Cognition in clinically isolated syndrome

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ABSTRACT. Cognitive abnormalities have been extensively studied in Multiple Sclerosis (MS). However, little is known about the cognitive involvement in patients with Clinically Isolated Syndrome (CIS). **Objective:** This study aimed to investigate cognitive impairment in patients with CIS compared with healthy subjects. **Methods:** 18 CIS patients and 18 controls were subjected to the Wechsler memory scale, Rey Auditory Verbal Learning, Rey Complex Figure, Paced Auditory Serial Addition, Digit Span, verbal fluency, Stroop color card test, D2, and Digit Symbol tests. **Results:** CIS patients had significantly worse performance on the Paced Auditory Serial Addition Test (PASAT) 2 seconds ($P=0.009$) and on verbal fluency tests ($P=0.0038$) than controls. **Conclusion:** CIS patients had worse cognitive performance than controls on neuropsychological tests evaluating executive functioning.

Key words: cognition, clinically isolated syndrome, neuropsychological tests.

INTRODUCTION

Clinically Isolated Syndrome (CIS) is defined as the first episode of a demyelinating and inflammatory disease of the central nervous system (CNS). A number of patients with CIS will convert to Multiple Sclerosis (MS), a chronic demyelinating disorder characterized by CNS lesions disseminated over time and space.1

Recent studies have demonstrated that cognitive dysfunction has a negative impact on the quality of life of such MS patients.2,8 Consequently, the study of cognitive function in MS has gained great importance. Cognitive dysfunction is found in 40 to 65% of MS patients4 and seems to be related with the number and localization of demyelinating lesions, axonal loss, and brain atrophy typically found in MS.5 Considering that these pathological features are progressive, it is important to establish in which phase of the disease the cognitive dysfunction begins. In this regard, some studies assessing cognitive functions in early MS and also in patients with CIS have been conducted.4,6,8-9 Several recent studies have shown that CIS patients may present mild cognitive impairment, especially in executive functions.7,8,10
The aim of the present study was to investigate a series of cognitive domains in Brazilian patients with CIS compared to healthy subjects.

METHODS

Subjects. Subjects aged 19-48 with CIS were recruited over a two-year period from the Multiple Sclerosis Clinic of the Santa Casa School of Health Sciences, Vitória, Espírito Santo – Brazil. The control group was composed of healthy subjects paired by age, gender, and educational level. The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais, Belo Horizonte, and Santa Casa School of Health Sciences, Vitória, Brazil, and informed consent was obtained from each participant. The diagnosis of CIS was defined according to the following criteria: one isolated neurological episode lasting at least 24 hours compatible with demyelination of the CNS and magnetic resonance imaging showing at least two lesions resembling those seen in MS. Patients with the first demyelinating episode with gadolinium-enhancing and non-enhancing lesions on baseline magnetic resonance imaging (MRI) were excluded according to the recent MS diagnostic criteria. Patients with severe cognitive impairment, defined as a score below 24 points on the Mini-Mental State Examination, or using psychotropic drugs were not included. All patients had not been using corticosteroids for at least three months leading up to the time of evaluation.

Neurologic and neuropsychological evaluation. The clinical evaluation included neurologic examination and determination of current disability using the Expanded Disability Status Scale (EDSS). CIS subjects and control individuals were subjected to neuropsychological evaluation comprising: verbal learning (Rey Auditory Verbal Learning Test); verbal memory (logical memory subtest from the Wechsler memory scale-revised); constructional ability and visual memory (Rey Complex Figure); and attention and executive function tests: speed of information processing, sustained and divided attention (Paced Auditory Serial Addition Test 3 and 2 seconds); working memory (Digit Span Test from the Wechsler memory scale revised), category restricted verbal fluency (letter and animals); selective attention and cognitive flexibility (Stroop Color test); concentration (D2 test); visual scanning, tracking, and motoric speed (Digit Symbol Test). The cognitive evaluation was performed in an air-conditioned environment at the same temperature.

Statistical analysis. Analyses were performed using R software, version 2.8.0. The normality of data distribution was assessed with the Shapiro Wilk test. As data presented a non-normal distribution, the Mann-Whitney test was used to compare neuropsychological parameters between CIS patients and controls. The level of significance was set at p<0.05.

RESULTS

The mean±SD time between demyelinating episode and cognitive assessment was 17.7±18.2 months. Demographic and clinical data of patients and controls are shown in Table 1.
Table 1. Eighteen CIS patients were included, 13 female and 5 male. The mean±SD age was 35.5±9.1 years. The mean±SD EDSS score of patients with CIS was 0.8±0.5. The mean±SD MEEM score and Wechsler Adult Intelligence Scale (WAIS) of patients with CIS was 28.4±1.3 and 113.3±10.1 and control group was 29.1±0.9 and 115.0±9.1, respectively.

In Table 2, the median scores on each neuropsychological test of patients and controls are shown. The performance of CIS patients in PASAT 2 seconds (correct answer), PASAT 2 seconds (no responses) and Fluency (with letter “S”) was significantly lower than controls.

DISCUSSION

To our knowledge, this was the first study evaluating cognitive functions in a series of Brazilian CIS patients. Previous studies have shown differences in cognitive performance between CIS patients and controls. Reduced semantic verbal fluency and delayed spatial recall, reduced information processing speed, changes in executive function, abnormalities in working and verbal memory have been shown in CIS patients. Our results are in line with previous studies showing executive dysfunction in CIS. Specifically, we found abnormalities in speed of information processing, sustained and divided attention, and category restricted verbal fluency; however, there was no difference in other executive functions such as working memory, selective attention and cognitive flexibility, concentration, and visual scanning, tracking, and motoric speed. Therefore, the present study confirmed that CIS may lead to mild cognitive impairment with variable executive dysfunction. This may have clinical implications. Given CIS is the first clinical manifestation of MS and that cognitive abnormalities can be found in CIS, our data suggest that neuropsychological evaluation as well neuropsychological follow-up

| Table 2. Cognitive results of patients with clinically isolated syndrome (CIS) and controls. |
|-----------------------------------------------|------------|---------------|
| **Median** | **Patients** | **Controls** | **P-value** |
| Logical Memory (Immediate Recall) | 11 | 15 | 0.692 |
| Logical Memory (Delayed Recall) | 11.5 | 12 | 0.924 |
| PASAT 3 Seconds (Correct responses) | 40 | 54.5 | 0.222 |
| PASAT 3 Seconds (False responses) | 2.5 | 1 | 0.220 |
| PASAT 3 Seconds (Absence) | 14 | 4 | 0.188 |
| PASAT 2 Seconds (Correct responses) | 18 | 46.5 | 0.0216* |
| PASAT 2 Seconds (False responses) | 2 | 2.5 | 0.721 |
| PASAT 2 Seconds (Absence) | 41 | 9.5 | 0.009* |
| Fluency (Letter) | 12.5 | 15 | 0.0038* |
| Fluency (Animals) | 19 | 20.5 | 0.899 |
| STROOP (Time) (Card3) | 22.5 | 20 | 0.366 |
| RALVT (Immediate Recall) | 9.5 | 10 | 0.975 |
| RALVT (Delayed Recall 30’) | 10 | 10 | 0.898 |
| RALVT (Total) | 69 | 73 | 0.751 |
| Rey Figure (Copy) | 36 | 36 | 0.771 |
| Rey Figure (Delayed 3’) | 21 | 20 | 0.691 |
| Digit Symbol (Score) | 61.5 | 62.5 | 0.837 |
| Digit Span (Forward) | 6.5 | 7.5 | 0.185 |
| Digit Span (Backward) | 5 | 6 | 0.109 |
| Digit Span (Total) | 11.5 | 14 | 0.127 |
| D2 (Gross) | 446 | 434.5 | 0.805 |
| D2 (Total Error) | 15 | 14 | 0.754 |
| D2 (Net) | 434 | 413 | 0.717 |
| D2 (Amplitude Oscillation) | 12 | 12 | 0.716 |

*Significant.
should be carried out soon after the first clinical episode of demyelination. This neuropsychological follow-up will allow a better understanding of the progression of cognitive findings in CIS and in MS.

The present study has some clear limitations. The sample size may be considered small and consequently may have led to underestimation of the differences between groups. Another limitation is the lack of systematic neuroimaging evaluation, precluding the determination of any correlation between cognitive findings and neuroimaging parameters. Future studies should evaluate the correlation between cognition, topography of MRI lesions and lesion load in patients with CIS. We were not able to evaluate the impact of psychiatric comorbidities such as depression and anxiety on cognition and did not evaluate fatigue symptoms or their impact on cognition. Future and larger studies with multivariate analysis should be able to assess the potential interference of psychiatric syndromes on cognitive test performance in CIS patients.

In conclusion, this study confirmed that mild executive dysfunction occurs in CIS. Future studies are needed to address whether this cognitive compromise is long lasting and/or associated with significant impact on daily activities.

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