Article

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Different cognitive profiles of Brazilian patients with relapsing-remitting and primary progressive multiple sclerosis

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ABSTRACT

Cognitive impairment is a symptom of multiple sclerosis (MS). Different clinical forms of multiple sclerosis have different cognitive profiles, according to findings of previous studies which used extensive batteries of neuropsychological tests. **Objective:** To investigate cognitive profiles of Brazilian patients with relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PPMS) by using a brief battery of neuropsychological tests. **Method:** Sixty-six patients, within 18-65 of age and 3-18 years of education, were paired with healthy control subjects, regarding gender, age, and education level. **Results:** On Symbol Digit Modalities Test and Hooper Visual Organization Test, cognition was affected in 50% in RRMS and 69% in PPMS. Fluency of "F" was impaired in 24% of RRMS and 81% of PPMS. Immediate recall was affected in 32% of RRMS and in 63% of PPMS; whereas late recall, in 46% of relapsing-remitting and in 69% of primary progressive. **Conclusion:** Cognitive profiles of relapsing-remitting and primary progressive patients are different

Key words: multiple sclerosis, cognitive profile, brief battery.

Diferentes perfis cognitivos de pacientes brasileiros com esclerose múltipla remitente-recorrente e progressiva primária

RESUMO

O comprometimento cognitivo é um sintoma da esclerose múltipla (EM). Formas clínicas diferentes da EM apresentam diferentes perfis cognitivos, de acordo com resultados de estudos anteriores que usaram bateria extensa de testes neuropsicológicos. **Objetivo:** Investigar o perfil cognitivo de pacientes com esclerose múltipla remitente-recorrente (EMRR) e esclerose múltipla progressiva primária (EMPP) utilizando uma bateria neuropsicológica breve. **Método:** 66 pacientes com idade de 18 a 65 anos, escolaridade 3 a 18 anos, foram pareados a controles por sexo, idade e escolaridade; e avaliados. **Resultado:** No Symbol Digit Modalitie Test e Hooper Visual Organization Test 50% com EMRR e 69% com EMPP apresentaram desempenho comprometido. Na fluência da letra "F" o comprometimento foi de 24% daqueles com EMRR e 81% com EMPP. Na evocação imediata o comprometimento foi de 32% na EMRR e 63% na EMPP e, evocação tardia em 46% na remitente-recorrente e 69% com progressiva primária. **Conclusão:** Os perfis cognitivos dos pacientes com esclerose múltipla remitente-recorrente e progressiva primária são diferentes.

Palavras-chave: esclerose múltipla, perfil cognitivo, bateria breve.

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Cognitive impairment is a symptom of multiple sclerosis (MS)[1]. Recent studies have shown that cognition is affected within a range of 54-65% of multiple sclerosis patients[1-3]. The functions most commonly affected, according to Rao[1] are: attention, information processing speed, explicit memory, verbal fluency, executive function, conceptual reasoning, and visuospatial perception. Studies performed in Brazil have confirmed Rao's[1] initial findings[3,4]. According to Rao[1], impairment of cognitive profile in multiple sclerosis patients is not uniform and may range from a mild deficit to an overt state of dementia.

Concerning attention, processing speed, verbal memory and visuospatial functions in patients with secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS) had poorer performance than those with relapsing-remitting multiple sclerosis (RRMS)[5-7]. Impairment in the verbal modality is more common in the progressive forms of multiple sclerosis; whereas visuospatial-related decline is more frequently seen in the relapsing-remitting multiple sclerosis form[8]. Overall cognitive performance of secondary progressive and primary progressive patients was poorer than those with relapsing-remitting multiple sclerosis[9].

A cohort of 88 Brazilian patients were evaluated using the (FS/EDSS) Kurtzke[10] scale and there was a low rate of cognitive dysfunction (5-6.5%)[11]. In another study, Negreiros and cols.[4] investigated the cognition of 54 relapsing-remitting multiple sclerosis patients and found cognitive impairment in 51.8% of them. The most affected cognitive functions were: semantic verbal fluency, short and long-term memory and recognition. In the primary progressive multiple sclerosis patients, Paes and cols[3] has found a rate of cognitive impairment close to 50% and reported that the most affected functions were phonemic verbal fluency, long-term memory and attention.

As far as the association of cognitive deterioration and psychopathological diseases are concerned, depression is a frequent symptom, but relationship with cognitive dysfunction lacks consistency[2,3,12].

Continuing the line of studies on cognition carried out in Rio de Janeiro, the present one used a brief neuropsychological battery to evaluate the cognitive profile of patients with relapsing-remitting multiple sclerosis and primary progressive multiple sclerosis.

METHOD

Study/patients

A case-control study was conducted between October 2007 and August 2009 in 66 MS patients within the age range of 18 to 65 years, 3 to 18 years of education diagnosed with definite MS, according to McDonald's criteria[13], 50 subjects (RRMS) and 16 (PPMS). A control group of healthy individuals was also recruited in order to be paired with the group of MS patients for gender, age and educational level. Four excluding criteria were employed to prevent possible interference: [1] visual, FS visual ≥4 and EDSS ≥8; [2] state of acute bout or worsening of symptoms; [3] use of psychoactive substances other than prescribed anti-depressants; and [4] co-existent clinical conditions (moderate or severe depression, thyroid alterations, systemic high blood pressure, HIV, syphilis and other neurological and psychiatric diseases) that interferes with cognition. All patients underwent standard medical and psychological interviews, analysis of medical records on neurological examination, MRI exam and cerebral spinal fluid investigation, in order to fulfill required criteria.

This study was approved by the research ethics committee (CER) of the university hospital - HUGG/UNIRIO and a written consent statement was signed by all subjects: MS patients and controls.

Neuropsychological testing

Patients and controls were submitted to a brief neuropsychological evaluation, which consisted of four tests, which assess four functions: the Rey Auditory Verbal Learning Test (RAVLT)[14] for short and long-term memory, the Hooper Visual Organization Test (HVOT)[15] the Controlled Oral Word Association Test (COWAT)[14] and the Symbol Digit Modalities Test (SDMT)[16]. The Beck Anxiety (BAI) and Depression Inventories (BDI)[17] were used to assess mood status. Neuropsychologists performed the neuropsychological evaluations individually in a single session. Tests were applied in a predefined order to both patients and controls.

Statistical analysis

Results are presented as means and their respective standard error (SEM). A two-tail student t-test was employed to detect mean significant differences in cognitive variables between the relapsing-remitting and primary progressive groups and their respective control group. The chi-square test was used to identify percentage differences between the two groups. A Pearson correlation analysis was used to assess the relationship between two variables. A p-value of 0.05 was considered statistically significant. Cognitive dysfunction was determined according to the procedure employed by Rao[1], which controls individual differences in pre-morbid cognitive abilities. A multiple regression was performed with the raw score for each of the cognitive indexes as dependent variable and demographic characteristics (gender, age and educational level) as independent variables. Since gender

is not a continuous variable, it was regressed as a dummy variable. A standardized residual was obtained by subtracting the regressed and the actual scores of each of the cognitive variables. Failure in each of these variables was determined from the fifth percentile or lower ones below the standardized residual score among paired control subjects. Cognitive deficit among multiple sclerosis patients was defined as the fifth percentile of the total number of failed cognitive indexes of control subjects. The frequency rate of cognitive dysfunction in multiple sclerosis group was found by calculating the difference between the percentage of multiple sclerosis patients who presented cognitive deficit from a false positive rate, defined as the percentage of paired control subjects misclassified as cognitively impaired.

RESULTS

In the RRMS group, 76% were female and in the PPMS, 81.2%. The mean age of RRMS patients was 34.8 years compared to a mean of 48.2 years for PPMS patients. Patients in the group attended school for approximately 13.6 years compared to 12.4 years in the PPMS group. No significant difference was observed between patients and controls in the aforementioned variables. As shown in Tables 1 and 2, relapsing-remitting patients obtained a mean score of 11.4 on the BAI and 10.1 on the BDI compared to 8.7 (BAI) and 12.3 (BDI) of patients in the primary progressive group. Table 3 shows the degree of sensitivity of the tests in RRMS and PPMS patients.

As presented in Table 4, the correlation between cognition and depression was 0.243 (p=0.015) in the re-

Table 1. Mean (SEM) of each variable of the brief neuropsychological battery in RRMS patients and healthy control subjects. The p-value of the two-tailed t-test comparison between the two groups, the percentage of RRMS patients below the fifth percentile of the control group (%MS<5%ile).

	RRMS		Control/RRMS		p	% RRMS
Variable	Mean	SEM	Mean	SEM	value	<5%ile
1st RT	5.6	0.21	5.8	0.20	0.540	10%
2nd RT	8.4	0.29	9.1	0.27	0.080	2%
3rd RT	9.5	0.34	11.0	0.31	0.002	30%
4th RT	10.5	0.31	11.9	0.33	0.003	10%
5th RT	11.4	0.29	12.7	0.24	<0.001	30%
RB	5.3	0.21	6.0	0.25	0.026	10%
1st RB	8.5	0.44	11.6	0.31	<0.001	32%
2nd RB	8.6	0.46	11.7	0.31	<0.001	46%
Rec	27.7	0.32	29.1	0.18	<0.001	28%
SDMT	47.9	1.99	55.5	1.09	0.001	50%
HVOT	21.9	0.54	23.8	0.37	0.006	50%
SF:ANIMAL	18.8	0.66	20.2	0.53	0.089	28%
SF:FRUIT	15.5	0.46	16.5	0.43	0.108	20%
SF:TOTAL	34.3	0.96	36.4	0.92	0.109	18%
F	12.4	0.60	15.1	0.57	0.002	24%
A	11.5	0.64	13.1	0.47	0.045	30%
S	11.6	0.57	13.7	0.60	0.010	10%
PF:TOTAL	35.7	1.58	42.1	1.43	0.003	18%
BAI	11.4	1.41	7.6	0.87	0.024	–
BDI	10.1	1.13	6.8	0.69	0.017	–
Duration	32.7	0.82	29.0	0.51	<0.001	–

RRMS: relapsing-remitting multiple sclerosis; SEM: standard error of the mean; 1st RT: first recall trial, list A; 5th: fifth recall trial, list A; RB: recall, list B; 1st RB: first recall after list B; 2nd RB: second recall after list B; Rec: recognition of list A; SF:ANIMAL: semantic fluency: animal category; SF:FRUIT: semantic fluency: fruit category; SF:TOTAL: total of animal and fruit categories; F: phonemic fluency with the letter "F"; A: phonemic fluency with the letter "A"; S: phonemic fluency with the letter "S"; PF:TOTAL: total phonemic fluency; Duration: 32.7 minutes was the average time required to apply the battery of tests.

Table 2. Mean (SEM) of each variable of the brief neuropsychological battery in PPMS patients and healthy control subjects. The p-value of the two-tailed t-test comparison between the two groups, the percentage of PPMS patients below the fifth percentile of the control group (%MS<5%ile) and the placement of percentages.

	PPMS		Control/PPMS		p	% PPMS
Variable	Mean	SEM	Mean	SEM	value	<5%ile
1st RT	4.8	0.36	5.4	0.34	0.262	19%
2nd RT	6.4	0.44	7.9	0.54	0.040	0%
3rd RT	8.3	0.38	9.9	0.69	0.047	31%
4th RT	8.8	0.48	11.7	0.55	<0.001	56%
5th RT	9.9	0.45	12.7	0.43	<0.001	75%
RB	3.9	0.46	6.1	0.56	0.005	25%
1st RB	6.8	0.67	10.9	0.69	<0.001	63%
2nd RB	6.8	0.65	10.7	0.79	<0.001	69%
Rec	27.2	0.66	28.9	0.38	0.029	38%
SDMT	34.4	2.87	51.7	1.87	<0.001	69%
HVOT	17.3	1.66	23.6	.96	0.003	69%
SF:ANIMAL	13.6	0.85	19.5	1.11	<0.001	38%
SF:FRUIT	13.1	0.97	15.6	.72	0.043	44%
SF:TOTAL	27.9	1.96	35.1	1.65	0.009	44%
F	10.3	1.01	16.6	1.13	0.001	81%
A	9.4	1.04	14.4	1.10	0.003	56%
S	10.0	0.99	14.9	1.04	0.002	38%
PF:TOTAL	28.4	2.45	45.8	2.94	<0.001	44%
BAI	8.7	1.53	7.8	2.01	0.731	–
BDI	12.3	1.53	7.3	1.48	0.025	–
Duration	34.4	1.13	30.8	1.15	0.031	–

PPMS: primary progressive multiple sclerosis; SEM: standard error of the mean; 1st RT: first recall trial, list A; 5th: fifth recall trial, list A; RB: recall, list B; 1st RB: first recall after list B; 2nd RB: second recall after list B; Rec: recognition of list A; SF:ANIMAL: semantic fluency: animal category; SF:FRUIT: semantic fluency: fruit category; SF:TOTAL: total of animal and fruit categories; F: phonemic fluency with the letter "F"; A: phonemic fluency with the letter "A"; S: phonemic fluency with the letter "S"; PF:TOTAL: total phonemic fluency; Duration: 33 minutes was the average time required to apply the battery of tests.

lapsing-remitting group; whereas correlation between depression and anxiety was 0.877 (p<0.001). Meanwhile, in the primary progressive group, these correlations were –0.294 (p=0.102) and –0.508 (p=0.003), respectively.

A rate of cognitive impairment was detected in 46% of the RRMS group and in 73% of primary progressive patients. In Table 1, mean scores on the RAVLT in RRMS group were 8.5 for immediate recall, 8.6 for delayed recall after 15 min. and 27.7 for recognition. The mean score on the Symbol Digit Modalities Test was 47 and on the Hooper Visual Organization Test, 21.9. On the COWAT evaluation of phonemic fluency on words that begin with the letter "A" the mean score was 11.5; whereas for semantic fluency with fruits it was 15.5.

In Table 2, the mean score of PPMS patients was 6.8 for immediate recall, 6.8 for delayed recall after 15 min. and 27.2 for recognition on the RAVLT.

The mean score on the Symbol Digit Modalites Test was 34.4 and on the Hooper Visual Organization Test, 17.3. On the COWAT, the mean score for phonemic fluency on words that begin with the letter "A" was 9.4 and for semantic fluency with fruits it was 13.1.

Table 3. Degree of sensitivity of the tests in RRMS and PPMS patients.

	% sensitivity	
Test	**RRMS**	**PPMS**
SDMT	50%	69%
HVOT	50%	69%
2nd RB	46%	69%
1st RB	32%	63%
3rd RT	30%	31%
5th RT	30%	75%
A	30%	56%
Rec	28%	38%
SF:ANIMAL	28%	38%
F	24%	81%
SF:FRUIT	20%	44%
SF:TOTAL	18%	44%
PF:TOTAL	18%	44%
1st RT	10%	19%
4th RT	10%	56%
RB	10%	25%
S	10%	38%
2nd RT	2%	0%

1st RT, first recall trial, list A; 5th, fifth recall trial, list A; RB, recall, list B; 1st RB, first recall after list B; 2nd RB, second recall after list B; Rec, recognition of list A; SF:ANIMAL, semantic fluency: animal category; SF:FRUIT, semantic fluency: fruit category; SF:TOTAL, total of animal and fruit categories; F, phonemic fluency with the letter "F"; A, phonemic fluency with the letter "A"; S, phonemic fluency with the letter "S"; PF:TOTAL, total phonemic fluency.

DISCUSSION

The aim of the current study was to investigate the cognitive profiles of Brazilian patients with the relapsing-remitting and primary progressive forms by using a brief neuropsychological battery. The frequency of cognitive impairment was lower in the RRMS group than in the PPMS group. These rates were similar those found in the literature for the two forms of the disease. Rao[1] reported rates of cognitive impairment in 54-65% of his sample, while Negreiros[4] reported it in 51.8% of his RRMS group and Paes[3], in 50% of PPMS patients.

To date, there is not enough evidence to demonstrate that RRMS and PPMS are, in fact, distinct diseases[6,18]. Nevertheless, demographic and clinical data show significant differences between these two courses of multiple sclerosis[19]. The RRMS form affects more women than men, between 20 and 40 years of age. It is characterized by non systematic neurological syndromes, suggesting disseminated inflammatory lesions in the CNS; while the progressive course of multiple sclerosis affects both men and women above 40 years of age[20,21] leading to an insidious and growing motor and sensitive dysfunction on lower limbs - in most of the cases - related to spinal cord commitment[22,23]. Those clinical differences were previously associated to a reduced inflammatory load detected in brain scans of PPMS patients versus the ones with the RRMS form. The different imaging pattern was used to justify a former concept, which claimed that cognitive alterations would be less common in the PPMS form[24]. Nowadays, it is well accepted that in PPMS, despite the fewer focal lesions found on brain white matter (BWM), there is, also on BWM, a more diffuse pattern apparently normal[25] including lesions on the cerebral cortex[26]. This would explain the greater cognitive decline observed in this group of patients, as confirmed not only on this current study, but also in others.

The indexes of cognitive impairment in relapsing-remitting and primary progressive groups were signif-

Table 4. Correlation between cognitive deficit with depression and anxiety.

RRMS	r	p	PPMS	r	p
Cognition × BDI	0.243	0.015	Cognition × BDI	0.294	0.102
BAI × BDI	0.877	<0.001	BAI × BDI	0.508	0.003

RRMS: relapsing remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

icantly higher than those found in control groups (Tables 1 and 2). As to the performance of patients with the two forms of the disease, Table 3 shows different failure rates on the tests. In the RRMS group, more failures occurred on the Symbol Digit Modalities Test, on the Hooper Visual Organization Test and delayed recall; whereas in PPMS group, failures occurred more often on phonemic fluency on words beginning with the letter "F", followed by the fifth recall trial of the RAVLT, on the Symbol Digit Modalities Test and on the Hooper Visual Organization Test.

Tables 1 and 2 show that cognitive impairment was more severe in PPMS patients compared to the ones with the RRMS form. Furthermore, PPMS patients have failed more often on the tests than RRMS patients. Similar findings were reported by De Sonneville and cols.[6], that is, progressive primary patients scored significantly more poorly than relapsing-remitting patients.

The cognitive functions most affected in RRMS patients, listed in order of performance, starting from the poorest one were: attention, information processing speed, visuospatial organization, and long-term memory. On the other hand, progressive primary patients presented most decline in the following functions: phonemic fluency on words that begin with the letter "F," long-term memory, sustained attention, information processing speed and visuospatial organization.

The difference in cognitive profiles of these two forms of multiple sclerosis is consistent with the findings of Gaudino and cols[8]. The authors reported a greater impairment in the progressive forms of MS (i.e., Secondary progressive and primary progressive) compared to RRMS. Such results also agree with the ones found by Negreiros[4] and Paes[3].

In the current study, the most affected cognitive functions in RRMS and PPMS were: attention/information processing speed, visuospatial perception, long-term memory, and phonemic fluency of the letter "A". However, other functions were also affected, albeit to a lesser extent (Tables 1 and 2).

Comparing these results with other Brazilian neuropsychological studies, which have used a extensive battery in RRMS[4] patients, the frequency of cognitive impairment was 51%, and the most sensitive items were: phonemic verbal fluency on words that begin with the letter "S," semantic fluency (fruits), and long-term memory (first and second recall trials and recognition).

The rate of cognitive impairment in the RRMS group was consistent whit current study. In this study, the most sensitive tests were: attention/information processing speed, visuospatial organization, and short and long-term memory, during first and second recall trials.

In the primary progressive group, the findings of Paes and cols[3] showed a rate of cognitive impairment of 50%, where the most sensitive items were: short-term memory (first recall trial of the list), phonemic fluency on words beginning with the letter "A," and attention/information processing speed. In the primary progressive group of this study, a higher rate of cognitive impairment was found. A similarity was observed between the two aforementioned studies, regarding impaired memory and phonemic fluency; however, the visuospatial function was not reported in those studies and information processing speed was evaluated using an adapted instrument, which may explain the discrepancies between both results.

Depression is a symptom of all forms of multiple sclerosis[2,3,7,12]. In our study, different degrees of depression and anxiety were observed in both groups of patients. Depression indexes were higher in PPSM than in RRMS patients; whereas RRMS patients achieved higher anxiety scores than PPMS subjects (Tables 1 and 2). It is worth mentioning that this particular finding has not been reported in investigated studies yet.

Table 4 shows no positive association between depression and cognitive dysfunction in either of the two groups. This particular finding is consistent with the results obtained by Rao[2,3] with others. The sensitivity of the brief neuropsychological battery for detecting cognitive impairment in MS patients has been confirmed in the literature[1,2,27]. According to Table 3, the sensitivity of the battery of tests applied to the subjects in this study was high on the three tests used to evaluate cognition in patients with the two forms of MS (i.e., Hoper Visual Organization Test, Symbol Digit Modalities Test, and the second recall trial of the RAVLT. This data is similar to others found in local and international literature, confirming the reliability of the instrument as a useful tool for detecting cognitive impairment in Brazilian MS patients.

The scores obtained by RRMS patients on the tests were higher than those achieved by PPMS patients and lower than scores of subjects on the control group in all functions evaluated. The most severely affected functions in both forms of the disease, in order of severity, were: information processing speed, visuospatial organization and late and immediate memory recall.

In conclusion, primary progressive patients performed more poorly on all cognitive tests used in this study. Thus, we can consider that their cognition was more severely affected than it was in relapising-remitting patients.

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