Predicting short-term disability progression in early MS: added value of MRI parameters

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Chapter 3.2

Abstract

Objective: Magnetic resonance imaging (MRI) and clinical parameters are associated with disease progression in Multiple Sclerosis (MS). The aim of this study was to investigate whether adding MRI parameters to a model with only clinical parameters could improve these associations.

Methods: 89 patients (55 women) with recently diagnosed MS had clinical and MRI evaluation at baseline (time of diagnosis) and at follow-up after 2.2 years. Detailed clinical data were available including disease type (relapse-onset or progressive-onset) and disability as measured by the expanded disability status scale (EDSS). MRI parameters included Normalised Brain Volume (NBV) at baseline, percentage brain volume change (PBVC/year), T2- and T1-lesion loads and spinal cord abnormalities. Progression of disability (increase in EDSS of at least 1 point at follow-up) was the main outcome measure. For a model containing only clinical parameters, the added value of MRI parameters was tested using logistic regression.

Results: PBVC/year and lesion loads at follow-up were significantly higher in the group with progression. Adding PBVC/year to a clinical model improved the model, indicating that MRI parameters added independent information ($p<.001$).

Conclusion: rate of cerebral atrophy conveys added information for progression of disability in early MS patient, suggesting that clinical disability is determined by neurodegenerative changes as depicted by MRI.

Introduction

Magnetic resonance imaging (MRI) is a sensitive method for detecting abnormalities in brain and spinal cord related to multiple sclerosis (MS) and is widely used in the management of MS. The most recent diagnostic criteria for MS incorporate MRI findings underlining the importance of imaging studies in making the diagnosis of MS. One of the major remaining challenges of MRI-research in MS is identifying parameters that are associated with patient outcome. Unfortunately, despite its powerful diagnostic properties, associations between MRI and disease progression are less straightforward. Correlations between conventional MRI measures like T2 or T1 lesion load and disability as measured by the expanded disability status scale (EDSS) are only moderate to poor in most cross-sectional or longitudinal studies.[1-7] Cerebral atrophy is widely used in clinical trials and other studies as a marker of neurodegeneration. Several studies showed that atrophy is already present at the earliest stages of disease in patients presenting with an isolated syndrome or early relapsing remitting (RR) MS.[8;9] Results suggest that atrophy is a clinically relevant marker: in cross-sectional studies atrophy correlates with disability.[3,7,10;11] In patients with well established MS, (rate of) brain atrophy seems to be associated with the development of disability at follow-up,[3,10,12-14] For newly diagnosed patients, the association between measures of atrophy and future disability is less clear and reported results are contradictory.[15;16]

However, most studies on associations between MRI parameters and disability did not include spinal cord parameters. There are good reasons to include these parameters. Spinal cord lesions are more often symptomatic and the EDSS (the most frequently used disability scale in MS) is heavily weighted towards motor functioning. Although up to half of all of spinal cord lesions may not lead to clinical symptoms, including these focal and diffuse spinal cord abnormalities improves the correlation between MRI abnormalities and clinical symptoms.[17]

Besides MRI parameters several clinical parameters like age at onset, sex and disease type (relapse or progressive onset) may be associated with neurological deterioration.[18-21] Probably the best prognostic models are composed of both clinical and MRI parameters. However, we are not aware of other studies that, rather than describing associations between (longitudinal) MRI and progression of disability, seek to describe the added value of MRI compared with use of clinical

data alone. Therefore the aim of this study was to investigate whether adding MRI parameters to a model with only clinical parameters could improve the associations with clinical disease progression after a follow-up period of two years in a group of recently diagnosed MS patients.

Methods

Patients

From a cohort of 133 patients participating in an ongoing natural history study of recently diagnosed MS-patients, 89 patients (55 women, 34 men) with clinically definite MS were studied.[22] These patients had clinical and MRI evaluation at baseline (at the time of the diagnosis) and at follow-up after a median of 2.2 years (interquartile range (IQR): 2.0 ; 2.4). The remaining 44 Patients could not be included because no pre-contrast T1-weighted scan was available (17 patients), patients did not want to undergo an MRI scan at follow-up (16 patients), or MRI scans were performed in another hospital (11 patients). No differences in disease duration, age, EDSS or use of disease modifying therapy were observed between studied group and excluded patients. Detailed clinical data were available including age at onset, disease duration at baseline and disability as measured by EDSS. Disease type was classified as relapse-onset or progressive-onset. When patients suffered from a relapse or used steroids, clinical and MRI evaluations were delayed with a minimum of 6 weeks. The institutional medical ethics committee approved the study and informed consent was obtained from every patient.

MRI

All baseline and follow-up MRI scans were performed on the same 1.0Tesla scanner (Magnetom Impact, Siemens, Erlangen, Germany) according to the same scanning protocol.

Brain: Axial T2 and T1-weighted images were acquired: 25 slices with a slice thickness of 5mm, gap 10% (2700/45, 90 and 700/15 [repetition time/echo time]). T1-weighted images were acquired before and after the administration of Gadolinium at baseline. At follow-up no gadolinium was used.

Baseline and follow-up T2 hyperintense lesion loads (T2LL, T2LLfu), T1 hypointense or black holes lesion loads (BHLL, BHLLfu) and baseline volume of gadolinium enhancing lesions (GADLL) were quantified using home-developed semi-automated software based on a thresholding technique after identification of lesions by an experienced reader. Ratio between BHLL and T2LL was calculated for baseline (Black Holes Ratio (BHR)) and follow-up (BHRfu).

Baseline Normalised Brain Volume (NBV) and percentage brain volume change (PBVC) were measured on the pre-contrast T1-weighted images using an automated method called SIENAX and SIENA respectively.[23] The SIENA procedure was started with brain and skull extraction. Normalisation was achieved by aligning the two images (i.e. each timepoint: baseline and follow-up) to each other, using the skull as a scaling constraint, then both brain images are resampled into the space halfway between the two. After this, the actual brain edge displacement analysis at subvoxel accuracy is carried out. This method showed a 0.15% error for SIENA and a brain volume accuracy of 0.5-1% for SIENAX.

Spinal cord: Spinal cord scanning included a cardiac-triggered sagittal dual-echo CSE (2,400 to 2,900/20, 80 [repetition time/echo time]) and a sagittal T1-weighted CSE sequence (500/15 [repetition time/echo time]) with a slice thickness of 3 mm, interslice gap 10%.

For the whole spinal cord number and size (expressed as their extension over a number of corresponding vertebral segments) of spinal cord abnormalities were scored by two readers in consensus. Focal lesions (i.e., sharply delineated areas of increased signal intensity [SI]) were considered to be present on CSE scans if seen on intermediate and T2-weighted MRI. Diffuse abnormalities were defined as areas with a subtle, poorly delineated increase of SI, best recognized as areas of SI higher than spinal CSF on intermediate-weighted images.[24]

Statistical analysis

Patients were dichotomised according to progression of disability: progression was defined as an increase in EDSS of at least 1 point (all patients had a baseline EDSS below 6). Although we did not routinely confirm the progression by repeating the clinical evaluation after 3 or 6 months and therefore do not meet the typically used definition of sustained progression, we are confident that our patients can be classified as such using the yearly obtained clinical evaluations. The non-

normal distribution of most data necessitated the use of non-parametrical tests: median and IQR was used. Spearman rank correlations for correlations between clinical parameters, MRI parameters and between clinical and MRI parameters. The Mann Whitney U test was used to test differences in clinical and MRI parameters between patients with or without progression. Pearson chi-square test was used to test differences in categorical parameters (sex, relapse/progressive onset, use of disease modifying therapy (DMT)) between patients with or without progression. Longitudinal MRI data were annualised to account for differences in duration of follow-up. To find parameters with the strongest associations with progression, three models were constructed using forward logistic regression (p-value for entry in model .05). The presence or absence of progression was the dependent variable in all models. All models were corrected for use of DMT and follow-up duration. Collinearity was checked using a correlation-matrix containing all independent variables. Correlation coefficients above 0.60 were found between number of focal spinal cord lesions and number of segments with focal spinal cord abnormalities and furthermore between T1 lesion load and BHR at baseline and between T1 lesion load and T2 lesion load at baseline. We then avoided the use of number of segments with focal spinal cord abnormalities and used a combined parameter to avoid collinearity: sum and difference of T1 and T2 lesion loads at baseline. Clinical parameters were age, disease duration, type of disease, sex and EDSS at baseline. MRI parameters were: (***conventional lesion loads***) sum and difference of T1 and T2 lesion loads at baseline, GADLL, BHR, percentage change in T1 and T2 lesion loads/year, (***spinal cord***) number of focal cord lesions, number of segments with diffuse cord abnormalities, (***brain atrophy***) NBV and PBVC/year. Firstly a model containing only clinical (clinical model) or MRI (MRI model) parameters was composed. Secondly, for a model containing only clinical parameters, the added value of MRI parameters was tested (combined model): the parameters found in the clinical model were entered and subsequently the MRI parameters found in the MRI model were added in a stepwise procedure. Comparisons between models were made using a likelihood ratio test and by comparing the area under the receiver operator characteristics (ROC) curve. For all statistical procedures SPSS 12.0 for Windows was used.

Results

1 Descriptive, clinical and MRI parameters at baseline and follow-up

Patient demographics and clinical data at baseline and follow-up are presented in Table 3.4. Similar patterns are seen for the whole group (Table 3.4a) and the relapse onset group (Table 3.4b).

Table 3.4. Clinical characteristics. a: whole group; b: relapse onset only

Table 3.4a

Measurement	Whole Group (n=89)	No Progression (n=53)	Progression (n=36)	*P* Value
Age (y)	36.5 (29.6 ; 43.5)	34.2 (29.4 ; 42.3)	39.3 (33.2 ; 47.6)	ns
Sex (M/F)	34/55	16/37	18/18	ns*
Disease type (relapse-onset/ progressive-onset)	74/15	49/4	25/11	0.008*
Use of DMT (yes/no)	21/68	14/39	7/29	ns*
Disease duration (y)	1.6 (0.7 ; 4.1)	1.5 (0.6 ; 3.7)	2.6 (0.8 ; 4.5)	ns
EDSS baseline	2.0 (2.0 ; 3.0)	2.5 (2.0 ; 3.0)	2.0 (1.6 ; 3.0)	ns
EDSS follow-up	2.5 (2.0 ; 3.5)	2.0 (1.8 ; 3.0)	3.5 (3.0 ; 5.4)	<0.001
Progression rate (change EDSS/y)	0.2 (0.0 ; 0.5)	0.0 (-0.3 ; 0.3)	0.7 (0.5 ; 1.0)	<0.001

Progression = increase in EDSS of at least 1 point; P-value = Mann Whitney *U* test was used to test for differences between the progression and the no progression group (* = Pearson chi-square); IQR = interquartile range (25%; 75%); M = male ; F = female ; DMT = disease modifying therapy.

Table 3.4b

Measurement	Whole Group (n=74)	No Progression (n=49)	Progression (n=25)	*P* Value
Age (y)	35.5 (29.4 ; 42.6)	34.2 (29.4 ; 42.8)	35.8 (27.5 ; 42.6)	ns
Sex (M/F)	23/51	14/35	9/16	ns*
Use of DMT (yes/no)	21/53	14/35	7/18	ns*
Disease duration (y)	1.7 (0.6 ; 4.4)	1.5 (0.6 ; 3.8)	3.7 (0.7 ; 4.8)	ns
EDSS baseline	2.0 (1.9 ; 2.6)	2.5 (2.0 ; 3.0)	2.0 (1.5 ; 2.5)	0.021
EDSS follow-up	2.5 (2.0 ; 3.0)	2.0 (1.5 ; 3.0)	3.0 (2.5 ; 4.0)	<0.001
Progression rate (change EDSS/y)	0.2 (0.0 ; 0.5)	0.0 (-0.3 ; 0.2)	0.7 (0.5 ; 1.0)	<0.001

Progression = increase in EDSS of at least 1 point; P-value = Mann Whitney *U* test was used to test for differences between the progression and the no progression group (* = Pearson chi-square); IQR = interquartile range (25%; 75%); M = male ; F = female ; DMT = disease modifying therapy.

Table 3.5. MRI measurements. a: whole group; b: relapse onset only

Table 3.5a

Measurement	Whole Group (n=89)	No Progression (n=53)	Progression (n=36)	*P* value
Brain				
NBV baseline (ml)	1467 (1422 ; 1513)	1478 (1433 ; 1520)	1466 (1400 ; 1499)	ns
T2LL baseline (ml)	3.9 (1.5 ; 11.9)	3.6 (1.0 ; 8.5)	5.1 (1.8 ; 21.3)	ns
BHLL baseline (ml)	0.3 (0.0 ; 0.9)	0.3 (0.0 ; 0.7)	0.4 (0.1 ; 1.5)	ns
GADLL baseline (ml)	0.0 (0.0 ; 0.2)	0.0 (0.0 ; 0.2)	0.0 (0.0 ; 0.2)	ns
T2LL follow-up (ml)	4.7 (1.9 ; 13.2)	3.3 (1.2 ; 9.8)	8.3 (2.4 ; 18.4)	0.011
BHLL follow-up (ml)	0.3 (0.0 ; 1.0)	0.2 (0.0 ; 0.4)	0.5 (0.1 ; 1.5)	0.018
BHR baseline	0.06 (0.00 ; 0.14)	0.04 (0.00 ; 0.13)	0.08 (0.02 ; 0.14)	ns
BHR follow-up	0.05 (0.01 ; 0.11)	0.04 (0.00 ; 0.11)	0.07 (0.03 ; 0.18)	0.048
PBVC/y (%/y)	-0.9 (-1.4 ; -0.4)	-0.8 (-1.3 ; -0.3)	-1.3 (-1.7 ; -0.5)	0.011
Change in T2LL/y (ml/y)	0.18 (-0.14 ; 0.69)	0.18 (-0.14 ; 0.40)	0.15 (-0.15 ; 1.27)	ns
Change in T2LL/y (%/y)	6.1 (-4.7 ; 14.9)	4.4 (-6.1 ; 12.8)	7.4 (-1.8 ; 24.1)	ns
Change in BHLL/y (ml/y)	0.00 (-0.06 ; 0.05)	0.00 (0.00 ; 0.02)	0.00 (-0.06 ; 0.07)	ns
Change in BHLL/y (%/y)	-3.3 (-19.5 ; 18.2)	-6.0 (-23.2 ; 19.6)	-2.4 (-13.1 ; 17.1)	ns
Spinal cord				
No. focal lesions baseline	3.0 (1.0 ; 4.0)	2.0 (1.0 ; 4.5)	3.0 (1.0 ; 4.0)	ns
No. segments with focal lesions baseline	2.0 (1.0 ; 3.4)	2.5 (0.8 ; 3.1)	2.0 (1.0 ; 4.3)	ns
No. segments with diffuse lesions baseline	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	ns
No. focal lesions follow-up	3.0 (1.0 ; 5.0)	3.0 (1.0 ; 5.0)	4.0 (2.0 ; 5.8)	ns
No. segments with focal lesions follow-up	2.5 (1.0 ; 5.0)	2.5 (1.0 ; 4.5)	2.5 (2.0 ; 6.7)	ns
No. segments with diffuse lesions follow-up	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	ns

Progression = increase in EDSS of at least 1 point ; P-value = Mann Whitney *U* test was used to test for differences between the progression and the no progression group ; IQR = interquartile range (25%; 75%); NBV = normalised brain volume; T2LL = T2 hyperintense lesion load; BHLL = T1 hypointense lesion load ('black holes'); GADLL = T1 gadolinium enhancing lesion load; BHR = ratio BHLL/T2LL; PBVC = percentage brain volume change.

Table 3.5b

Measurement	Whole Group (n=74)	No Progression (n=49)	Progression (n=25)	*P* value
Brain				
NBV baseline (ml)	1468 (1430 ; 1516)	1479 (1440 ; 1520)	1466 (1405 ; 1505)	ns
T2LL baseline (ml)	3.9 (1.7 ; 12.3)	3.9 (1.3 ; 10.0)	3.8 (1.9 ; 24.2)	ns
BHLL baseline (ml)	0.3 (0.0 ; 0.9)	0.3 (0.0 ; 0.7)	0.3 (0.0 ; 1.3)	ns
GADLL baseline (ml)	0.0 (0.0 ; 0.2)	0.0 (0.0 ; 0.2)	0.0 (0.0 ; 0.2)	ns
T2LL follow-up (ml)	4.7 (2.0 ; 14.2)	4.1 (1.5 ; 10.2)	8.5 (2.6 ; 22.5)	0.034
BHLL follow-up (ml)	0.2 (0.0 ; 1.1)	0.2 (0.0 ; 0.6)	0.8 (0.1 ; 1.6)	0.018
BHR baseline	0.06 (0.00 ; 0.13)	0.04 (0.00 ; 0.14)	0.07 (0.02 ; 0.13)	ns
BHR follow-up	0.05 (0.01 ; 0.12)	0.04 (0.00 ; 0.11)	0.07 (0.02 ; 0.18)	ns
PBVC/y (%/y)	-0.9 (-1.5 ; -0.4)	-0.7 (-1.3 ; -0.3)	-1.4 (-2.0 ; -0.8)	0.006
Change in T2LL/y (ml/y)	0.18 (-0.14 ; 0.69)	0.18 (-0.14 ; 0.52)	0.57 (-0.07 ; 1.78)	ns
Change in T2LL/y (%/y)	6.5 (-4.6 ; 14.9)	4.4 (-5.7 ; 12.8)	8.6 (-1.2 ; 32.4)	0.040
Change in BHLL/y (ml/y)	0.00 (-0.06 ; 0.05)	0.00 (-0.08 ; 0.04)	0.06 (-0.06 ; 0.11)	ns
Change in BHLL/y (%/y)	-2.5 (-19.5 ; 27.8)	-5.8 (-24.2 ; 20.6)	2.5 (-10.0 ; 35.9)	ns
Spinal cord				
No. focal lesions baseline	2.5 (1.0 ; 4.3)	2.0 (1.0 ; 4.5)	3.0 (1.0 ; 4.0)	ns
No. segments with focal lesions baseline	2.0 (0.9 ; 3.1)	2.0 (0.5 ; 3.3)	2.0 (1.0 ; 3.4)	ns
No. segments with diffuse lesions baseline	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	ns
No. focal lesions follow-up	3.0 (1.0 ; 5.0)	3.0 (1.0 ; 5.0)	4.0 (2.5 ; 6.0)	ns
No. segments with focal lesions follow-up	2.5 (1.4 ; 5.1)	2.5 (0.8 ; 4.5)	2.5 (2.0 ; 6.9)	ns
No. segments with diffuse lesions follow-up	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.0)	0.0 (0.0 ; 0.1)	ns

Progression = increase in EDSS of at least 1 point ; P-value = Mann Whitney *U* test was used to test for differences between the progression and the no progression group; IQR = interquartile range (25%; 75%); NBV = normalised brain volume; T2LL = T2 hyperintense lesion load ; BHLL = T1 hypointense lesion load ('black holes'); GADLL = T1 gadolinium enhancing lesion load; BHR = ratio BHLL/T2LL; PBVC = percentage brain volume change.

At baseline median disease duration was 1.6 years (IQR 0.7; 4.1) (Table 3.4a). Most patients had relapse onset disease (74; 83.1%); the other 15 (16.9%) patients had progressive onset disease. At baseline, minimal disability (EDSS <3) was present in most patients (62; 69.7%), 8 (9.0%) patients had EDSS >=4. At follow-up, the number of patients with minimal disability decreased to 43 (48.3%), EDSS >=4 was present in 18 (20.2%) and >= 6 in only 8 (9.0%).During follow-up progression was noted in 36 (40.4%) patients. Median EDSS increased from 2.0 (IQR 2.0; 3.0) to 2.5 (IQR 2.0; 3.5).

MRI characteristics are presented in Table 3.5. Similar patterns are seen for the whole group (Table 3.5a) and the relapse onset group (Table 3.5b).

As expected for patients this early in the disease, low T2LL (median 3.9ml, IQR 1.5; 11.9) and BHLL (median 0.3ml, IQR 0.0; 0.9) were found at baseline (Table 3.5a). Most patients (56; 62.9%) had no enhancing lesions on the baseline scan. Only 12 patients did not have any spinal cord abnormality. Median number of focal cord lesions at baseline was 3.0 (IQR 1.0; 4.0) and unchanged at follow-up (3.0, IQR 1.0; 5.0) (Table 3.5a). Diffuse spinal cord abnormalities were observed in 13 patients.

T2LL increased significantly during follow-up. Change in T2LL was 6.1%/ year (IQR -4.7; 14.9). Median BHLL decreased slightly during follow-up (-3.3%, IQR -19.5; 18.2). Rate of atrophy as measured by PBVC/year was -0.9%. Moderate correlations were found between conventional MRI parameters at baseline (T2LL (r=-0.44, P<.001), BHLL (r=-0.21, P=0.021), GADLL (r=-0.36, P=0.001)) and rate of atrophy (PBVC/year) during follow-up. Strong correlations were found between baseline and follow-up spinal cord parameters, the strongest being the number of focal lesions (r=0.90, P<.001), probably reflecting a lack of change: 40 (44.9%) patients did not change. Baseline spinal MRI parameters and subsequent changes in number of focal lesions or segments with focal lesions were not correlated.

We also explored the correlations between clinical and MRI parameters at baseline. The only significant correlations between baseline EDSS and baseline MRI parameters were NBV (r=-0.42, P<.001) and number of segments with focal (r=0.25, P=0.019) or diffuse abnormalities (r=0.23, P=0.034).

2 Clinical and MRI parameters associated with disease progression

The group of patients that showed progression of disability was older and consisted

of more male patients compared to the group with stable disease although the differences between groups were not statistically significant (Table 3.4). Patients with relapse onset (49 out of 53; 92%) had more often stable disease compared to patients with progressive onset (25 out of 36; 69%) (*P*=0.008).

None of the brain and spinal MRI parameters at baseline was significantly different between groups with or without progression of disability (Table 3.5a). At follow-up however, T2LL, BHLL and BHR were significantly higher in the group with progression: 8.3ml compared to 3.3ml (T2LL, *P*=0.011), 0.5ml compared to 0.2ml (BHLL, *P*=0.018) and 0.07 compared to 0.04 (BHR, *P*=0.048). At baseline and follow-up, the number of focal lesions in the spinal cord was higher in the group with progression although this difference was not statistically significant.

Significant correlations were found between EDSS at follow-up and all brain MRI parameters (except for BHR at baseline) at any time point. The strongest correlation was found between NBV at baseline and EDSS at follow-up (*r*=-0.44, *P*<.001) (Figure 3.2). Number of baseline spinal cord lesions (*r*=0.23, *P*=0.034) and number of segments with diffuse abnormalities (*r*=0.28, *P*=0.009) were correlated weakly with EDSS at follow-up.

Of the changes in MRI parameters during follow-up, only rate of atrophy in PBVC/year was significantly higher in the group with progression of disability compared to the group without progression (-1.3 (IQR -1.7; -0.5) compared to -0.8 (IQR -1.3 ; -0.3), *P*=0.011) (Figure 3.3a). PBVC/year was also correlated with annualised change in EDSS (*r*=0.23, *P*=0.030) (Figure 3.3b).

The first logistic regression model was created using only clinical parameters. Type of disease, age and EDSS at baseline was selected as the three independent parameters in the final clinical model (Table 3.6).

Area under the ROC curve for this clinical model was 0.72 (fair).[25] Older patients with progressive onset and lower disability at baseline are at the highest odds of progression. Only baseline and changes in MRI parameters for both brain and spinal cord were used in the second model. Rate of atrophy (PBVC/year) was the only MRI parameter that was selected in the final MRI model (area under ROC curve 0.68) (Table 3.7), indicating that a higher rate of atrophy was associated with disability progression.

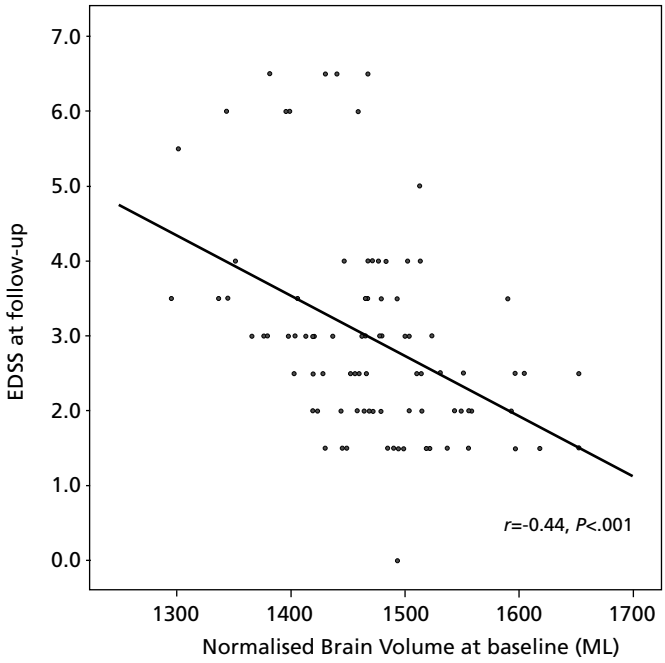

Figure 3.2. Scatterplot EDSS at follow-up versus NBV. Scatterplot showing EDSS at follow-up versus normalised brain volume at baseline, r = -0.44; P<0.001 (Spearman rank correlation).

Table 3.6. Clinical model

Predictor	B	OR	95% CI	*P* value
Intercept	-0.61			
Use of DMT (yes/no)	0.23	1.26	0.40–3.91	0.696
Duration of follow-up (y)	-0.11	0.90	0.29–2.74	0.846
Disease type (relapse-onset/progressive-onset)	2.28	9.81	2.17–44.3	0.003
Age (y)	0.06	1.06	1.00–1.12	0.066
EDSS at baseline	-0.90	0.41	0.21–0.80	0.009

Outcome of logistic regression with all clinical parameters, dependent variable: presence or absence of progression (increase in EDSS of at least 1 point). OR = odds ratio ; DMT = disease modifying therapy.

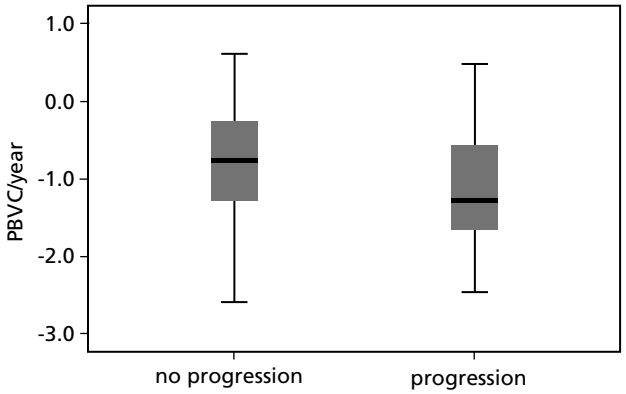

Figure 3.3a. Rate of atrophy for progression and no progression group. Progression = increase in EDSS of at least 1 point ; PBVC = percentage brain volume change. Black line in box represents median, lower and upper boundaries represent the 25% and 75% percentile, respectively. The whiskers represent minimum and maximum values.

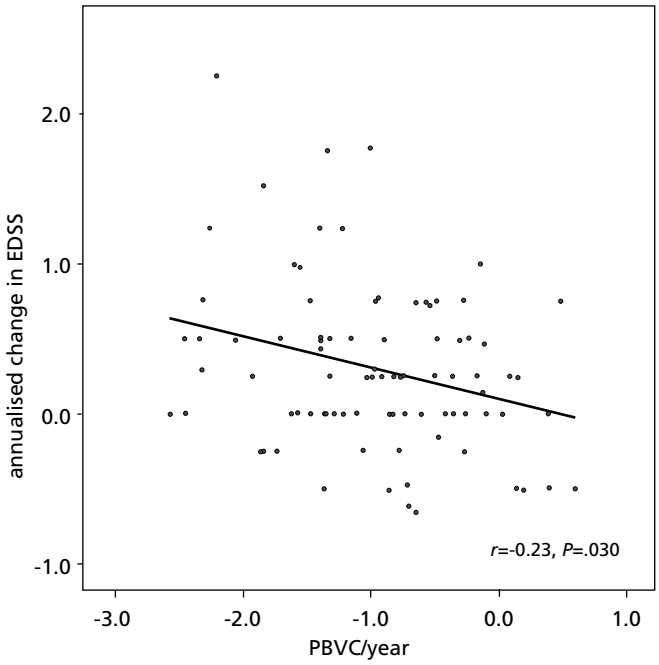

Figure 3.3b Scatterplot annualised change in EDSS versus pbvc/y. Scatterplot showing annualised change in EDSS versus PBVC/year, *r*=-0.23; *P*=0.030 (Spearman rank correlation). PBVC=percentage brain volume change.

Table 3.7. MRI model

Predictor	B	OR	95% CI	*P* value
Intercept	-0.51			
Use of DMT (yes/no)	-0.76	0.47	0.15–1.43	0.183
Duration of follow-up (y)	-0.27	0.76	0.26–2.25	0.624
PBVC/y (%/y)	-0.89	0.41	0.21–0.78	0.007

Outcome of logistic regression with all MRI parameters, dependent variable: presence or absence of progression (increase in EDSS of at least 1 point). OR = odds ratio ; DMT = disease modifying therapy; PBVC = percentage brain volume change.

Finally, we tested in the combined model whether or not adding MRI information could improve the model that contains only clinical parameters. DMT, time between baseline and follow-up examination, age, type of disease and EDSS at baseline were entered into the model. A subsequent forward stepwise procedure selected rate of atrophy in the final combined model, indicating that this MRI parameter added independent information to the clinical model. More formally this was confirmed by a likelihood ratio test (change between models is significant, *P*<.001) and increased area under the ROC curve when comparing the clinical only (fair, 0.72) and the combined model (good, 0.82).[25] Progression was higher in the progressive onset group (11 patients, 73%) compared to the relapse onset group (25 patients, 34%). To exclude the possibility that the group of patients with a progressive onset drives the results, the logistic regression procedure was repeated after exclusion of the progressive onset group. This confirmed the results of the whole group analysis.

Discussion

The precise role of MRI in the management and diagnosis of MS continues to be debated, MRI is reported to have[26] or have not[27] added value. The present study describes clinical and MRI parameters that are associated with progression of disability as measured by changes in EDSS in 89 patients with a recent diagnosis of MS. The main finding from logistic regression models is the observation that adding MRI parameters (rate of cerebral atrophy) to a model using only clinical parameters results in stronger models.

Cerebral atrophy rate as measured by PBVC/year is the MRI parameter that is most strongly associated with progression of disability. Although several MRI parameters are in use as summary measures of axonal loss and other processes of neurodegeneration, atrophy is most commonly used.[28-30] Measures of brain atrophy are robust and even agreement between centers is excellent (Jasperse *et al.*, JMRI 2007, *in press*). Atrophy is already present at the earliest stages of the disease and progresses during further follow-up.[8,31] The atrophy rate in our study (0.9%) is in line with previous studies. Reports on the short-term associations between (rate of) atrophy and subsequent disability in patients early in the RR course of the disease are contradictory. Tiberio *et al.*[15] did not find associations between changes in atrophy measures and changes in disability in a small and not so progressive early MS cohort, whereas in another study of 53 early RRMS patients, in line with our results, atrophy was associated with disease progression.[16] Those apparently contradictory results may be caused by inability of applied clinical scales to registrate real changes in disability, differences in-group size (as in small groups changes might exist undetected), lack of progression of disability and others. However we excluded the results to be driven by the progressive onset patients.

Despite these difficulties it seems important to pick up differences in (rate of) progression early in the disease course: it has been shown that time to reach EDSS 4 (regarded as a critical threshold) varies widely between patients, while beyond this threshold disease progression is quite uniform.[18] Probably, the availability and effectiveness of defense/repair mechanisms differ between patients early in the disease but beyond a critical point (our study indicates that this may occur when axonal damage surpasses a certain threshold) they fail in a predictable fashion.

Compared to T2LL and BHLL, atrophy seems to reflect neurodegeneration more closely and is stronger correlated with disability. Several studies showed atrophy to be more strongly associated with future disability than any conventional MRI parameter.[32-34] Our study results are along the same lines: none of the conventional MRI parameters was shown to be associated with disease progression in the final model. Lack of correlation between conventional MRI parameters and clinical changes might be explained by several mechanisms. Firstly, as expected in a group of newly diagnosed MS patients, changes in and total amount of T2LL and BHLL are low in this study. Secondly, disease progression on the EDSS was limited. Thirdly, variability in the clinical expression of MS plaques in different anatomical locations

was not taken into account.[26] Extending the duration of follow-up and thereby increasing the variance of the measures is likely to enhance correlations between MRI parameters and clinical outcome. This study suggest that conventional MRI parameters are modestly associated with future disability; although not included in the logistic models, T2LL and BHLL at baseline correlate with EDSS at follow-up and lesion loads at follow-up are significantly higher in the group with progressive disease. Of interest is the time lag needed to establish this association, indicating that a certain amount of time elapses between the development of lesions, and possible subsequent (damage to axons and) development of disability. Such a time lag may explain why studies with a much longer follow-up,[2] the number of lesions at baseline was the best predictor for disability at 14 years.

Since our final model with MRI and clinical parameters included does not explain all the variance in progression of disability, it is clear that other factors that were not included may also play a role. We can only speculate on these factors but it seems logical to address the changes that go undetected on conventional MRI but appear to be going on outside MRI visible lesions in the so called normal appearing brain tissue (NABT). MTR, T1 relaxation times and other methods for studying the NABT showed evidence of disease activity outside of MRI visible lesions and seem to correlate with disability.[35-37] Finally, the redundancy of neuronal pathways in the CNS and the role of cortical adaptation have been depicted using functional MRI.[38;39]

Several spinal cord MRI parameters were correlated with EDSS at follow-up although none of them made it into the final model. Apparently, no independent information is to be gained from conventional spinal cord imaging. This is disappointing since neglect of spinal cord involvement is one of the possible explanations for suboptimal clinico-radiological correlations. Several studies showed correlations between EDSS and spinal cord atrophy:[40-42] probably more (independent) information is to be gained when adding measures of spinal cord atrophy, a measure that could not be embedded in our present study. Another limitation of our study is the relatively short duration of follow-up and the fact that many patients had to be excluded due to missing data (though with similar baseline characteristics as those retained).

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