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ARTICLE

Cognitive performance of neuromyelitis optica patients: comparison with multiple sclerosis

Desempenho cognitivo de pacientes com neuromielite óptica: comparação com esclerose múltipla

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ABSTRACT

The aim of the present research was to investigate cognitive pattern of patients with neuromyelitis optica (NMO) and to compare it with multiple sclerosis (MS) patients' performance. Methods: Fourteen NMO, 14 relapsing remitting multiple sclerosis (RRMS), and 14 healthy control patients participated in the investigation. Neuropsychological functions were evaluated with the Brief Repeatable Neuropsychological Battery for MS; Symbol Digit Modalities Test; Digit Span; and Semantic Fluency. Results: Fifty-seven percent of NMO patients and 42.85% of the MS ones had abnormal performance in at least two cognitive tests. The NMO Group showed abnormal performance in verbal fluency, verbal and visual memories, with greater attention deficits. NMO patients outperformed healthy control in the paced auditory serial addition test (PASAT). However, no difference was found between NMO and RRMS patients. Conclusions: The NMO Group showed more dysfunction in attention and verbal fluencies than in verbal and visual memories. When compared with the MS patients, a similar dysfunction pattern was found.

Key words: neuropsychology, neuromyelitis optica, depression, multiple sclerosis, autoimmune diseases.

RESUMO

O objetivo da presente pesquisa foi investigar o padrão cognitivo de pacientes com neuromielite óptica (NMO) e compará-lo com o desempenho de pacientes com esclerose múltipla (EM). Métodos: Quatorze pacientes com NMO, 14 com esclerose múltipla recorrente remitente (EMRR) e 14 participantes do Controle saudáveis participaram da presente investigação. As funções neuropsicológicas foram avaliadas com a Bateria Breve de Testes Neuropsicológicos de Rao, Teste Símbolo Digit e a Fluência Semântica. Resultados: Cinquenta e sete por cento dos pacientes com NMO e 42,85% daqueles com EM apresentaram desempenho anormal em pelo menos dois testes cognitivos. O Grupo NMO apresentou desempenho anormal na fluência verbal e nas memórias visual e verbal, com maiores déficits de atenção. Pacientes com NMO superaram os controles saudáveis em PASAT. No entanto, não foi encontrada diferença entre os pacientes com NMO e aqueles com EMRR. Conclusões: O Grupo NMO mostrou mais disfunção nas fluências de atenção e verbais do que nas memórias verbal e visual. Quando comparados com os pacientes com EM, um padrão de disfunção semelhante foi encontrado.

Palavras-Chave: neuropsicologia, neuromielite óptica, depressão, esclerose múltipla, doenças autoimunes.

Neuromyelitis optica (NMO) is an uncommon disease that affects the optic nerves and spinal cord[1]. The recent identification of a specific antibody for aquaporin 4 (AQP4) water channel at the blood-brain barrier in NMO patients (IgG-NMO) makes it the first central nervous system autoimmune channelopathy[2].

Little is known about cognitive dysfunction in NMO, its frequency, and its relationship with clinical variables. Blanc et al.[3] reported impairment of attention, speed of information processing, and word generation in NMO patients. Nilsson et al.[4] also found cognitive impairment (CI) in patients diagnosed with isolated optic neuritis (ON) from 24 to 31 years earlier. Finally, He et al.[5] evidenced cognitive alterations in NMO patients after an acute relapse, and encountered an association between neuropsychological performance and routine activities[6].

During the past 20 years, numerous researches have indicated frequent CI in multiple sclerosis (MS) patients. Working memory, attention, verbal fluency, and speed of information processing are often affected[7-9].

The differences between MS and NMO neuropathology suggest distinct cognitive patterns, but only one previous study compared these patients and found no significant variations in cognitive measures[3].

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The aim of the present study was to describe the cognitive pattern of NMO patients and compare it with that of MS ones, considering pathophysiological mechanisms, diagnostic criteria, evolution, and treatments of these diseases.

METHODS

Participants

Fourteen patients diagnosed with NMO, 14 with relapsing remitting MS (RRMS), and 14 healthy controls were evaluated. Twelve females and 12 males were recruited in all groups. NMO patients were diagnosed in the Neurology Service at the J. M. Ramos Mejia Hospital, Buenos Aires, Argentina. The RRMS patients were selected, considering gender, age, and education to match them with NMO participants: (±) 3 in age and (±) 2 in education. The inclusion or exclusion criteria were: confirmed diagnosis as defined by Wingerchuk's[10] in the NMO Group, and as by McDonald's of RRMS; 18 years or older; being in remission period; absence of psychiatric illness; history of alcohol or drug abuse; no physical disability that could impair performance of tests; no uncontrolled systemic disease or that could cause cognitive impairment. Healthy controls without history of neurological disease and mini mental state examination (MMSE) scores >26 were also recruited.

Standard protocol approvals, registrations, and patient consents

This study was approved by the J. M Ramos Mejia Hospital Bioethical Committee, and all participants signed an informed consent.

Outcome measures

Physical disability was measured through the Expanded Disability Status Scale (EDSS)[11]. The Brief Repeatable Battery of Neuropsychology Tests (BRB-N)[12], translated into Spanish and culturally adapted to this Latin American population[9], was administered by a trained neuropsychologist. The procedure started with six learning trials from a brief version of the Selective Reminding Test (SRT), from which measures of learning (long-term storage or LTS) and consistency of recall (consistent long-term retrieval or CLTR) were derived. Next, a visual/spatial memory test, the 7/24 Spatial Recall Test, was administered. The Rao version of the Paced Auditory Serial Addition Task (PASAT) was then completed, requiring rapid calculations and divided attention. The Word List Generation (WLG) test and the oral version of the Symbol Digit Modalities Test (SDMT)[13] were administered prior to the delayed recall testing.

The test 7/24 Spatial Recall and SDMT were not managed in three patients due to visual impairments.

Beck's Depression Inventory II (BDI-II)[14] was carried out as a depression measure.

Procedure

All patients underwent a complete neurological examination. The neurologist scored the EDSS and registered demographic and clinical data, such as age, education, and duration of the disease. NMO ones underwent brain magnetic resonance imaging (MRI) examination with and without contrast (sequences T1, T2, and FLAIR, performed in a 1.5-Tesla resonator according to the MS protocol of the consortium)[15].

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM). Inferential calculations were performed using analysis of variance (ANOVA), Pearson's r correlations, and logistic regression analysis. The level chosen for alpha was 0.05. Patients with two or more affected domains (verbal memory – SRT; visual memory – 7/24 visual spatial; verbal fluency – controlled oral world association (COWA); attention – PASAT) were considered cognitively impaired. Scores in a cognitive domain below the fifth percentile of normal values[9] were considered abnormal.

RESULTS

No significant differences were found between the groups with respect to age (p=968) or education (p=553). Furthermore, the NMO and MS Groups did not differ in the EDSS (p=0.114) or disease duration (p=0.367). Data are shown in Table 1.

Regarding the ANOVA, there was a major significant effect among the groups on SRT-CLTR (p=0.04), SRT delayed recall (p=0.048), PASAT-2 seconds (p=0.004), and COWA (p=0.043). Following *a posteriori* Tukey's tests, the NMO patients performed significantly worse than the controls in PASAT-2 (p=0.003). The MS Group had a worse performance than the controls on SRT-LTR (p=0.034), SRT delayed recall

Table 1. Demographic and clinical data of neuromyelitis optica and multiple sclerosis patients and healthy controls.

	NMO	MS	Healthy Controls	p-value
	n=14	n=14	n=14	
Mean age (years)	36.86±12.42	37.93±10.57	37.07±12.39	ns
Mean instruction level (years)	11.26±3.29	12.79±3.55	11.86±4.07	ns
Mean disease course (years)	8.62±4.35	6.62±6.52		ns
Mean EDSS	4.31±2.59	2.2±1.68		ns

NMO: neuromyelitis optica; MS: multiple sclerosis; EDSS: expanded disability status scale.

(p=0.048), and 7/24 Correct Answers Trails 1 to 5 (p=0.048). However, no differences were found between the NMO and MS Groups, which can be seen in Table 2.

When comparing the performance of NMO patients with local normative scores, it was found that 35.71% of them showed abnormal performance in verbal memory, 9.09% had some problem in visual memory, 64.28% had in attention, and 48.85% presented abnormal performance in verbal fluency. In the MS Group, 61.53% of the participants showed abnormal performance in verbal memory, 61.53% had problem in visual memory, 33.33% in attention, and 38.46% showed abnormal performance in verbal fluency.

Characteristic of the Neuromyelitis optica Group

Considering the amount of impaired tests (35.71%), the sum of these percentages exhibited no alteration (7.14%), had one impaired test (28.57%), had two impaired tests, and (28.57%), had three or more impaired tests.

Regarding association between MRI and the amount of impaired tests, five out of eight patients with a normal MRI and four out of six with lesions had at least one cognitive impaired test. Comparison of cognition among patients with and without lesions using MRI revealed a significant difference only in one test, namely SRT-CLTR (p=0.016), therefore patients without lesions (n=7) performed better than those with such thing. Concerning the levels of depression, eight subjects showed score within the normal range (Grade 1), while six revealed signs of depression; one showed mild depression (Grade 2), three presented moderate depression (Grade 3), whereas the remaining three had severe depression (Grade 4). The data are summarized in Table 3.

Correlations between the neuropsychological measures and BDI-II and demographics variables are presented in Table 4. BDI-II correlated significantly and negatively to PASAT-3 (r=-0.652, p<0.05) and PASAT-2 (r=-0.688, p<0.01). However, the BDI-II scores did not correlate significantly with EDSS or disease duration. Furthermore, scores on SRT delay recall and PASAT-3 test were significantly correlated to age and education. However, cognitive tests did not correlate to evolution disease and EDSS (data not shown).

Table 2. Neuropsychological test results for the neuromyelitis optica and multiple sclerosis patients and healthy controls.

Test store	NMO	MS	HC	p-value
SRT-LTR	40.50± 20.53	37.62±11.75	49.79±13.98	0.128
SRT-CLTR	28.50±17.20	22.69±13.73	38.36±15.45	0.040
SRT-Delayed recall	7.29±3.14	6.62±2.95	9.21±2.00	0.048
7/24-Correct answers trails 1 to 5	26.82±5.05	22.46±6.96	28.50±6.68	0.054
7/24-Immediate recall	5.64±1.50	4.42±2.42	5.29±1.93	0.328
7/24-Delayed recall	5.55±1.57	4.25±1.91	5.93±1.81	0.060
PASAT-3"	31.36±18.36	38.25±15.53	41.86±12.16	0.208
PASAT-2"	21.36±15.12	26.92±9.54	37.86±11.52	0.004
COWA	28.07±12.12	29.23±7.44	38.08±11.89	0.043
Symbol digit modalities test	43.00±10.75	37.85±14.53	46.07±8.09	0.187
BDI-II	18.30±11.09	11.90±8.22	5.42±4.51	0.001

NMO: neuromyelitis optica; MS: multiple sclerosis; HC: healthy controls; SRT: selective reminding test; LTR: long-term storage; CLTR: consistent long-term retrieval; PASAT: paced auditory serial addition test; COWA: controlled oral word association; BDI-II: Beck depression inventory II.

Table 3. Individual neuropsychological results of neuromyelitis optica.

Patient number	Brain MRI	BDI-II	Cognitive domains			
			Verbal memory	Visual memory	Verbal fluency	Attention
1	Normal	1	0	0	0	1
2	Unspecific lesions	3	1	0	1	1
3	Normal	1	0	1	0	1
4	Normal	4	0	0	1	1
5	Typical lesions AQP4	2	0	0	0	0
6	Unspecific lesions	3	1	0	0	1
7	Normal	1	0	0	0	0
8	Typical lesions AQP4	1	1	0	1	1
9	Unspecific lesions	1	0	0	0	0
10	Normal	1	0	0	0	0
11	Normal	1	1	NA	1	1
12	Normal	1	0	0	0	0
13	Normal	4	0	NA	1	1
14	Unspecific lesions	4	1	NA	1	1

MRI: magnetic resonance imaging; BDI: Beck depression inventory; AQP4: Aquaporin 4; cognitive domains=0: within normal range, 1: below the fifth percentile, NA: not applied visual alterations; BDI II=grades 1: 0 to 13 (without depression); 2: 14 to 19 (mild); 3: 20 to 28 (moderate); 4: 29 to 63 (severe).

Table 4. Correlations between neuropsychological measures, depression, age, and education in neuromyelitis optica patients.

	BDI-II	Age	Education
	r-value	r-value	r-value
SRT-LTR	-0.223	-0.318	0.522
SR-CLTR	-0.156	-0.390	0.565*
SRT-Delayed recall	-0.243	-0.577*	0.771**
7/24-Correct answers trails 1 to 5	-0.006	-0.054	0.056
7/24-Immediate recall	0.231	0.279	-0.047
7/24-Delayed recall	-0.469	-0.277	-0.110
PASAT 3"	-0.652*	-0.631*	0.679**
PASAT 2"	-0.688**	-0.464	0.503
COWA	-0.549	-0.572*	0.765**

SRT: selective reminding test; LTR: long-term storage; CLTR: consistent long-term retrieval; PASAT: paced auditory serial addition test; COWA: controlled oral word association; BDI-II: Beck depression inventory II; *p<0.05 level; **p<0.01 level.

DISCUSSION

NMO patients presented a significantly lower neuropsychological performance than healthy controls of similar age and education. Surprisingly, 57.14% of the NMO Group showed CI. Similarly, Blanc et al.[3] found 56.7% of CI in their sample and He et al.[5] also reported it.

Regarding cognitive performance, the few descriptions found in the literature on patients with NMO accounted a pattern of subcortical cognitive impairment, characterized by reduced speed of information processing, changes in executive functions, attention, and memory. In this research, the NMO Group showed more dysfunction in attention and verbal fluency than in memory. Blanc et al.[3] described alteration of long-term memory and executive functions, while He et al.[5] found memory deficit and decreased speed of information processing and attention, after an acute relapse. This stage of the disease might not be the most appropriate for the evaluation of patients, because many factors involved in the pathogenesis of a relapse go beyond those involved in that of the disease itself.

Cognitive performance of NMO patients was found to be similar to that of MS ones coinciding with Blanc et al.[3]. However, when compared with the published local norms, a higher proportion of MS patients showed visual memory impairment and a higher proportion of the NMO Group evidenced attention issues. Furthermore, CI in NMO patients could be considered surprising, since NMO is thought to be restricted to damage of optic nerves and spinal cord.

At the early stage of the disease, MRI brain lesions are almost inexistent, with a few exceptions of little subcortical white matter lesions. However, recent MRI and pathological anatomy findings suggest that tissue damage in NMO is more extensive and includes the compromise of other areas, such as brain stem, cerebellum, and cortex[16-18]. Although this study was not meant to examine the relationship between cognition and MRI findings, cognitive alterations were found both in patients with and without lesions in MRI. He et al.[5] reported evidence of microscopic brain lesions using diffusion tensor imaging, which could explain the presence of cognitive alterations in those without lesions in conventional MRI measures.

A high number of patients (6 out of 14) manifested signs of depression, ranging from mild to severe, coinciding with the findings of Chanson et al.[19], who found influence of depression on the quality of life of patients with NMO. Moreover, He et al.[6] reported a significant correlation between cognition, depression, and routine activities in patients assessed after an acute relapse of the disease. Depression was related to attention measures, but not with physical disability or disease durations. The negative influence of depression in attentional functions has already been reported in MS[20]. In NMO, Blanc et al.[3] did not observe an association between cognition and depression.

Cognition is not associated with physical disability and disease duration, this is consistent with the findings of Blanc et al.[3]. The limitations of this study include the administration of neuropsychological test with a visual component and the lack of control of symptomatic pharmacological treatments. Studying a larger group of patients would be needed to improve the description of cognitive pattern, as well as the impact on patients' quality of life. In future, longitudinal research will shed light on the evolution of cognitive disorders and possible predictors of this symptom in NMO.

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