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Memory decline evolves independently of disease activity in MS

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Background The natural history of cognitive impairment in multiple sclerosis (MS) and its relationship with disease activity is not well known. In this study, we evaluate a prospective cohort of 44 MS patients who were followed every 3 months for 2 years. Cognitive evaluation was done at baseline and by the end of the study using the Brief Repeatable Battery-Neuropsychology. Clinical evaluation included assessment of new relapses and changes in disability (Extended Disability Status Scale (EDSS)) confirmed at 6 months.

Results We found that verbal memory performance deteriorates after 2 years in patients with MS. These changes were observed in stable and active patients both in terms of relapses and disability progression, even at the beginning of the disease, and in patients with or without cognitive impairment at study entry. Attention and executive functions measured with the symbol digit modality test (SDMT) declined after 2 years in patients with confirmed disability progression. Furthermore, SDMT performance correlated with the EDSS change.

Conclusions Our findings indicate that verbal memory steadily declines in patients with MS from the beginning of the disease and independently of other parameters of disease activity. *Multiple Sclerosis* 2008; **14:** 947–953. http://msj.sagepub.com

Key words: brief repeatable battery-neuropsychology; cognitive impairment; longitudinal study; multiple sclerosis; selective reminding test; symbol digit modality test

Introduction

Cognitive impairment is frequent in patients with multiple sclerosis (MS), affecting up to 60% of cases, and it is present even at the beginning of the disease. Information processing speed is commonly affected, and the cognitive domains more often affected are memory, attention, and executive functions [1,2]. Although cognitive abnormalities in MS are not easily detected without appropriate neuropsychological batteries, they are frequently identified correctly by patients and might cause significant functional impairment in patient's daily activities. Indeed, their impact in daily life, in addition to physical disability and behavioral changes, might explain why up to 70% of patients after a long disease duration are unemployed, divorced, and socially isolated [3,4].

The natural history of cognitive impairment in patients with MS is still not well known. For example, whether cognitive abnormalities correlate with disease progression or if the pattern of such dysfunction differs between disease subtypes is still a matter of discussion [5–8]. Moreover, we still do not know in detail how cognitive functions decline with the disease, and what the relationship is with Magnetic Resonance Imaging (MRI) and neurophysiology measurements [8]. The unraveling of the natural history of cognitive impairment in MS will improve our understanding of which patients will benefit from therapeutic interventions such as cognitive therapy [9] or new cognitive enhancing drugs [10,11] will develop specific social support programs for coping with such impairment.

The aim of our study was to study the changes in cognitive performance during a 2-year observation

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period in a cohort of patients at the early to medium phase of their disease. We were interested in identifying the most sensitive cognitive domains to changes and their relationship with clinical disease activity variables.

Patients and methods

Patients and controls

We studied 44 patients with MS and 25 healthy controls. Patients were recruited consecutively in the MS center of a referral hospital from April 2004 to May 2005. Controls were matched by sex, age, and educational level with the patient group, and they were used for controlling for practice effect of neuropsychological test (but not for obtaining normative values, which have been previously published [2]). All subjects gave their informed consent, and the local Ethics Committee approved the study. Inclusion criteria were 1) having MS [12]; 2) suffering from the disease for less than 10 years and Extended Disability Status Scale (EDSS) < 6.0; 3) any disease subtype; 4) no history of psychiatric or neurological disease (other than MS) or any other major medical illness were included, and no history of alcohol or drug abuse that could interfere with neuropsychological performance; 5) being right-handed (>70% Oldfield scale [13]) native Spanish speakers. The use of immunomodulatory therapies for MS was allowed. Exclusion criteria were 1) presence of visual, motor (dominant hand), or auditory deficits that prevent the completion of the tests; 2) having suffered a relapse within the past 3 months; 3) presence of psychiatric disorders identified with the Cummings' Neuropsychiatry Inventory [14], the Hamilton's Depression Rating Scale [15] (≥8 points), the Hamilton's Anxiety Rating Scale [16] (≥6 points). No subjects were suffering clinical relapse at the time of the neuropsychological assessment at baseline and endpoint of the study. We screened 61 patients recruited for a study for determining the diagnostic accuracy of retinal abnormalities in predicting disease activity in MS [17]. Of them, 44 patients were included in the study (Table 1). After 2 years, we were able to reassess with the neuropsychology battery in 39 patients (Table 1). Five patients dropped out of the study (3 clinically isolated syndrome and 2 relapsing-remitting patients): one was discarded immediately after study inclusion because of the presence of active isquemic cardiopathy and another four because they changed their residency by the middle of the follow-up ($n = 2$) or declined to perform a second cognitive evaluation ($n = 2$). The clinical characteristics of dropped-out patients did not differ from the overall cohort.

Clinical evaluation

Patients were clinically followed every 3 months for 2 years and we recorded presence of new relapses and change in disability. The clinical characteristics of this cohort are described in detail elsewhere [17]. Physical disability was evaluated in every visit using the EDSS [18] and the Multiple Sclerosis Functional Composite (MSFC) [19]. Disability progression was defined as an increase in 1 point in the EDSS (0.5 point in patients with EDSS > 5.5) confirmed in a second visit 6 months apart [20]. Finally, we assessed the homogeneity between active and stable patients (patients with or without disability progression and patients with or without relapses) to avoid potential confounders within the sample, such as different baseline patterns of cognitive impairment, EDSS, MSFC, or disease duration. Both groups did not statistically differ in those baseline variables ($P > 0.05$ in all cases).

Cognitive performance assessment

Neuropsychological performance was assessed using the validated Spanish version of the Brief Repeatable Battery-Neuropsychological (BRB-N).

Table 1 Clinical information of patients with MS at baseline and by the end of the study (2-year follow-up)

	MS baseline ($n = 44$)	MS follow-up ($n = 39$)	HC ($n = 25$)	*P*
Age (years)[a]	36 ± 9.43	37.95 ± 9.84	39 ± 13.9	ns
Sex ratio (M/F)	14/30	12/27	7/16	ns
Education (years)[b]	14 (7 to 28)	14 (7 to 28)	13 (7 to 29)	ns
MS subtype	15CIS/21RR/4SP/4PP	6CIS/22RR/7SP/4PP	—	—
Disease duration (years)[b]	6.25 (1 to 36)	7 (3 to 38)	—	—
EDSS score[b]	2 (0 to 7.0)	2.5 (0 to 8.0)	—	—
MSCF score[b]	0.25 (–1.81 to 1.08)	0.37 (–5.66 to 1.27)	—	—

MS, multiple sclerosis; ns, no significant differences between healthy control (HC) and MS at baseline; CIS, clinically isolated syndrome; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive; EDSS, Expanded Disability Status Scale; MSFC, MS Functional Composite. Data are expressed in mean ± standard deviation[a] or median (range)[b] depending on the parametric or non-parametric distribution of the variable.

Normative values in our population have been obtained previously in a cohort of 150 healthy individuals [2]. Neuropsychological evaluation was carried out by a single trained neuropsychologist (BD). The BRB-N was administered twice (baseline and by the end of the study) using a Spanish parallel version (for all subtests, except for verbal fluency tests because in this case it is not applicable) to minimize possible learning effects swing to repeated exposure. The BRB-N included 1) Bushke Selective Reminding test (SRT); 2) 10/36 Spatial Recall Test (SPART); 3) Symbol Digit Modalities Test (SDMT); 4) Paced Auditory Serial Addition Task at 3 s (PASAT 3); and 5) Word list generation (WLG). PASAT was saturated between baseline and end of the study by the administration of the MSFC scale every 3 months. We assessed the inter-rater reliability between two researchers (JS and BD) using 20 randomly selected patients. Intraclass coefficient for the BRB-N tests were high in all cases and varied from 0.703 ($P = 0.003$) to 0.972 ($P < 0.001$). None of the individuals had previously been subjected to these tests and no one refused to perform them. We defined presence of cognitive impairment if they obtained abnormal results in the BRB-N lower than 1.5 SD using the normative cut-off values, in at least two tests. We also calculated the BRB-N-Z score, as described previously [2].

ApoE genotyping

Fluorogenic allele-specific TaqMan probes and primers were used for ApoE isoforms genotyping as described [21]. Five samples previously genotyped in our laboratory by restriction fragment length polymorphism analysis (Hha1 restriction enzyme) were included in the TaqMan experiments as internal controls. Final step analysis was performed in an ABI7300 Real-Time PCR Systems (Applied Biosystems, Foster City, California, USA). Allele calling was carried out using the allelic discrimination analysis module of the ABI Sequence Detection Software (Applied Biosystems, Foster City, California, USA).

Statistical analysis

The normal distribution of the variables was assessed with the Kolmogorov-Smirnof test. Demographic variables were compared between MS and healthy control groups using *t*-test or X^2 when appropriate. We used the paired *t*-test for comparing normally distributed variables and the Wilcoxon test for non-parametric ones. Correlation between the BRB-N tests and the patient's disability changes were assessed by using the Pearson or Spearman correlation test. Level of significance was set at $P < 0.05$. Statistical analyses were performed using SPSS 13.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Clinical characteristics of the patient's cohort

During the follow-up period, 20 patients were relapse-free, and the disease course changed from clinically isolated syndrome (CIS) to relapsing-remitting multiple sclerosis (RRMS) in six patients and from RRMS to SPMS in three patients. Relapse rate along follow-up period was 1.15. The increase in the EDSS at the end of the study for the overall cohort was 0.35 ± 0.69, and 11 patients had disability progression confirmed at 6 months.

Longitudinal changes in cognitive performance and disease activity

We found a decrease in the scores of verbal memory tests after the 2-year follow-up (Table 2), mainly in storage and retrieval. The decrease in the verbal memory performance after 2 years was present in both relapse-free and non-relapse-free patients, in patients with or without disability progression, and in patients with or without cognitive impairment at baseline (Figure 1). Thus, we found a decrease in verbal memory performance that was not associated with the presence of relapses, increase in physical disability, or previous cognitive impairment. Because the sample size of patients with progressive forms of MS was small, we did not perform comparisons between disease subtypes. However, we found that CIS patients that converted to RRMS have a tendency for a decrease in the verbal memory storage score ($P = 0.06$) compared with the ones that were not converted ($P = 0.21$). Moreover, we found that patients with disability progression during the follow-up but not stable patients have a decline in the SDMT performance ($P = 0.024$). Indeed, we found that the SDMT score by the end of the study correlated with changes in EDSS during the follow-up period ($r = –0.459$; $P = 0.003$).

Changes in the prevalence of cognitive impairment after two years

To define the changes in the prevalence of cognitive dysfunction in patients with MS with disease evolution, we divided the patients in two subgroups based on the number of tests failed at baseline: unimpaired (<2 subtest below 1.5 SD of

Table 2 Mean scores of BRB-N battery in controls and patients with MS at baseline and follow-up

BRB-N	MS			Controls		
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*
SRT-S	49.93 ± 11.27	44.51 ± 12.19	<0.001	52.61 ± 12.74	53.65 ± 9.79	ns
SRT-R	39.95 ± 12.94	33.1 ± 15.3	<0.001	45.13 ± 13.51	44.91 ± 13.2	ns
SRT-D	9.11 ± 2.33	8.38 ± 2.38	0.021	10.3 ± 1.46	10.17 ± 1.77	ns
SPART	19.41 ± 4.87	19.77 ± 5.62	ns	22.96 ± 5.62	21.57 ± 6.61	ns
SPART-D	7.36 ± 1.94	6.95 ± 2.35	ns	8.39 ± 2.16	9.09 ± 3.11	ns
SDMT	51.68 ± 14.31	50.31 ± 15.73	ns	51.78 ± 16.15	51.52 ± 17.38	ns
WGLS	27.7 ± 5.65	27.79 ± 8.26	ns	29.17 ± 9.61	28.83 ± 7.77	ns
WGLP	21.0 ± 6.73	21.59 ± 7.57	ns	21.37 ± 6.59	21.64 ± 6.48	ns
PASAT3	49.95 ± 11.6	49.16 ± 11.69	ns	42.65 ± 11.19	45.35 ± 13.44	ns

BRB-N, Brief Repeatable Battery-Neuropsychological; MS, multiple sclerosis; SRT-S, Selective Reminding Test Long-Term Storage; ns, not significant; SRT-R, Selective Reminding Test Long-Term Retrieval; SRT-D, Selective Reminding Test Delayed Recall; SPART, 10/36 Spatial Recall Test; SPART-D, 10/36 Spatial Recall Test Delayed; SDMT, Symbol Digit Modality Test; WLGS, Word List Generation Semantic; WLGP, Word List Generation Phonetic; PASAT3, paced auditory serial addition task at 3 seconds interval. The data were expressed in mean ± standard deviation.

the normative data) and impaired group (more than two subtest with a performance <1.5 SD than the normative data) [2]. The prevalence of memory dysfunction (one subtest below 1.5 SD normative data) increased from 31% to 41% over the 2-year follow-up, and the prevalence of cognitive impairment (two or more subtests below 1.5 SD of the normative data) rose from 29% to 48%.

We assessed whether a unified measurement of the cognitive impairment, such as the BRB-N-Z score [2], is sensitive to detect changes along time in a 2-year observation period. We found no differences between BRB-N-Z scores between baseline and by the end of the study, neither considering the whole cohort nor when analyzing different subgroups (e.g., patients with or without cognitive impairment, relapses, or disability progression).

Finally, we assessed the influence of genetic markers and cognitive decline in patients with MS, such as the ApoE4 genotype because it is associated with the presence of cognitive impairment in MS [22]. In our cohort, eight patients were ApoE4 positive (including two homozygous individuals) and 28 were ApoE4 negative. We found no association between the ApoE4 genotype and the degree of cognitive impairment (data not shown). However, because of the small sample size of ApoE4 individuals, especially for the presence of ApoE4 homozygous, we might lack enough power to detect any association.

Discussion

In this prospective study, we found that, in a 2-year period, verbal memory declines in a significant proportion of patients. Our results are in agreement with the previous findings that verbal memory, in addition to information processing speed, is the most frequently affected cognitive domain in MS [1,8] and indicates that such impairment evolves over short period of time, starting at the beginning of the disease and independently of other parameters of disease activity such as clinical relapses and disability accumulation. Moreover, the variable distribution of MS lesions and the presence of cortical damage [23,24] might explain the independence between verbal memory deterioration and clinical relapses. All together, our results suggest that assessment of verbal memory in MS can be useful, in addition with the evaluation of physical disability, for identifying disease activity. However, we cannot exclude that different ways for measuring disease activity, longer follow-up, or the use of more sensitive methods such as MRI, might identify a relationship between cognitive impairment and disease activity. The differential onset and decline of cognitive and physical disability might be due to the fact that cognition depends on widespread brain networks that are more sensitive to gray matter atrophy and long-tracts disconnection, a process that also starts and progresses steadily from the beginning of the disease [25,26].

A degree of controversy exists on the correlation between cognitive impairment and the degree of physical disability measured with the EDSS scale [5,27–30]. We found that SDMT decline was associated with the progression of physical disability. This result is in agreement with our previous results showing that SDMT correlates with physical disability measured with the EDSS [2]. Because of its multifactor nature, the SDMT performance is highly dependent of the integrity of several brain networks. For this reason, the impairment in SDMT performance might reflect a more widespread brain damage, explaining the partial correlation with physical disability deterioration or with the progressive phase [27,31,32]. Indeed, higher EDSS and progressive course are associated with worse

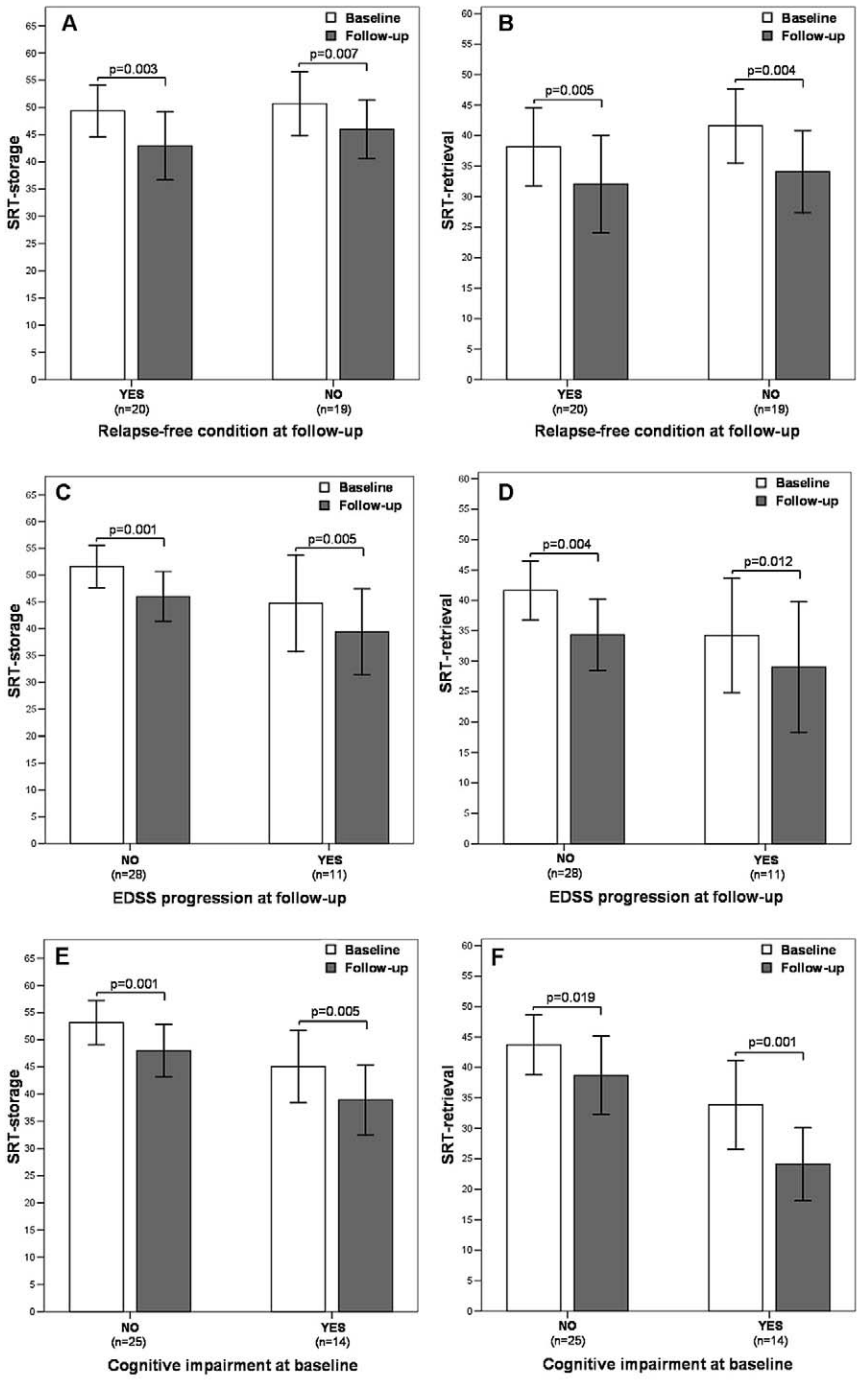

Figure 1 Association between verbal memory performance, clinical relapses, disability progression, and previous cognitive impairment in patients with multiple sclerosis. We observed significant decrease in the 3 scores of verbal of the Selective Reminding Test (SRT), storage (A), retrieval (B), and delayed recall (C), between baseline (white bar) and 2-year follow-up (gray bar). Patients with relapses have a decrease in the SRT scores (SRT-S: $P = 0.003$; SRT-R: $P = 0.005$) and patients without relapses (SRT-S: $P = 0.007$; SRT-R: $P = 0.004$; SRT-D: $P = 0.046$). D) Clinically isolated syndrome patients converting to RRMS during follow-up have a trend for impaired SRT-S performance ($P = 0.06$). Patients with physical disability progression (decrease in the Expanded Disability Status Scale confirmed at 6 months) during the follow-up have an impaired performance in the SRT-S ($P = 0.05$) and SRT-R ($P = 0.012$). Patients without disability progression also have a decrease in the SRT-R ($P = 0.004$) and SRT-D ($P = 0.047$) by the end of the study. Patients with cognitive impairment by the time of the study entry have a decrease in the performance of SRT-S ($P = 0.005$), SRT-R ($P = 0.001$) and patients without cognitive impairment at baseline (SRT-S: $P = 0.001$; SRT-R: $P = 0.019$).

cognitive outcome, indicating that although physical and cognitive impairment may evolve independently, they tended to converge in the long-term [8].

Several studies have found that attention and spatial or verbal memory deteriorates with disease duration [7,30,33,34]. Similar to our findings, other studies found that cognitive deterioration in patients with MS raises from 20–30% to close to 50% in a similar period of time [7,28,35,36]. However, some other studies did not confirm such cognitive deterioration rates [8,37–39], which may be related to the small sample size used or patient loss during follow-up. Nevertheless, the overall evidence indicates a progressive cognitive decline over time in a big proportion of patients with MS and also suggests that the profile of cognitive deficits tends to extend to cognitive domains previously preserved [8].

Several methodological limitations might difficult the interpretation of our findings. Our study, although it was hospital-based, included consecutive patients to control for population bias. The sample size was big enough for being able to detect differences previously described and to identify progressive decline in verbal memory and was similar to previous well-controlled studies [7,28,35], although it was small for confirming the influence of ApoE4 in cognition. Our results should not be interpreted as a lack of effect of ApoE4 in cognitive deterioration, but a suggestion that the magnitude of its effect is not very high. Although 2-year follow-up might be a short period compared with the time over which MS evolves, such a period is the most used for identifying clinical and biological markers or testing new therapies. Thus, our results will be informative in this context and might be helpful for the design of new clinical studies. We controlled for mood and psychiatric disorders as well for the use of psychoactive drugs that might interfere with neuropsychiatry evaluation. Moreover, the drop-out rate in our study was small and none of them related to disease progression. In our study, practice effects were controlled by the use of alternative versions and by saturating some tests such as PASAT. Finally, because the pathogenic basis of disease progression may vary between different disease subtypes, it is possible that the rate of cognitive deterioration may vary based in the underlying mechanism of brain damage.

Based on our study and previous studies, we proposed assessing verbal memory (SRT storage and retrieval) and SDMT for monitoring cognitive deterioration in patients with MS, when more comprehensive batteries cannot be administered or for a quick evaluation in clinical practice or during the conduction of clinical trials. Verbal memory seems to be the more sensitive cognitive function for identifying disease activity and attention, and executive functions, assessed with SDMT, might be more specific for detecting tissue damage as suggested by its correlation with physical disability. Finally, integrated scores such as the BRB-N-Z score seem to lose sensitivity to detect changes. Longer prospective studies are required to improve our knowledge about the natural history of cognitive impairment in MS.

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