Executive function and memory in patients with relapsing-remitting multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system very heterogeneous in its characteristics. In contrast to the well known sensitive/motor deficits, the cognitive dysfunction has only been analyzed in the last few decades. Attention, executive function, and memory were assessed in 28 patients with recurrent-remittent MS (RRMS) (duration, median 7 years; EDSS median 2) by means of a specific neuropsychological battery. Depression (BDI), anxiety (STAI) and fatigue (FSS) were also assessed. Twenty-five of these patients were selected for statistical study because they presented deficits in some cognitive areas. Twenty-four percent of the patients displayed memory deficits and 80% showed attention and executive function deficits related to prefrontal lobe function. No global memory difficulties were found, except for immediate visual memory of complex elements (immediate recall of the Rey figure), although the visual reproduction I subtest of the WMS-R was unaffected. In RRMS patients with a relatively short duration and low level of incapacity, cognitive impairments mainly affected prefrontal functions. The difficulties in immediate visual memory of complex elements could also be explained by a failure in these areas, due to the alteration of the organization and strategic use of the material to be encoded.

Función ejecutiva y memoria en pacientes con esclerosis múltiple recurrente-remitente. La esclerosis múltiple (EM) es una enfermedad inflamatoria crónica del sistema nervioso central muy heterogénea en sus manifestaciones. A diferencia de los déficits sensitivos-motores, muy bien estudiados, los aspectos cognitivos están siendo analizados sólo en las últimas décadas. A 28 pacientes con EM recurrente-remitente (EMRR) (tiempo de evolución, mediana 7 años; EDSS, mediana 2) se les realizó una evaluación de atención, función ejecutiva y memoria mediante una batería neuropsicológica específica. Se evaluaron también el grado de depresión (BDI), ansiedad (STAI) y fatiga (EGF). Veinticinco fueron seleccionados para el estudio por presentar alteración en algún aspecto cognitivo. El 24% mostraba disminución en memoria y el 80% en atención y funciones ejecutivas relacionadas con regiones prefrontales. No se observaron dificultades globales de memoria, salvo en memoria inmediata visual de elementos complejos (Figura de Rey reproducción inmediata), sin afectarse la prueba de reproducción visual I de la WMS-R. En pacientes con EMRR con un tiempo medio de evolución y bajo nivel de incapacidad, las alteraciones cognitivas afectan fundamentalmente a funciones atribuidas a regiones prefrontales. Las dificultades en memoria inmediata visual de elementos complejos se explicarían también por un fallo de estas áreas al alterarse la organización y uso estratégico del material a codificar.

Multiple Sclerosis (MS) is a chronic inflammatory disease of Central Nervous System (CNS) that mainly affects a young people. It is characterized by multiple lesions in cerebral white matter, named «plaques», constituted by perivascular cuffing with inflammatory mononuclear cells, predominantly T cells and macrophages, demyelination and gliosis. There is also a variable axonal damage since the beginning of the disease (Anthony, Hughes, & Perry, 2000).

The MS manifests a great heterogeneity in all aspects: clinical, evolution, prognosis, pathogenesis and anatomy. The most common evolution type is relapsing/remitting MS (RRMS) accounting for 85% of MS cases at onset. The 60-70% of these will develop a secondary progressive MS (SPMS). A 10-20% of cases are progressive since the beginning, the primary progressive MS (PPMS). In the same way, the prognosis is very variable among patients; the benign types, about 10-20% of the cases, will not develop important impairment against time, while malign types, less than 5% of cases, will develop it in a few years (Martínez, S., Ballabriga, Martínez, A., Hernández, & Arbizu, 1998; McDonald, Compston, Miller, & Smith, 2006).

Cognitive function is highly prevalent in multiple sclerosis. Between 45 and 65% of these patients present some type of cognitive deficit (Bagert, Complair, & Bourdette, 2002; Rao,

1995; Rao, Leo, Ellington, Nauertz, Bernardin, & Unverzagt, 1991). The domains mainly affected are the speed of processing, memory, learning, attention, executive function and performance in visuoconstructive tasks; linguistic processing is usually conserved (Achiron, Ziv, Djaldetti, Goldberg, Kuritzky, & Melamed, 1992; Amato, Poziani, Siracusa, & Sorbi, 2001; Douglas & Pfeiffer, 2000; Paul, Beatty, & Schneider, 1998; Rao, 1995; Rao et al., 1991).

It has been estimated that between 30 and 70% of patients with MS have memory problems, mainly data acquisition with verbal material and acquisition and storage of data with visual material (Beatty, W.W., Goodkin, Monson, Beatty, P.A., & Herrtsgaard, 1988; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998; Demaree, Gaudino, DeLuca, & Ricker, 2000; Rao, 1995). The worse results are obtained in patients with progressive multiple sclerosis (Gaudino, 2001; Wachowius, Talley, Silver, Heinze, & Sailer, 2005). In case-control studies, in the early stages of RRMS without physical impairment, most of the neuropsychological deficits are found in processing speed, attention, memory and executive function (Deloire et al., 2006; Nocentini et al., 2006; Olivares, Nieto, Sánchez, Wollmann, Hernández, & Barroso, 2005; Santiago, Guardìa, & Arbizu, 2006; Schulz, Kopp, Kunkel, & Faiss, 2006). Although some works have shown in these patients an altered performance in tasks that evaluate abstract reasoning, categorization, mental flexibility and planning, measured by the Wisconsin Card Sorting Test (WCST), the substitution task of Grassi blocks or Hanoi's tower, few studies have explored these aspects of executive function in relation to clinical course (Arango, DeLuca, & Chiaravalloti, 2007; Goverover, Chiaravalloti, & Deluca, 2005; Peyser, Rao, LaRocca, & Kaplan, 1990). Schulz et al. (2006), in a sample of 21 patients with a mean evolution of 15.1 months after diagnosis, found that 24% of patients presented impaired executive function.

MS patients may show some degree of physical disability. The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis, used as a primary clinical rating scale. It is an ordinal composite measure of neurological impairment with scores ranging from zero (normal neurologic examination) to 10 (death). The score is determined by the Functional System (FS) scores and by an assessment of ambulation, ability to transfer, upper extremity function and bulbar function. The eight FS allows to the neurologists assign a Functional System Score in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. In addition this measure shows low interrater/intrarater reability (Kurtzke, 1983).

The objective of this study is to assess specifically executive function and memory in patients with RRMS.

Methods

Participants

Twenty-eight patients with RRMS (criteria of McDonald et al., 2001) from the MS Unit of Getafe University Hospital were studied because they had symptoms of cognitive dysfunction, mainly in memory. The analysis was carried out in twenty-five individuals who presented altered performance of at least one test. The remaining three patients performed the tests normally. There were 17 women and 8 men, with a mean age of 35.8 years (23-55).

The mean degree of physical impairment measured by the EDSS (Kurtzke, 1983) was 2 (median 2). The mean evolution time from the first outbreak was 8.4 years (median 7) and since diagnosis was 5.17 (median 5) years. All the subjects were right-handed. Most of them had completed secondary education (5 of patients had primary studies, 12 secondary studies, 8 higher education).

Instruments

Memory, attention domains, and executive function were evaluated by the neuropsychological battery of tests shown in Table 1.

Seventy-six percent of patients complained of fatigue (mean 4.7; median 5) assessed by Fatigue Severity Scale (Krupp, Álvarez, LaRocca, & Scheinberg, 1988, Spanish version EGFve: Tola, Yugueros, Fernández-Buey, & Fernández-Herranz, 1998).

The degree of depression was assessed by the BDI (Beck Depression Inventory, spanish version; Conde & Useros, 1975). The degree of anxiety was quantified by the STAI (State-trait anxiety inventory) (Spielberger, Gorsuch, & Lushene, 1970).

Procedure

The tests were conducted in two sessions each of one hour duration and performed when the patients were free of disease activity (last outbreak at least 3 months before). The results of the different tests were compared with normative values of each test. Scores one-two standard deviations lower than the normative values were considered to reflect impaired cognitive function.

In addition to the demographic data, the time of evolution since the first clinical manifestation and since diagnosis, the degree of physical impairment measured by the EDSS, and the degree of fatigue measured by the Spanish version of the Fatigue Severity Scale (EGFve) were all recorded.

Table 1 Administered Tests	
Cognitive functions	**Tests**
Memory: • Verbal memory. • Visual memory. • Discrimination of complex stimuli, immediate visual memory.	• WMS-R: Logical Memory I and II, Visual Reproduction I and II, and Visual Association I and II. • Rey Complex Figure. • Benton Visual Form Discrimination Test.
Attention and Executive Function: • Working memory. • Abstract reasoning. • Classificatory thinking. • Use of strategies. • Ability for changing the cognitive strategy. • Cognitive flexibility. • Attentional shifting. • Resistente to interference. • Processing speed. • Temporal sequencing.	• WCST. • Words and Colors Stroop Test. • Trail-Making Test (TMT): Part A and B. • WAIS-III: Subtests of Similarities, Matrix Reasoning, Picture Arrangement, Arithmetic, Digit Span, Letter-Number Sequencing, Block design and Working Memory index (WM).
WMS-R: Wechsler Memory Scale- Revised; WCST: Wisconsin Card Sorting Test Manual (revised and expanded); WAIS-III: Wechsler Adult Intelligence Scale-Third Edition.	

Data analysis

The statistical analysis was done using the SPSS 12.0 computer package. The relationship between degree of depression, anxiety, fatigue and cognitive variables was studied by Pearson's bivariate correlation. The relationship between educational level and cognitive performance was analyzed by one factor ANOVA and post hoc multiple comparisons by Tukey (assuming equal variances). The cognitive variables were studied by descriptive statistics and T statistics for related samples.

Results

Twenty-for percent of the patients showed an impaired performance in the memory tasks and 80% in the attention and executive function tasks related with prefrontal regions.

Memory

In the tasks associated with memory processes (Table II), the mean scores for logical memory I, logical memory II, visual reproduction I and visual reproduction II were higher than mean scores obtained for the general population. It is noteworthy that although the values are within normal limits, there are significant differences between logical memory I and II (immediate and delayed recall) (t(24)= 2.529; sig (bilat.) 0.018<0.05) and between visual reproduction I and II (immediate and delayed) (t(24)= 2.406; sig (bilat.) 0.024<0.05), at the expense of the delayed material, verbal or visual, detecting a loss of information over time. Significant differences were not found between the type of material used (verbal or visual) in immediate and delayed recall (logical memory I and visual reproduction I: t(24)= 1,195; sig (bilat.) 0.244>0.05; logical memory II and visual reproduction II: t(24)= -0.804; sig (bilat.) 0.429>0.05).

A diminished performance was observed in the immediate reproduction of Rey's figure, with a mean percentile of 34.48. There are no significant differences in the comparison of means of the immediate and delayed reproduction of Rey's figure (direct scores t(24)= -1,405; sig (bilat.) 0.173>0.05).

The mean scores in Benton's visual discrimination and in the working memory (WM index, WAIS-III) were found within the range of normality (Table 2).

Attention and executive function

In Stroop's test, a task associated with attention processes and executive function, the typical scores are diminished in P, C and PC, but an adequate score is maintained in interference (Table 2).

In the WCST, a diminished mean percentile was obtained in variables relating to percent response to conceptual level, number of complete categories, attempts to complete the first category, failure to maintain the attitude and learning to learn, variables related to the capacity to conceptualize (difficulty to discern rules), categorization and capacity to maintain a non-automatic strategy.

Association between cognitive performance and educational level, depression-anxiety and clinical variables

The only cognitive variables with a statistically significant relationship with the educational level, assuming variants to be equal, were Rey's figure: copy time (F= 4.106 sig. 0.031>0.05),

immediate reproduction (F= 5.481 sig. 0.012<0.05) and delayed reproduction (F= 4.253 sig. 0.27<0.5). When using the post hoc multiplex comparisons of the means of all cognitive variables, the group of subjects with higher education had significantly higher results than the other two groups (primary and secondary studies), with similar scores in the tests to the normative values, while the other two groups both had similar scores that were lower than scores obtained by the normal population.

We did not obtain any correlation between the degree of depression (BDI) and the cognitive variables.

Fatigue (EGFve) was positively correlated with the EDSS scale (0.48), the degree of depression (BDI; 0.61), the degree of anxiety (STAI A/E 0.57 and A/R 0. 66) and attempts to complete the 1st category of the Wisconsin card sorting test (WCST) (0.56), and negatively with the trail making test (TMT) B errors (-0.42).

The time of evolution of the disease was not correlated with the cognitive variables except for the delayed trial of Rey's learning test (-0.42) and Stroop C (-0.47), which were negatively correlated.

Table 2
Patients' performance in the cognitive tests (mean and SD)

	Normal range of tests	Mean	SD
Memory			
WMS-R	Pc	Pc	
• Logical Memory I	50	62,44	28,330
• Logical Memory II	50	52,80	26,099
• Visual Reproduction I	50	69,20	22,476
• Visual Reproduction II	50	57,56	33,166
Rey Complex Figure	Pc	Pc	
• Copy	50	71,68	24,392
• Time of copy	50	47,16	24,622
• Immediate recall	50	34,48*	32,507
Benton Visual Discrimination[1]	24-25	24,64	4,636
Attention and executive function			
Trail Making Test (TMT)	t-score	t-score	
• TMT A	50	13,44*	19,107
• TMT B	50	5,44*	7,252
Stroop	t-score	t-score	
• Stroop W	50	40,32*	9,499
• Stroop C	50	38,80*	9,055
• Stroop WC	50	41,36*	10,594
• Interference	50	50,72	8,886
WCST	Pc	Pc	
• N errors	50	51,28	25,101
• N perseverations	50	58,40	29,256
• % conceptual level	50	47,32	24,970
• N categories completed	>16	14,20*	3,786
• Trails completed 1st	>16	13,32*	5,313
• Failure maintain set	>16	14,16*	4,571
• Learning to learn	>16	14,83*	3,953
WAIS-III	Scalar Score	Scalar Score	
• Block design	10	10,24	3,711
• Picture arrangement	10	8,40*	2,466
• Similarities	10	11,56	2,615
• Matrix	10	9,44	2,800
Index	Index	Index	
Working Memory Index	100	100,36	15,919

[1] Visual Form Discrimination (Benton et al, 1983): the 24-25 score are considered as score of cohorte established to suppose alteration; 23 score as moderate alteration and less than 23 score as severe alteration. (*) Is considered significant.

The EDSS showed a positive significant correlation with the EGFve (0.48) and a negative correlation with the story board subtest of WAIS-III (-0.48), Rey's figure (-0.48) and A-time TMT (0.39).

Discussion

A total of 89.3% of our patients presented some cognitive deficit. Even this very high prevalence can be explained by a selection bias (our patients were assessed if they complained of cognitive problems), is not excluded that it is real, Drew et al. (2008) also observed in a recent study that 91% of the patients had shown cognitive impairments, specifically in memory and executive function.

In our population of MS patients, the degree of depression, anxiety and fatigue did not influence the yield in the different cognitive tasks, as observed previously in other studies (Nieto, Sánchez, Barroso, Olivares, & Hernández, 2008; Nocentini et al., 2006; Schulz et al., 2006), on the one hand probably due to a small sample size, and secondly because the mean scores of the group in the BDI and STAI were not significant. By contrast, the educational level did affect the results of Rey's learning test, with subjects with a higher level of education obtaining higher scores.

Of our patients, 80% had diminished executive function, especially in conceptual tasks, tasks of categorization, maintenance of non-automatic strategies and affectation in tasks of temporal ordering, usually attributed to prefrontal regions. Although these results must be interpreted with caution because of the reduced sample size, deficits in executive function are already detected in RRMS with a low level of physical and functional inability and a short disease duration, observations made previously by other authors (Arango et al., 2007; Roca et al., 2008). However authors like Nieto et al. (2008), with a sample of 52 patients with RRMS and mild neurological dysfunction, found no executive function déficits.

These results support the hypothesis that the frontal lobules are highly sensitive due to their numerous connections with the other cortical regions and with subcortical structures, and damage in any part of the brain would trigger effects in these areas (Goldberg, 1992; Goldberg, 2001; Goldberg, Kluger, Griesing, Malta, Shapiro, & Ferris, 1997; Nobler et al., 1994).

Only 24% of our patients presented memory affectation in some of the tasks and processes evaluated, in contrast to the high percentages found in the literature (Beatty et al., 1988; Brassington & Marsh, 1998; DeLuca et al., 1998; Demaree et al., 2000; Diamond, DeLuca, Jonson, & Nelly, 1997; Nocentini et al., 2006; Olivares et al., 2005; Schulz et al., 2006). In our series, the mean scores in the memory tasks were similar to the normative values, except for the immediate recall task in the complex Rey's figure, in which performance was impaired. Alterations in this task would be explained by the involvement of strategic and organizational aspects, which require a good executive function dependent on the frontal lobules and not memory alterations dependent on the temporal lobules, since the patients performed the visual reproduction tests (I and II) adequately, which are visual memory tasks that require less organization and strategic use. This interpretation questions the finding in other studies that the immediate visual memory deficits obtained are dependent on medial temporal regions (Denney, Sworowski, & Lynch, 2005; Nocentini et al., 2006; Olivares et al., 2005; Schulz et al., 2006). Another possible explanation for the disparity between our results and those published in the literature is that the battery of tests used in this study is more effective at isolating executive tasks. Although further studies are required to verify this, our results shed light on a possible alternative theoretical explanation.

In spite of a normal yield in memory tasks in most patients, these did complain of memory problems that made it difficult to carry out daily tasks. This could possibly be explained by the concept of «active memory» described by Goldberg (2001), who establishes the involvement and importance of the prefrontal cortex in memory. According to this concept, the memory we use to remember things in order to solve problems, in other words, the subject decides when he/she wants to recover information, is a decision directed by the prefrontal cortex. Hence, a patient with affectation in this region will have more difficulty in situations requiring memory for daily living than in a situation in which memory is assessed but an examiner directs the action (Fuster, 1997; Goldberg, 2001; Goldman-Rakic, 1987).

In conclusion, in our RRMS patients with a relative short time of evolution of the disease and little physical discapacity, the cognitive alterations mainly affected functions attributed to prefrontal regions, as well as other authors have shown (Vitkovitch, Bishop, Dancey, & Richards, 2002; Prakash, Erickson, Snook, Colcombe, Motl, & Kramer, 2008). Difficulties in the immediate visual memory of complex elements would be more due to a failure in these areas as the organization and strategic use of the material to be coded is disturbed, rather than an affectation of medial temporal regions. However, further studies are required in larger samples to confirm these findings.

Acknowledgements

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