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Attention impairment associated with relapsing-remitting multiple sclerosis patients with mild incapacity

Prejuízo da atenção em pacientes com esclerose múltipla na forma remitente-recorrente com incapacidade leve

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ABSTRACT

Neuropsychological studies have consistently reported cognitive dysfunctions associated with multiple sclerosis. One-hundred fifteen subjects with relapsing-remitting multiple sclerosis (RRMS) were compared with forty health controls according to a neuropsychological test battery, which included digit span, trail making, cancellation and stroop test. Both groups were matched for age, sex and educational level. Subjects with RRMS had a worse performance the speed of response. Subjects with RRMS spent more time to complete the test in either sections A (p=0.001) or B (p=0.001), although there was no significant difference in terms of number of errors. The total time required to finish the Stroop test was higher for subjects with RRMS (p<0.001), being the time difference between groups significant at trial 4 (p<0.001). Attention impairment in subjects with RRMS is related to slowed central processing, which may be affected in all stages, including impairment of automatic and controlled processing of information and in the motor program.

Key words: multiple sclerosis, cognition, attention.

RESUMO

Estudos neuropsicológicos demonstram alterações cognitivas associadas à esclerose múltipla. Foram avaliados, através de uma bateria neuropsicológica, 115 pacientes com esclerose múltipla remitente-recorrente (EMRR), comparada a um grupo controle com 40 indivíduos saudáveis. A bateria inclui os testes, span de dígitos, trilhas, teste de cancelamento e stroop. Os grupos foram pareados por sexo, idade e escolaridade.Os pacientes com EMRR tiveram um pior desempenho na rapidez de resposta (p=0,001), os pacientes gastaram um tempo maior para realizar o trilhas A (p=0,001) e o trilhas B (p=0,0001), não havendo diferenças significativas no número de erros. O tempo total no teste stroop foi maior dos sujeitos EMRR (p<0,001), apresentando diferença significativa na tentativa 4 (p<0,001). Os pacientes EMRR apresentaram lentificação do processamento central, podendo estar prejudicado em todos os estágios da doença, incluindo prejuízo do processamento de informações automático e controlado.

Palavras-chave: esclerose múltipla, cognição, atenção.

Cognitive dysfunction is a common problem among patients with multiple sclerosis (MS). The prevalence of cognitive dysfunction is estimated at 54% to 65% of the patients[1]. Although patients with MS tend to have worse results than controls in neuropsychological assessments, those results are not homogeneous, and the variability of neuropsychological assessments among MS patients is high[2]. Cognitive dysfunctions are non-specific symptoms, being the deficits most observable in some specific functions (information processing speed, recalling and problem-solving thinking) and may occur at early stages of the disease and tend to be under-recognized. The degree of cognitive impairment is independent of physical disability[1]. Findings on attention dysfunction in patients with MS remain controversial. Some authors observed that MS patients have an impaired attention[3,4], while other authors found no differences between MS patients and controls[1,5]. One possible reason for such results could be the different definitions used for attention in each of those studies, as well as the assessment tools. Attention consists of a number of different sub-systems, including those for selective, sustained and spatial attention. There are evidences that separable attentional circuits for sustained attention, selective attention and spatial exist in the brain, and this can have important rehabilitation implications.

In the present study, we aimed to investigate whether MS patients have impaired these kinds of attention, through the digit span test - forward and backward, the trail making test, the cancellation test and the stroop test in patients with mild incapacity.

METHOD

Patients – One hundred-fifteen patients who met the Mac Donald[6] criteria for MS, with relapsing-remitting course (RRMS) were recruited from the outpatients MS unit (CATEM) at the Santa Casa School of Medical Sciences (São Paulo). The physical disabitity of the patients was measured with the expanded disability status scale (EDSS)[7]. Disease course was determined by medical history[8]. Patients had EDSS assessed by trained neurologists and were interviewed by psychologists, who rated their anxiety and depression symptoms with the hospital anxiety and depression scale (HAD)[9], Portuguese version, validated[10]. General cognition was tested with a translated version of the mini-mental state examination (MMSE)[11] and structurated interview to evaluate mental disorder, wich included alcoholism and chemical addiction.

Inclusion criteria: patients with age between 17-59, level of education $\geq$4 years, EDSS ranged from 0 to 3.5, normal performance at MMSE. Exclusion criteria included relapses in the past four months, use of corticotherapy, immunosupression or previous immunomodulatory therapy, EDSS >3.5, use of psychotropic drugs including benzodiazepines, history of alcohol abuse or illicit drug abuse and comorbid neurological or psychiatric condition which could affect cognitive performance.

Forty healthy volunteers, matched for age, gender and education level were enrolled as control. Volunteer subjects could not use psychotropic drugs, illicit drugs; have no history of alcohol abuse, neurologic disease, visual or motor impairment and neither have a clinical condition on which could affect cognitive performance.

All subjects gave their informed consent, and the study was approved by the Institutional Review Board and was conducted in compliance with the Declaration of Helsinki.

Procedure – Participants completed a battery of neuropsychological tests administered by two experienced neuropsychologists over one session. Tests used in this study evaluate some aspects of attention with special emphasis in frontal lobe functions: digit span test - forward and backward[12], trail making test[13], cancellation test[14] and the stroop test[15]. While forward digit span assesses the ability on maintaining attention, backward span evaluates the ability to perform the reverse procedure, and the working memory. The trail making test assesses the perception, motor speed and ability to alternate concepts. The cancellation test evaluates the speed and precision of reaction. The stroop test evaluates the ability to inhibit response.

Analysis procedure – Homogeneity of demographic characteristics in both groups was analyzed through the Student t test and the Fischer exact test. Neuropsychological outcomes were compared with the Mann-Whitney test, because there were observed a non-normal distribution for the most of variables at the Kolmogorev-Smirnov test. A p value less than 0.05 was considered to be significant. All the analyses were performed with SPSS-PC software, version 10.0 for Windows.

RESULTS

Of the 115 RRMS patients enrolled, 36 were male and 79 were female. Mean age (years±SD) was 34.6± 9.2 and education level (years±SD) was 12.8±3.4. Mean duration of the disease (months±SD) was 66± 61.33 and mean EDSS score was 2.21±1.49. HAD scores (mean±SD) were 6.36±3.36 for anxiety and 4.39±3.92 for depression. A score $\leq$8 is considered normal for both anxiety and depression.

In the control group of volunteers, we had 9 men and 31 women, with mean age of 33.8±9.54 years and mean education level (years±SD) of 13.2±2.55. There were no significant differences in demographical aspects between patients and controls (Table 1).

Table 1. Characteristics of the patients and of the control group as to the variables of age, gender, and education.

	Multiple sclerosis (n=115)	Control (n=40)	p
Gender			
Male	79 (68.7%)	31 (77.5%)	
Female	36 (31.3%)	9 (22.5%)	
Ratio F/M	2.2:1	3.4:1	0.527
Age (years)			
Mean (standard deviation)	34.6 (9.2)	33.9 (9.7)	
Age range	17-57	17-50	0.619
Education			
Mean	12.8 (3.4)	13.3 (2.6)	
Range of education	4-20	5-16	0.542

Without statistically significant diff e rences between the groups using the Student-t test and Fisher's exact test. F, female; M, male; p, significance; n, number of subjects.

In the comparison of the MS and control group, we observed that in the digit span test (Table 2), there was no significant difference between the groups, both in the forward (FO) (p=0.077) and in the backward order (BO) (p=0.245), however, 36 patients (31.3%) had performance on the limit border on FO and 75 (65.2%) on BO.

Table 2. Attention tests: digit span and cancellation test: comparison between the results obtained by the patients with multiple sclerosis and control group.

	Multiple sclerosis (n=115) Mean (sd)	Control (n=40) Mean (sd)	p
Digit span			
Forward order	6.36 (1.40)	6.90 (1.21)	0.077
Backward order	4.30 (1.26)	4.69 (1.40)	0.247
Cancellation test			
Number of answers	96.98 (45.62)	139.05 (30.04)	<0.001*
Total (errors + omissions)	10.77 (14.03)	13.92 (16.58)	0.591
Q/N	0.11 (014)	10.00 (0.10)	0.487

*With statistically significant diff erences between the groups verified by the Mann-Whitney test. Q/N, total/number of answers; p, significance; sd, standard deviation; n, number of subjects.

As to the attention tests that involved visual-motor speed, mental flexibility and control of inhibitory responses, we observed significant differences between the performance of the patients and control group. In the cancellation test, we observed that response speed was lower in the patients (p= 0.001), showing slowness in general performance. When the quality of the responses was analyzed, no significant difference was seen (p=0.591). In the same way, the global performance in this test, measured by the relation Q/N, was similar for both groups (0.487).

In the trail making test no difference was observed between the groups as to the number of errors; however patients presented a poorer performance regarding time to complete the test, both in part A (p=0.001) and B (p=0.001). When we calculated the difference between the performance in the Trails B and A, this proportion remains the same (p=0.010) (Table 3).

Table 3. Evaluation of the frontal lobe: trail making test comparison between the results obtained by patients with multiple sclerosis and the control group.

	Multiple sclerosis (n=115) Mean (sd)	Control group (n=40) Mean (sd)	p
Trail making test			
Trails A			
Time (s)	54.13 (21.88)	41.08 (16.21)	0.001*
Error	0.11 (0.38)	0.13 (0.34)	0.220
Trails B			
Time (s)	110.33 (59.82)	74.54 (20.13)	0.001*
Error	0.42 (0.81)	0.54 (1.23)	0.922
Trails B-A			
Time (s)	51.81 (51.99)	29.58 (22.63)	0.010*

*With statistically significant diff e rences verified by the Mann-Whitney test; s, seconds; p, significance; sd, standard deviation; n, number of subjects.

In the stroop test, the patients required more time to complete the three last stages of the test, with statistical significance for trial 4 (p<0.001) and in the total time (p<0.001), as shown in Table 4.

Table 4. Evaluation of the frontal lobe: stroop test comparison between the results obtained by the patients with multiple scle - rosis and the control group.

	Multiple sclerosis (n=115) Mean (sd)	Control (n=40) Mean (sd)	p
Trial 1			
Time (s)	16.57 (4.92)	18.88 (2.2.76)	0.058
Error	–	–	
Trial 2			
Time (s)	14.30 (4.45)	13.13 (4.11)	0.082
Error	0.04 (0.26)	–	–
Trial 3			
Time (s)	18.44 (6.93)	14.21 (2.89)	< 0.001*
Error	–	–	–
Trial 4			
Time (s)	28.47 (13.25)	21.82 (6.81)	< 0.001*
Error	0.38 (1.51)	0.15 (0.43)	–
Total			
Time (s)	77.51 (25.76)	64.03 (10.75)	<0.001*
Error	0.38 (1.51)	0.21 (0.57)	–

*With statistically significant diff e rences verified by the Mann-Whitney test. s, seconds; p, significance; sd, standard deviation; n, number of subjects.

DISCUSSION

Cognitive alteration in patients with MS has been the focus of several studies, but still there is no consensus on several aspects of this subject. Much of what is known about these alterations is based on hypotheses and inferences. Tests that evaluate complex cognitive functions, such as abstract thinking and conceptualization, show dysfunctions similar to those found in frontal lobe syndrome, with authors suggesting that there is a pattern of deficits similar to those observed in subcortical dementias[16]. The probable mechanism for the appearance of these deficits is the interruption in the intra- and inter-hemispheric communication, with interruption in connection routes between the sub cortical and frontal and limbic cortex structures, secondary to demyelinization and axonal degeneration observed in these patients[3,17].

Attention plays a role in the cognitive process, participating in the processing of information and is considered an important function for certain types of learning, being fundamental to other conditions, such as the possibility of selective recognition of a determined stimulus (automatic processing) and the inhibition of responses to irrelevant stimuli (controlled processing) in order for the process to be effective[2]. The limitation of this capacity may be a result of deficits in the automatic or controlled processing of information, as well as in the incapacity to store and manipulate temporary information, the function known as working memory.

We did not observe differences in performance of the patients in both the forward and the backward order at digit span test (Table 2), like other authors[1,18,19]. Rao et al.[20] in a series of 100 patients observed a worse performance in the backward order of the test, however 61 patients presented the chronic form of the disease, and the mean EDSS scores was two times higher than the observed in our series. A longitudinal study of these patients may show performance deterioration and lead to similar results.

In the cancellation test (Table 2), we observed that there was worse performance in patients with MS at the number of answers, however at the quality of the cancellations expressed by the sum of the errors and omissions no difference was observed, as well as in the final score test, suggesting that there is impairment in the processing speed of information, though sustained attention is kept.

In the analysis of the trail making test we observed that patients with MS need more time than the control group in both parts of the test (Table 3). In the calculation of the difference between the time in trails B and A, whose result excludes motor function and is considered an indicator of executive functions, we observed a worse performance in the MS patients. These results indicate that there is impairment in the psychomotor speed, in the capacity to realize visual tracing, and in the executive functions. Van den Burg et al.[21] also found alterations in the trail making tests, parts A and B, suggesting that these were influenced by motor difficulties, but there may be an disexecutive syndrome, as indicated by the increase of B-A index.

The stroop test does not require motor action and alteration in this test suggests subcortical or frontal lesions. The patients required more time to finish the test, however the number of errors was similar in the two groups (Table 4). These results suggest that MS patients have a disturbance in some aspects of flexibility, since there is not the occurrence of persevering or stereotyped actions, having the need for greater time to execute the same function. Dujardin et al.[22] observed that there is an impairment of spontaneous flexibility, which requires a quick change of strategy, with the reactive flexibility preserved, where the inhibition and maintenance events of simple attention are necessary.

It is a well-known fact that MS causes slowing of information processing[19,23,24]. The reaction time is generally slower and the rate of scanning, considered a pure cognitive measure, has also been found to be impaired in comparison to normal individuals[24]. Other studies suggest that the slowing of information processing is related to alterations in working memory[19,23,25].

It is known that processing of information begins with a sensory input and ends with a motor output, in a system able to use automatic or controlled mechanisms to process the information. The automatic processes presuppose the processing of isolated information, without contact of information from other subsystems. In controlled processing there is use multimodal information, with the use of several sensory systems being necessary to assemble an efficient and global network of communication, where several subsystems come in contact with one another. The end of this process is done by the motor program, which can be evaluated by the time needed for the individual to plan the action and execute the movement[26]. The majority of individuals need more time to execute complex tasks than simple tasks. The difference between them reflects the time necessary to execute a motor program[13].

Kujala et al.[26] in a study observed that the automatic processing of information is slower, even in the group of patients without detectable cognitive impairment, however the controlled process of information becomes affected later, suggesting that this deficit is correlated with the impairment of working memory. Other authors suggest that the automatic processing of information is intact in patients with MS, in contrast to the controlled processing of information[3,24,25,27].

Our findings corroborate those found by Kujala et al.[26]. The decreased speed for information processing observed in the cancellation test, a simple test of visual recognition, suggests that there is impairment in the automatic processing of information in our sample.

In this same way, the increased time necessary to execute the trail making test, parts A and B, and the Stroop test, indicate an alteration in the controlled processing of information, which is in agreement with the findings of several[2,20,25,26,28]. This slowness in the MS patients is probably secondary to diffuse alterations of myelinization, which lead to the interruption of some essential connections to the network of information processing. The lack of correlation with functional disability and the indication that disease duration may interfere in these results corroborate this explanation.

The slowing in the motor program was also observed in our series. The alteration in the subtraction between parts A and B of the trail making test demonstrates that these patients plan more slowly their motor actions. The results do not allow for us to conclude that this alteration is secondary to attention deficit or if the stimulus reaches the individual more slowly, taking longer for the initiation of the activation of the motor program. It is known that action planning is associated to lesions of the frontal lobe, and that this is an area with extensive network connections. The disconnection within these routes could be the main cause of the slowing down of the motor program.

It is difficult to evaluate the exact contribution of the frontal lobe to the cognitive impairment of these patients. Though several studies have tried to verify the impairment of executive functions in patients with MS using tests of verbal fluency, working memory, use of strategy and planning, information processing, among others, the alterations are not always superimposed, and do not always occur in a constant manner. Though there is an undeniable contribution of the frontal lobes to these deficits, studies suggest that the impairment of executive functions in these patients is secondary to a process that diffusely affects cerebral function, leading to a disconnection between the pre-frontal and limbic cortex, and association routes[3,27].

In conclusion, our results indicate that attention impairment in MS is related to the slowing down of information processing, and may be affected in all of its stages, with alteration in automatic and controlled processing and in the motor program. Recognizing attention deficit as secondary to MS allows correct orientation of neurologists, patients and family members, as to the planning of compensatory strategies implementation, allowing the maintenance of an adequate performance of professional and daily life activities.

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