0 (0%)
RRMS n = 34	29 (85%)	20 (59%)	21 (62%)	12 (35%)	1 (3%)	25 (74%)	6 (18%)
PPMS n = 30	29 (97%)	22 (73%)	25 (83%)	9 (30%)	5 (17%)	27 (90%)	17 (57%)
SPMS n = 29	29 (100%)	20 (69%)	27 (93%)	17 (59%)	7 (24%)	28 (97%)	16 (55%)

Table 4. Number (percentage) of people with clinically isolated syndrome or multiple sclerosis with focal spinal cord lesions (of any type; types 1-4 individually; involving grey matter) and with diffuse abnormalities. Note: Three peoples' scans were excluded from analysis due to motion artefacts on images: clinically isolated syndrome (n = 1), relapsing remitting MS (n = 1) and secondary progressive MS (n = 1).

Number of people	Type I	Type II	Type III	Type IV	All focal lesions	Grey matter involvement
CIS n = 24	0.33, 0 (0-1)	0.33, 0 (0-2)	0.08, 0 (0-1)	0, 0 (0)	0.8, 0 (0 - 4)	0.42, 0 (0-3)
RRMS n = 34	1.06, 1 (0-5)	1.21, 1 (0-4)	0.47, 0 (0-3)	0.03, 0 (0-1)	2.8, 2.5 (0 -8)	1.71, 1 (0-5)
PPMS n = 30	1.20, 1 (0-4)	1.83, 1.5 (0-6)	0.33, 0 (0-2)	0.17, 0 (0-1)	3.5, 3 (0 - 7)	2.33, 2 (0-6)
SPMS n = 29	1.27, 1 (0-5)	2.37, 2 (0-6)	0.75, 1 (0-3)	0.28, 0 (0-2)	4.7, 4 (2 - 9)	3.41, 3 (0-8)

Table 5. Mean, median (range) per subject of the number of spinal cord lesions in each category and involving the grey matter in each of the four clinical subgroups.

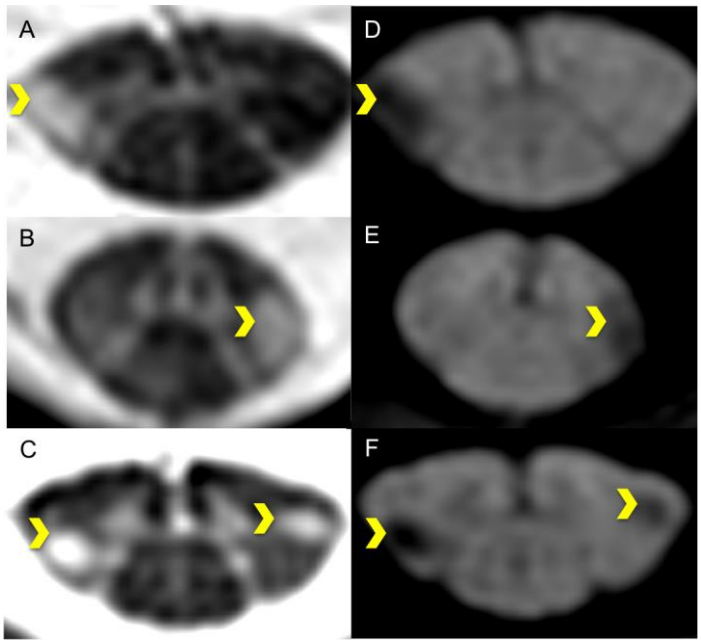

Figure 1. Three cases of lesions involving a single spinal cord column restricted to the white matter (Type I lesions). 1A-C: 3D-fast field echo 0.5 x 0.5 mm^2 in plane resolution, 1D-F: 3D-phase sensitive inversion recovery 0.5 x 0.5 mm^2 in plane resolution. Focal lesions are marked by a single yellow chevron and are located in the right lateral column (Figures A/D and C/F) and in the left lateral column (Figures B/E and C/F). Figure A/D: 36 year old female with RRMS, EDSS 2. Figure B/E: 42 year old male with RRMS, EDSS 2.5. Figure C/F: 60 year old male with PPMS, EDSS 4.

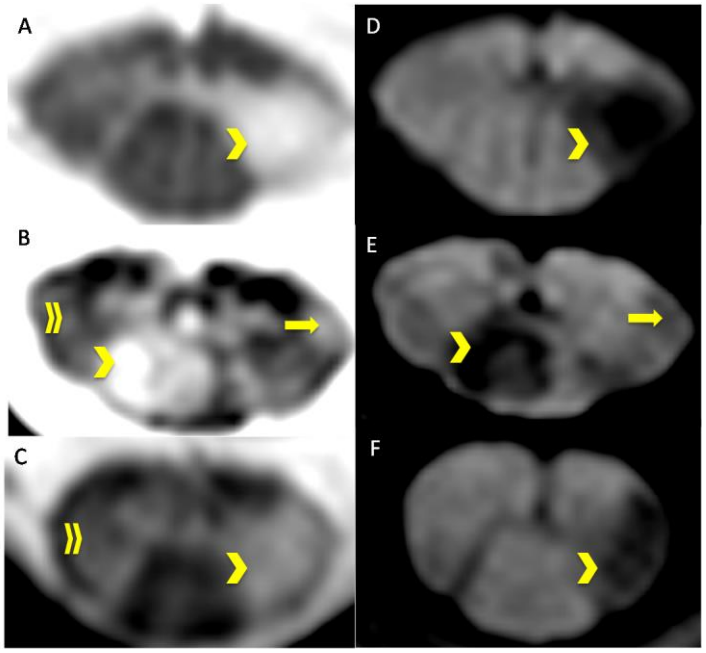

Figure 2. Three cases of focal lesions involving a single spinal cord column also extending to the grey matter (Type II lesions). 2A-C: 3D-fast field echo 0.5 x 0.5 mm^2 in plane resolution, 2D-F: 3D-phase sensitive inversion recovery 0.5 x 0.5 mm^2 in plane resolution. These focal lesions are demonstrated in the left lateral column by a single chevron in A/D and C/F. A focal lesion involving the posterior column is demonstrated in Figures B/E. A separate focal lesion restricted to the white matter (Type I lesion) is demonstrated in the left lateral column (Figure B and E) indicated by a single arrowhead. Diffuse abnormalities are demonstrated on the 3D-fast field echo images 2B and 2C in the right lateral column indicated by a double chevron. Figure A/D: 36 year old female with RRMS, EDSS 2. Figure B/E: 42 year old male with RRMS, EDSS 2.5. Figure C/F: 35 year old female with RRMS, EDSS 1.

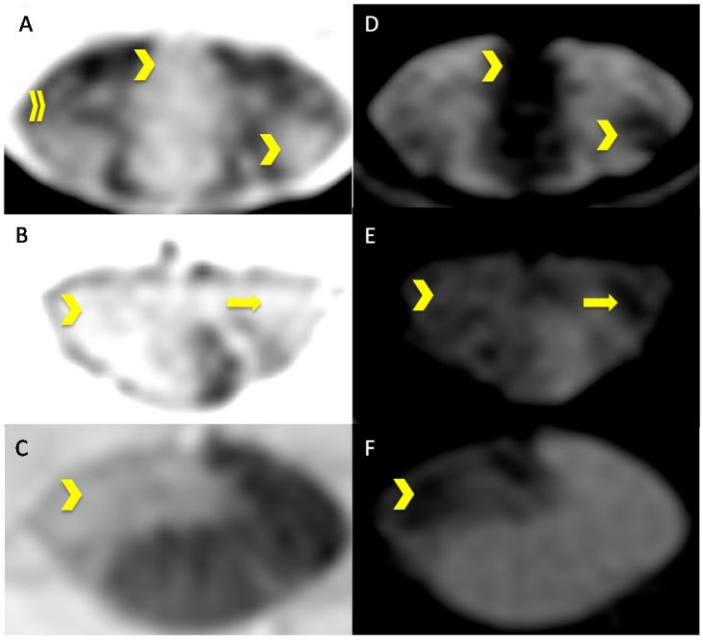

Figure 3. Three cases of focal lesions (indicated by single chevrons) involving two spinal cord columns and extending to the grey matter (Type III lesions). 3A-C: 3D-fast field echo 0.5 x 0.5 mm^2 in plane resolution, 3D-F: 3D-phase sensitive inversion recovery 0.5 x 0.5 mm^2 in plane resolution. A focal lesion involving the anterior and posterior columns and extending to grey matter is demonstrated in Figures A and D. Figure A also shows diffuse abnormalities in the right lateral column (indicated by double chevron). Figure B and E demonstrate a lesion involving the right lateral and posterior column and extending to grey matter (type III) and also a separate focal lesion in the left lateral column only (type I) indicated by a single arrowhead. A focal lesion involving the right lateral and anterior column and extending to grey matter is demonstrated in Figure C and F. Figure A/D: 53 year old male with PPMS, EDSS 7.5. Figure B/E: 55 year old female with SPMS, EDSS 6. Figure C/F: 24 year old female with RRMS, EDSS 0.

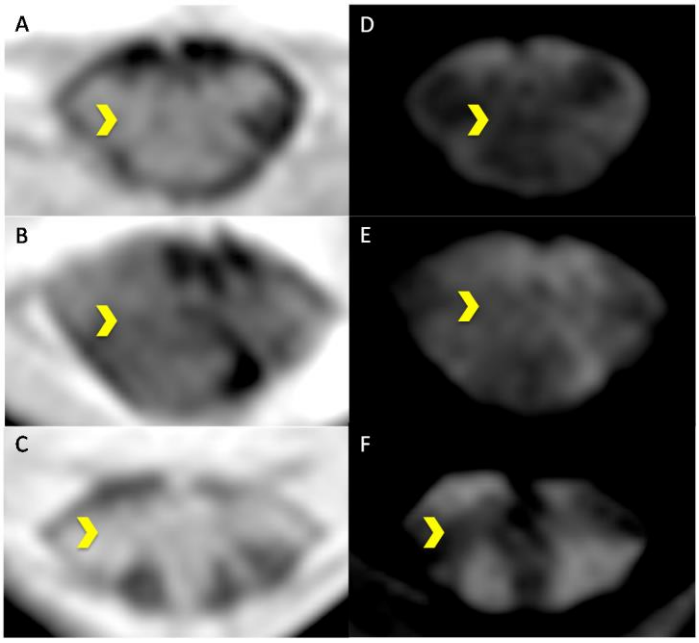

Figure 4. Three cases of lesions involving three spinal cord columns and extending to the grey matter (Type IV lesions). 4A-C: 3D-fsat field echo 0.5 x 0.5 mm^2 in plane resolution, 4D-F: 3D-phase sensitive inversion recovery 0.5 x 0.5 mm^2 in plane resolution. Focal lesions are labelled in all images by a single chevron. Figure A/D: 45 year old male with PPMS, EDSS 6.5. Figure B/E: 55 year old female with SPMS, EDSS 6. Figure C/F: 24 year old male with RRMS, EDSS 3.

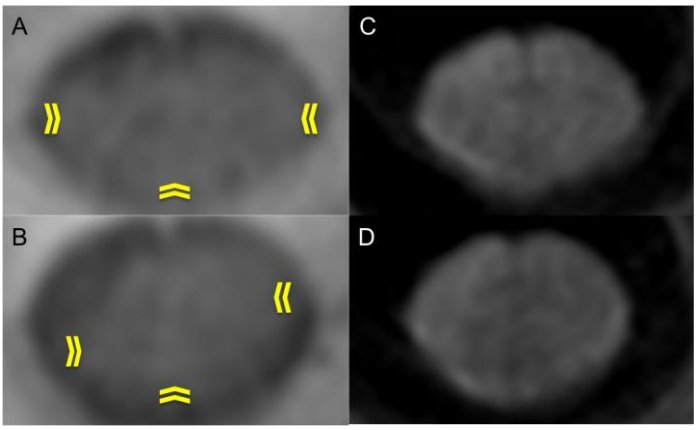

Figure 5: Images demonstrating diffuse abnormalities on 3D-fast field echo images (A and B) shown by double chevrons. Corresponding slices of 3D-phase sensitive inversion recovery images are shown in images C and D. Figures A/C: 55 year old male with PPMS, EDSS 5. Figures B/D: 49 year old female with PPMS, EDSS 7.5.