

MRI predictors of cognitive outcome in early multiple sclerosis

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ABSTRACT (215 words)

Objective: To determine MRI predictors for cognitive outcome in early relapsing remitting multiple sclerosis (MS) patients.

Methods: Inception Cohort. Forty-four patients recently diagnosed with clinically definite MS, were followed-up with clinical and cognitive evaluations at 1, 2, 5 and 7 years and underwent brain magnetic resonance imaging (MRI) including magnetization transfer (MT) imaging at baseline and two years. Cognitive evaluation was also performed in 56 matched healthy subjects at baseline. Cognitive testing included the Brief Repeatable Battery (BRB). Imaging parameters included lesion load, brain parenchyma fraction, ventricular fraction (VF), mean MT ratio (MTR) of lesion and normal appearing brain tissue (NABT) masks.

Results: At baseline, patients presented deficits of memory, attention and information processing speed (IPS). Over 2 years all MR parameters deteriorated significantly. Over 7 years, EDSS deteriorated significantly. Fifty percent of patients deteriorated on memory cognitive domain and 22.7% of patients on IPS domain. Seven-year change of memory scores was significantly associated with baseline diffuse brain damage (NABT MTR). IPS z score change over 7 years was correlated with baseline global atrophy (BPF), baseline diffuse brain damage and central brain atrophy (VF) change over 2 years.

Conclusion: The main predictors of cognitive changes over 7 years are baseline diffuse brain damage and progressive central brain atrophy over the 2 years after MS diagnosis.

INTRODUCTION

Cognitive impairment is an important feature of Multiple Sclerosis (MS) and may affect everyday activities. Deficits in memory, information processing speed (IPS), attention, working memory, and executive functions are frequently seen¹. Cognitive dysfunction has long been considered to be confined to patients at later stages of the disease but such impairments have been described in clinically isolated syndromes (CIS)² and in early relapsing-remitting MS (RRMS)³.

The association between cognitive deficiencies and several magnetic resonance imaging (MRI) markers, including lesion load (LL), diffuse brain abnormalities and brain atrophy, has been investigated¹.

However, little is known about the value of these parameters at the early stages of MS to predict cognitive decline over time and the value of magnetization transfer (MT) imaging parameters. We designed a longitudinal study in newly diagnosed clinically definite MS (CDMS) patients to investigate MRI markers predictive for deteriorating cognitive function. Cross-sectional data at baseline showed that cognitive impairment was associated with MR parameters evaluating diffuse brain damage³. We hypothesized that diffuse brain damage outside lesions in early RRMS detected at baseline and their change over 2 years predict the deterioration of cognitive performance over 7 years. Baseline values of various MR parameters, including LL, MT ratio (MTR) metrics, and global and central atrophy, and their change over 2 years were investigated for predicting the deterioration of cognitive performance over 7 years.

METHODS

Patients and controls

Fifty-eight patients, diagnosed with RRMS within the previous six months without other selection criteria, were included by the coordinating centre between November 2000 and November 2001. Patients were consecutively referred by practicing neurologists from a neurological network in south western France for the purpose of that study. None of these patients received disease-modifying therapies before the second exacerbation.

One patient was excluded from the study due to reconsideration of the MS diagnosis. Forty-four patients (77.2%) completed all evaluations during the 7-year study period and were used for the analysis. All patients underwent clinical and cognitive assessment at baseline (year 0) and after years (y) 1, 2, 5 and 7, and underwent brain MRI at y0 and y2. A sample of 56 healthy subjects matched for sex, age, and educational level was also studied at baseline. Baseline clinical, imaging, and cognitive characteristics of patients and controls have been published previously³.

Standards Protocol Approvals and Patient consents:

The study was approved by the institutional review board (CPP Bordeaux #2000/28) and patients gave written informed consent.

Clinical evaluation

Clinical evaluation included Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and Montgomery and Asberg Depression Rating Scale (MADRS).

Neuropsychological assessment

The neuropsychological assessment was previously described in detail³. It included the similarities test and the Brief Repeatable Battery (BRB-N) with the Selective Reminding Test (SRT, and 3 subscores: SRT- LTS = Long term storage; SRT-CLTR = Consistent Long term retrieval ; SRT-DR = delay recall; verbal memory), the 10/36 spatial recall test testing short- (SPART) and long-term visuo-spatial memory (SPART DR), the Symbol Digit Modalities Test (SDMT, attention and IPS), the PASAT 3 and 2 second versions (PASAT 3s and PASAT 2s; working memory and IPS) and the Word List Generation test (WLG; verbal fluency). At y7, we applied alternate forms for all these neuropsychological tests to limit practice effect. Data concerning other tests used at baseline (Go/No-Go; Stroop, similarities, Boston and RFF tests) and for all tests at y1, 2 and 5 follow-ups were not used in this report, because no alternate forms were used.

At baseline, patients were classified as patient cognitively impaired (PCI) if they performed less than the 5th percentile of matched controls on at least two tests of the battery (n=22) and patient cognitively unimpaired (PCU) if they did not (n=22).

At each time point, the raw scores of each cognitive score were transformed to z scores using the mean and standard deviation (SD) baseline scores of the 44 patients as the reference data. Z scores were used to study longitudinal changes of cognitive tests and correlations. Additionally, two domain-specific z-scores were created for memory (SRT-LTS, SRT-CLTR, SRT-DR, SPART and SPART-DR) and IPS (SDMT, PASAT 3s and 2s).

MRI evaluation

Image acquisition: Methods for image acquisition and analysis have been detailed previously³. Brain MRI scans were obtained on a Philips Gyroscan ACS-NT 1.5 T scanner, including Fast Fluid-Attenuated Inversion-Recovery (FLAIR) images (TR/TE/TI: 11000/140/2725), MT images using a proton density sequence (TR/TE: 37/2.3 and flip angle = 8) both with and without an MT saturation pulse, and T1-weighted images (TR/TE: 450/12) before and after administration of gadolinium-DTPA (0.1 mmol/Kg). For all sequences, 26 contiguous interleaved axial slices were acquired with 5 mm slices, 256x256 matrices and 230 x230 fields of view. The slices were positioned to run parallel to a line joining the most inferoanterior and inferoposterior parts of the corpus callosum.

Native and pre-processed data were displayed on workstations running software developed by Bio-Clinica, Inc. (Lyon, France). Following parameters were considered in the analysis: LL, Brain Parenchymal Fraction (BPF), which is defined as the ratio of whole brain parenchyma volume to the intracranial volume⁴, Ventricular Fraction (VF), defined as the ratio of ventricular volume to the intracranial volume⁵, and means of lesion and normal-appearing brain tissue (NABT) MTR masks.

Statistical analysis

Statview version 5.0 (Windows) was used for statistical analysis. Matching between MS patients (n= 44) and healthy controls (n= 56) was verified using the Chi square test for gender and the t test for age and years of education. For each score, the percentages of patients deteriorating or improving more than 1.0 SD of controls scores or stable over 7 years were calculated in whole group, PCI and PCU groups. For IPS and memory domains, patients were classified in the deterioration group if they have more than one SD decrease based on baseline scores of healthy controls. Additionally, at the follow-up evaluations, the patients were considered cognitively deteriorated according to their deterioration score modified from

Kujala⁶. For each domain (IPS , memory), if the subject scored below -1.0 SD compared with the norms, he/she received one deterioration point; if below -1.5 SD, two; if below -2.0 SD, three.

All comparisons were performed using the t test when distribution of values was normal or by non parametric Wilcoxon test when it was not.

Participants who fulfilled all follow-ups were compared to the original sample with regard to demographic data (age, gender, and years of education), baseline neuropsychological scores, EDSS, MSFC, MADRS, disease duration; LL, MTR means, BPF, and VF.

Differences were considered significant, for all analyses, when p values were less than 5%.

Correlations between change in cognitive scores and MADRS scores were studied by Pearson's correlation coefficient.

Univariate linear regressions were performed to assess correlation between individual baseline MR variables or changes over the first two years (LL, mean lesion MTR, BPF, VF and mean NABT MTR) and changes over 7 years of the domain specific cognitive z scores (memory and IPS) in the whole group.

To determine which MRI parameters were the best predictors of cognitive change over 7 years in the whole group, we performed two stepwise multiple linear regression models for each cognitive change over 7 years (memory and IPS domains) as dependent variable. Independent variables were baseline MRI parameters (LL, mean lesion MTR, BPF, VF and mean NABT MTR) in the two first model and MRI parameters changes over 2 years (LL, mean lesion MTR, BPF, VF and mean NABT MTR) in the other models. In all models, we entered age, education level, gender and MADRS scores as independent variables and baseline EDSS was forced in all models as a covariate. Only independent variables with a conservative significance level of $p < 0.25$ at the univariate analysis were entered simultaneously in the linear regression model. All parameters with $p > 0.05$ were removed from the model by stepwise elimination.

Logistic regression analyses were also performed (see Table e-1 at www.neurology.org).

RESULTS

Demographics, clinical and MRI data

Table 1 summarizes demographics and disease characteristics of patients and controls at baseline. MS patients were matched to healthy controls according to gender ($p = 0.16, \chi^2 = 1.98$), age ($p = 0.67, t = 0.42$),

and mean number of years of education ($p=0.72$, $t=-0.36$). No statistical difference was observed for baseline demographics, clinical, and cognitive scores and MRI parameters between the 44 patients who completed all follow-ups over 7 years and the entire original cohort of 56 patients (all p values >0.05).

The percentage of patients receiving disease-modifying therapies at any time during the study was 95.6%. During the follow-up period, 9 of the 44 patients followed over 7 years converted from RRMS to secondary progressive MS.

None of the patients reached the MADRS threshold for severe depression ($MADRS>34$)⁷ at baseline and only one patient at 7 years ($MADRS = 46$). Mild depression ($MADRS$ score between 7 and 19) was diagnosed in 9 patients at baseline and in 16 patients at y7. MADRS median [range] increased over the 7 years (3.0 [0-21] at baseline and 10.5 [0.0-46] at y7, $p<0.001$, $z = -3.712$), and deteriorated in both groups (in CI : 3.0 [0-18] at baseline and 11[0-46] at y7, $p=0.017$, $z = -2.39$, in CU : 4.0 [0-21] at baseline and 10.5[0-31] at y7, $p=0.004$, $z = -2.80$).

Median EDSS deteriorated between y0 (2.0 [0.0-5.5]) and y7 (2.5 [0.0-8.0]) ($p<0.001$, $z = -3.586$). but the MSFC did not change during seven years ($p= 0.20$, $t =1.31$). The number of patients with EDSS <3 was 77.3 % (34/44) at baseline and 59.1% (26/44) at y7. The number of patients with EDSS ≥ 6 was 0 at baseline and 3 at y7 (6.8%). Median EDSS increase is 1.0 [-2.0- +5.0]. During follow-up, disability progression was noted in 21 (48%) patients.

Over 2 years, all MR parameters deteriorated ($p<0.05$) in the whole group (Table 2).

Cognitive evolution during follow-up:

The baseline results have been published³. Differences were observed between RRMS patients and matched controls for memory, attention, IPS, inhibition, and conceptualization.

Nineteen out of 44 patients (43.18%) had a global deterioration score >2 (sum of memory and IPS domains deterioration scores) and 9/44 (20.45%) a score >4 . The proportions of patients deteriorating by cognitive domains more than 1.0 SD of controls scores, improving more than 1.0 SD of controls scores and stable over 7 years are presented in Table 3 for the three groups (all patients, PCI and PCU) without any difference (Fisher test) between the PCI and PCU groups, for memory ($p= 0.37$, OR = 2.05; 95% CI = 0.57-8.2) and IPS ($p= 1.0$, OR = 1.0, 95% CI = 0.19-5.2). The proportion of patients deteriorating was

50% for memory (9 patients deteriorated for one score, 8 patients for two score and 5 patients for more than 2 scores), 22.7% for IPS (5 for one score and 5 for at least 2 scores) and 13.6% for the WLG at y7.

Changes over 7 years in cognitive scores were not correlated with baseline MADRS scores or MADRS change over 7 years (whole, PCI, and PCU groups) (Pearson's correlation coefficient $|r| < 0.30$, $p > 0.05$).

Regression analyses (Tables 4)

For memory or IPS z scores change over 7 years as dependent variable, two multiple regression models were performed with (i) baseline MRI parameters (LL, mean lesion MTR, BPF, VF and mean NABT MTR) as independent variables and (ii) MRI changes over 2 years (LL, mean lesion MTR, BPF, VF and mean NABT MTR). In univariate linear regression analyses, memory z score change over 7 years was associated with baseline LL and mean NABT MTR and with VF changes over 2 years. IPS z score change over 7 years was correlated with baseline MRI parameters (LL, BPF, VF and mean NABT MTR) and with VF and BPF changes over 2 years (all p value < 0.05 , see Table 4). Parameters with $p < 0.25$ in univariate analyses and the baseline EDSS were entered in the two multivariate models (Table 4). After stepwise elimination, the only independent predictor of memory decline was the baseline NABT MTR. After stepwise elimination, baseline NABT MTR and BPF and 2 years change of VF remained in the models for prediction of IPS decline.

No MR parameter predicted WLG z score change in multivariate analysis.

DISCUSSION

This study emphasizes the frequency of cognitive deterioration in the early stages of MS. This deterioration, which may have many impacts in the daily life of patients, including working and social activities, needs to be detected in order to adapt therapeutic strategies. The present study was designed to determine which MR parameter, measured early in MS course, could help predict subjects who will deteriorate. The results showed that MRI parameters reflecting diffuse brain damage (BPF, VF and mean NABT MTR) predict more strongly cognitive deterioration than lesions.

The mechanisms of cognitive dysfunction in MS are not fully understood, but convergent evidence suggests that disconnection between cortical areas might be the basis of this dysfunction⁹. Although focal lesions might contribute to this disconnection, several cross-sectional studies using

diffusion and MT imaging suggested that axonal damage largely contributes to cognitive alterations by interrupting critical networks^{3,9-15}. In the present longitudinal study in early MS we observed that baseline NABT MTR, which reflects diffuse brain injury accumulated so far, but no MR parameters studying focal lesions, predicts cognitive changes over 7 years in the two main domains memory and IPS, in multivariate analyses. Although, LL was associated with cognitive outcome in univariate analyses, it did not remain in multivariate models. These results confirmed the importance of diffuse brain damage in cognition alteration in RRMS. Such disconnections could interfere to the allocation of brain resources for a specific task and may explain that the most common cognitive impairment in MS concerned IPS¹⁶.

Recent reports have shown correlations between cognitive disabilities and central atrophy and are in agreement with the hypothesis that disconnection between the sub-cortical and cortical structures involved in these networks may contribute to cognitive dysfunction¹⁷⁻²³. Although atrophy measures did not correlate with cognitive functions at baseline³, baseline BPF, a measure of global atrophy and two-year VF change, a measure of central brain atrophy predict decline in IPS performance over 7 years. Although periventricular white-matter atrophy could contribute to VF change, and in particular corpus callosum atrophy, which has been implicated in cognitive impairment in MS²⁴, it is likely that damage of the deep gray-matter and the surrounding white matter is determinant in cognitive deterioration affecting IPS in early RRMS. These results are in agreement with a recent study that analyzed the rates of atrophy in different parts of the brain and correlated them to various clinical indexes including the PASAT as part of the MSFC²⁵. The authors found that a worse performance on the PASAT at follow-up was predominantly related to atrophy development around the ventricles and, to a lesser extent, brainstem atrophy.

Several studies investigated the association between MR parameters and cognition evolution in RRMS but none used MT imaging. One study showed that one-year global atrophy rate was associated with cognitive deficiencies measured several years later²⁶. In that study, prediction of cognitive deterioration could not be evaluated since cognitive data were only measured at the last follow-up. Another study that examined the relation between changes of LL and brain parenchymal volumes over 2 years together with change in cognition during the same time-frame and found that the best predictor was brain parenchymal volumes²⁷. These two studies did not specifically evaluate central atrophy. Another

study found that only neocortical volume changes, but not deep gray matter volume changes, were significantly associated with deteriorating cognitive performance over 2.5 years²⁸. It is possible that atrophy of the cerebral cortex accounts for more of the cognitive deterioration when the disease progresses, since the mean disease duration was longer in that later study than in ours (4.0 ± 2.8 vs. 2.0 ± 2.2 years). It has been suggested that deep central atrophy may peak at earlier stages compared to whole brain atrophy²⁹ and that central atrophy progresses preferentially in the early stages of the disease³⁰. These data can explain that, although baseline BPF which reflects brain whole atrophy developed so far is predictive of cognitive deterioration, it is only the central atrophy change which account for cognitive deterioration in attention/IPS domain. We hypothesized that disruption of deep central brain cognitive networks involved in attentional occurs in our population. It is worth mentioning that cortical atrophy also occurs in early MS^{31,32} but appears to progress less rapidly than central atrophy²⁹. In our study, we did not specifically study neocortical volume.

Interestingly, it was recently shown that memory performance and mesial temporal volumes, in particular hippocampal atrophy, were correlated in MS^{33,34}. This suggests regional specificity of correlations between atrophy and alterations of a given cognitive domain. In our study, we did not find correlation between memory change and atrophy measures although a trend was observed with VF change (data not shown). However baseline NABT MTR predicted memory changes over 7 years suggesting that diffuse alterations contribute also to the memory deficits by interrupting the relevant networks.

There are some limitations to this study. When performing imaging, it would have been informative to study regional changes in brain volume and MTR, for example, using voxel-based morphometry. Unfortunately those techniques were not available at the beginning of this study. Concerning cognition, the main limitation of longitudinal studies in MS is that relatively few patients deteriorate for cognitive scores and that a relatively large number of them remain stable. One possible reason is practice effect. To limit practice effect we used alternate forms at the 7 year evaluation, never used in the previous evaluations, but we cannot exclude that some practice effect remains. Another explanation for the limited changes in cognitive performances is that cognitive skills deteriorate slowly at the early stages of MS because of the presence of compensatory mechanisms³⁵.

Further studies are needed to determine which therapeutics strategies could limit diffuse brain damage at the early stage of MS and therefore ongoing cognitive deterioration.

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Table 1: Demographic and clinical baseline characteristics of RRMS patients as well as separately for CPU and CPU groups included in the follow-up

	Patients			Controls (n= 56)
	n= 44	PCI n= 22	PCU n=22	
Gender (male/female)	10/34	5/17	5/17	20/36
Age (years)	39.0 (8.7)	40.4 (9.9)	37.7 (7.2)	38.2 (10.5)
Educational level (years of schooling)	12.2 (2.5)	11.3 (2.3)	13.2 (2.3)	13.05 (2.6)
Disease duration (months)	24.3 (27.4)	22.5(21.7)	26.1(32.6)	
EDSS	2.0 [0.0-5.5]	2.0 [0.0-3.5]	1.5 [0.0-5.5]	
MSFC	-0.053 (0.701)	<u>-0.409(0.681)</u>	0.339 (0.490)	
MADRS	3.0 [0-21]	2.0 [0-18]	4.0 [0-21]	

PCI= patients cognitively impaired; PCU: patients cognitively unimpaired. For all clinical data, scores are expressed as mean (SD) except for EDSS and MADRS which are median (range). EDSS: expanded disability status scale; MSFC: multiple sclerosis functional composite; MADRS: Montgomery and Asberg depression rating scale.

Table 2: MRI parameters.

MRI parameters	Patients								
	n=44			PCI n=22			PCU n=22		
	Baseline	Y2	t-score	Baseline	Y2	t-score	Baseline	Y2	t-score
LL (cm ³)	9.57±11.26	11.26±12.0**	-2.967	11.76±13.43	12.78±12.59 NS	-1.313	7.38±8.34	9.77±11.52**	-2.851
BPF	0.881±0.032	0.865±0.045***	3.895	0.878±0.037	0.861±0.052**	2.879	0.883±0.027	0.869±0.038*	2.565
VF	0.024±0.010	0.027±0.012***	-5.051	0.025±0.010	0.028±0.013**	-3.790	0.023±0.009	0.025±0.011**	3.07
Mean lesion MTR	46.66±2.29	46.07±3.11*	1.973	46.24±2.64	45.84±3.35 NS	1.153	47.08±1.84	46.29±2.93 NS	1.584
Mean NABT MTR	48.44±0.865	47.64±0.954***	5.841	48.39±0.874	47.64±0.927 ***	6.494	48.49±0.873	47.63±1.00**	3.413

PCI= patients cognitively impaired; PCU: patients cognitively unimpaired. MRI parameters are expressed as mean (SD). LL : lesion load; BPF : Brain Parenchymal Fraction; VF : Ventricular Fraction; NABT : Normal-appearing brain tissue. MTR: Magnetization Transfer Ratio. P values and t-scores concerned comparison between baseline and y2. NS : p > 0.05; * p < 0.05; ** p < 0.01; *** p < 0.001.

Table 3: Number of patients with deterioration, no change or improvement for the two main cognitive domains over 7 years.

	All Patients (n=44)			PCI (n= 22)			PCU (n=22)		
	Improvement	No change	Deterioration	Improvement	No change	Deterioration	Improvement	No change	Deterioration
Memory domain (SRT-LTS, SRT-CLTR,SRT-DR, SPART,SPART-DR)	1	21	22	1	12	9	0	9	13
IPS domain (SDMT, PASAT 3s & 2s)	0	34	10	0	17	5	0	17	5

PCI= patients cognitively impaired at baseline; PCU= patients cognitively unimpaired at baseline (see methods).

SRT, Selective Reminding Test; SRT-LTS, long-term storage; SRT-CLTR, consistent long-term retrieval; SRT-DR, delayed recall; SPART, Spatial Recall Test; SPART-DR, Delayed recall; SDMT, symbol digit modalities test; PASAT, paced auditory serial addition test.

TABLE 4: Linear regression models predicting change in cognitive z scores over 7 years from MR parameters at baseline or changes over 2 years.

Cognitive z scores change (y7-baseline)	MR parameters Included in models	R Univariate analyses	P values Univariate analyses	Adjusted R ² model	P values multivariate analyses
Memory domain	Baseline EDSS	-0.095	0.54	0.144	<0.05
	<i>Baseline LL</i>	<i>-0.333</i>	<i><0.05</i>		
	Baseline BPF	0.126	0.42		
	Baseline VF	-0.175	0.26		
	<i>Baseline mean lesion MTR</i>	<i>0.253</i>	<i>0.10</i>		
	Baseline mean NABT MTR	0.377	<0.05		
	Baseline EDSS	-0.095	0.54	0.009	0.54
	<i>LL change over 2 years</i>	<i>-0.085</i>	<i>0.59</i>		
	<i>BPF change over 2 years</i>	<i>0.200</i>	<i>0.19</i>		
	<i>VF change over 2 years</i>	<i>-0.290</i>	<i><0.05</i>		
Mean lesion MTR change over 2 years	-0.090	0.57			
Mean NABT MTR change over 2 years	-0.057	0.72			
IPS domain	Baseline EDSS	-0.273	0.07	0.416	<0.0001
	<i>Baseline LL</i>	<i>-0.425</i>	<i><0.01</i>		
	Baseline BPF	0.551	<0.0001		
	<i>Baseline VF</i>	<i>-0.414</i>	<i><0.01</i>		
	Baseline mean lesion MTR	0.148	0.34		
	Baseline mean NABT MTR	0.511	<0.001		
	Baseline EDSS	-0.273	0.07	0.326	<0.001
	<i>LL change over 2 years</i>	<i>0.117</i>	<i>0.45</i>		
	<i>BPF change over 2 years</i>	<i>0.435</i>	<i><0.01</i>		
	VF change over 2 years	-0.545	<0.0001		
Mean lesion MTR change over 2 years	0.163	0.29			
Mean NABT MTR change over 2 years	-0.016	0.92			

Memory domain includes the Selective Reminding Test (long-term storage; consistent long-term retrieval; delayed recall) and the Spatial Recall Test (recall score and Delayed recall). IPS domain includes the Symbol Digit Modalities Test, the Paced Auditory Serial Addition test (3 and 2 sec versions).

LL : Lesion Load; MTR: Magnetization Transfer Ratio; NABT: normal appearing brain tissue; BPF; Brain Parenchymal Fraction; VF: Ventricular Fraction.

Univariate analyses for age, MADRS scores, gender and educational levels showed not significant results ($p>0.05$). Variables with a p value <0.25 in univariate analyses were included in multivariate analyses . Variables included in multivariate analyses but not significantly correlated with cognitive Z scores changes in final models were in italic police. Variables significantly correlated to cognitive change in multivariate analyses are in bold police. For statistical analysis and further details, see methods.