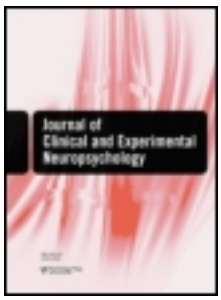

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Epidemiological characteristics of cognitive impairment of multiple sclerosis patients in a Latin American country

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We assessed cognitive performance and physical disability in 111 multiple sclerosis (MS) patients and 222 healthy controls in a multicenter study in Argentina to obtain the prevalence of cognitive impairment (CI) in a population of MS outpatients in Argentina. MS patients presented significantly lower scores in all Brief Repeatable Battery of Neuropsychology (BRB-N) tests than did the control group. The prevalence of CI was 43.2%. This study allowed us to obtain actual figures on the number of MS patients with CI in a Latin American sample. This validation is a very useful tool for clinical practice and for research studies to assess cognition in MS.

Keywords: Multiple sclerosis; Neuropsychology; Cognitive impairment; Brief repeatable battery; Epidemiology.

INTRODUCTION

Cognitive impairment (CI) is one of the clinical features of multiple sclerosis (MS) since the earliest descriptions of the disease (Charcot, 1877). Cognitive disturbances have a great impact on the activities of daily living affecting their quality of life (Beatty, Blanco, Wilbanks & Paul, 1995; Benedict et al., 2005; Benedict & Zivadinov, 2006; Demaree, DeLuca, Gaudino, & Diamond, 1999; Rao, 1995; Rao, Leo, Ellington, et al., 1991).

Previous prevalence estimates of MS-related CI range from 40 to 60%, depending on the data sources (e.g., community-based studies, outpatient MS centers; Bobholz & Rao, 2003; Rao, Leo, Bernardin, & Unverszagt, 1991). To our knowledge, no reports have been found about the prevalence of CI in Argentine MS patients or any other Latin American population.

These impairments have been found to correlate weakly with physical disability and disease duration (Mcintosh-Michaelis et al., 1991; Payser, Rao, LaRocca, & Kaplan, 1990) and cannot be identified by scores on the Mini-Mental State Exam (MMSE; Aupperle, Beatty, Shelton, & Gontkovsky, 2002; Beatty, Paul, et al., 1995; Beatty & Scott, 1993).

As a comprehensive neuropsychological examination is too costly and time consuming in a routine clinical setting, a number of shorter batteries have been developed (Solari, Mancuso, Motta, Mendozzi, & Serrati, 2002). One of them is the Brief Repeatable Battery of Neuropsychology Tests (BRB-N) which is a sensitive and specific instrument to detect CI in MS patients and is the most widely used neuropsychological battery (Boringa et al., 2001; Rao & Cognitive Function Study Group, 1990).

The BRB-N assesses verbal and visual memory, attention, executive functions, and verbal fluency (Rao, 1991). This battery is fairly short (i.e., 35 min), and it can be easily administered.

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Cognitive evaluation instruments ought to be duly validated and adapted to the social and cultural features of each population (Hernández Sampieri, Fernández Collado, & Baptista Lucio, 1991; Parkin, 1996; Spreen & Strauss, 1998). The BRB-N has not yet been validated for Argentina.

The goals of the present study were: (a) to provide regional data about the prevalence of cognitive impairment in MS, (b) to validate the BRB-N battery for Argentina, and (c) to determine the correlation between cognitive impairment, physical disability, and the clinical forms of MS.

METHOD

Study area

The RECONEM (acronym in Spanish meaning Cognitive Impairment Survey in MS patients) research group conducted this descriptive multicenter cross-sectional epidemiological study. Twenty-eight MS centers from eight different Argentine provinces (i.e., Tucumán, Santa Fe, Cordoba, Neuquén, Chubut, Santa Cruz, Mendoza, and Buenos Aires) participated in this study. Participants attended MS clinics and hospitals from the northern, central, southern, western, and eastern regions of the country. Thus, this sample is representative of the whole Argentine MS population. Each center had a neurologist and a neuropsychologist trained in workshops organized by the coordinating center in Buenos Aires before the beginning of the study.

Neuropsychological assessment

The investigators received training on the administration of the following instruments: BRB-N Versions A and B translated into Spanish and culturally adapted to this Latin American population, the MS functional composite (MSFC; Fischer, Jak, Kniker, Rudik, & Cutter, 2000; Rudick et al., 1997), Expanded Disability Status Scale (EDSS; Kurtzke, 1983), and Beck Depression Inventory (BDI; Beck, Ward, Medelson, Mock, & Erbaugh, 1961). The BRB-N includes the following tests: (a) The Selective Reminding Test (SRT), which measures consistent long-term retrieval (LTR) and long-term storage (LTS) through presentation of a list of 12 words and five subsequent learning trials; (b) the 7/24 Spatial Recall Test, which assesses visual learning and recall by recreating the pattern of 7 checkers on a 6×6 checkerboard viewed for 10 s; (c) the Paced Auditory Serial Addition Task (PASAT), which evaluates sustained attention and information-processing speed and is measured by asking the patient to add each number to the one immediately preceding it while numbers are presented every three seconds and every two seconds; (d) the Word List Generation (WLG) task, which measures semantic verbal fluency, evaluating the spontaneous production of words beginning with a particular letter during 60 s; and (e) the Symbol Digit Modalities Test (SDMT), which measures complex attention and concentration, requiring the subject to associate symbols with numbers and quickly generate the number when shown the symbol for 90 s. The last task is an additional task not originally included in the BRB-N and is the inverse of the Digit Symbol Test. The MSFC used in our study included the timed 25-foot walk, the 9-Hole Peg, and the PASAT–3 tests. Participants were administered the tests in two separate scheduled sessions.

Subjects

We obtained written informed consent from all eligible patients or their caregivers. Internal review boards of each center approved this study. Each center interviewed 5 MS patients randomly selected from a set of clients eligible for the study and 10 healthy controls. Inclusion criteria were: age 18 or older, all clinical forms of MS according to Poser et al. (1983) and McDonald's criteria (McDonald et al., 2001)—that is, relapsing–remitting (RR), primary progressive (PP), secondary progressive (SP), and relapsing progressive (RP)—and healthy controls with no history of neurological diseases. All participants had to have MMSE scores > 26 in order to be included in the study. Exclusion criteria included psychiatric syndromes, visual and hearing deficits, history of alcohol or drug abuse and dependence, depression (as measured by BDI scores > 10), physical disability that could impair appropriate performance of the tests, uncontrolled systemic disease, and the presence of any disease that could cause cognitive impairment (e.g., endocrinological, toxic, genetic–degenerative, metabolic, infectious diseases).

Statistical analysis

We used the NCSS97 (Number Cruncher Statistical System; Hintze, 2006) for the statistical analysis. We used chi-square or the Fisher's exact probability tests for comparing categorical outcomes and the Student t test to compare continuous variables between both groups. All test scores were adjusted for age, gender, and level of education, using linear regression modeling. Logistic regression analyses and adjusted mean values were used for the statistical comparison. In order to evaluate which cognitive tests and demographical variables better predicted CI, we used logistic regression modeling. Significance level was set at .05. We reported two-tailed p-values.

RESULTS

We interviewed 111 out of the 121 MS patients initially contacted and 222 out of the 235 healthy controls initially contacted. The patients and controls excluded did not meet the inclusion criteria or refused to participate.

The groups did not differ in age, years of education, or gender composition. Average age of both samples was 40.8 years ($SD = 11.3$). The participants had on average 13.8 ($SD = 3.1$) years of education, and 82.9% ($n =$

276) of the participants were women. The average duration of the disease for the MS patients was 7.4 years (SD = 7.0). The most common clinical presentations among participants were RR (n = 93; 83.8%), followed by SP (n = 10; 9.0%), PP (n = 4; 3.6%), and RP (n = 4; 3.6%).

MS patients presented significantly lower scores in all the tests of the BRB-N than did the control group (Table 1). In order to determine CI, the fifth percentiles of BRB-N were calculated for the healthy control group according to the specifications published elsewhere (Rao, Leo, Bernardin, et al., 1991). These percentiles were used as a cutoff to determine the number of MS patients with cognitive impairment (Table 1). A MS patient was considered to have CI when there were at least two BRB-N tests below the fifth percentile of the controls. According to this criterion, 46% (n = 51) of MS patients presented CI. After adjusting for age and level of education, the frequency of CI in MS patients was 43.2% (n = 48).

LTR and total delay of the SRT test, the PASAT–3 and PASAT–2 versions, and the Symbol Digit Test presented large effect sizes (i.e., Cohen's $d \geq 0.8$). Also, the LTS of the SRT, the total correct response of the 7/24 Spatial Recall Test, and the WLG presented moderate effects (i.e., $0.5 \leq$ Cohen's $d < 0.8$). Only the two subtests of the 7/24 Test (the immediate and delay recall) presented small effect sizes (i.e., Cohen's $d < 0.5$).

MS patients with and without CI did not differ in age or gender (Table 2). CI was more frequent in subjects with fewer years of education, although the difference was not significant (Table 2). CI prevailed in PP and SP, over RR MS ($p < .05$, Table 2). MS patients with CI had longer disease duration than MS patients without CI (Table 2).

TABLE 1
BRB-N scores for MS subjects and controls

Tests	*MS group mean (SD)*	*Control group mean (SD)*	*Cohen's d*	*5th %ile score for the control group*	*MS group with test results below the 5th %ile % (n)*
Selective Reminding Test					
Long-term storage	43.6 (13.8)*	51.7 (10.3)	0.7	32.2	18.9 (21)
Long-term retrieval	31.1 (14.5)*	42.0 (12.7)	0.8	24.6	33.3 (37)
Total delay	8.2 (2.6)*	9.9 (1.7)	0.8	6.5	18.9 (21)
7/24 Spatial Recall Test					
Correct responses	28.1 (6.4)*	30.7 (4.5)	0.5	21	15.3 (17)
Number correct recall	5.3 (2.0)*	5.9 (1.5)	0.4	2.7	9.9 (11)
Number correct delay recall	5.2 (2.0)*	5.8 (1.5)	0.4	3.2	14.4 (16)
List B	3.7 (1.9)*	4.7 (1.6)	0.6	1.7	13.5 (15)
Word List Generation	35.5 (11.9)*	42.1 (9.8)	0.6	26.9	20.7 (23)
PASAT–3 (seconds)	38.9 (13.0)*	47.3 (9.4)	0.8	30.3	24.3 (27)
PASAT–2 (seconds)	30.0 (12.7)*	38.9 (9.5)	0.8	23.5	25.2 (28)
Symbol Digit Modalities	38.5 (13.4)*	50.1 (10.9)	1.0	31.5	29.7 (33)

Note. BRB-N = Brief Repeatable Battery of Neuropsychology Tests. MS = multiple sclerosis. PASAT = Paced Auditory Serial Addition Test.
*$p < .01$.

TABLE 2
Comparison of demographic characteristics between MS patients with CI and without CI

	MS patients with CI (n = 48) mean (SD)	*MS patients without CI (n = 63) mean (SD)*
Age	41.5 (11.2)	40.3 (11.4)
Education (in years)	13.4 (2.2)	13.9 (2.9)
Disease duration (in years)	8.6 (7.5)	6.5 (6.4)
	% (n)	*% (n)*
Gender (females)	85.4 (41)	81.0 (51)
Clinical forms		
RR	72.9 (35)*	92.1 (58)
PP	8.3 (4)*	0.0 (0)
SP	12.5 (6)*	6.3 (4)
RP	6.3 (3)*	1.6 (1)

Note. MS = multiple sclerosis; CI = cognitive impairment; RR = relapsing–remitting; PP = primary progressive; SP = secondary progressive; RP = relapsing progressive.
*$p < .05$.

LTR, PASAT–3, and 7/24 Spatial Recall (i.e., correct answer number) were the only significant predictive variables to determine CI in a logistic regression model.

Patients with CI presented higher degrees of disability. MS patients with CI presented significantly higher EDSS scores than patients without CI (mean = 3.79, $SD = 1.99$ vs. mean = 2.73, $SD = 1.56$, $p < .01$). We found no differences between MS patients with and without cognitive impairment regarding MSFC scores.

DISCUSSION

CI has a significant impact on the MS population, increasing the need for personal assistance and causing the reduction of social interaction. Therefore, it is essential to obtain accurate data to provide a successful intervention and to focus on the study of the sociocultural variables of each particular population in order to obtain normative values of the BRB-N in each case. Argentina presents the sociocultural variables typical of that of a developing country; thus, the BRB-N normative values for a developed country would not be expected to apply to the MS population.

As far as the educational level of the MS patients under study is concerned, it can be clearly stated that is relatively high. Surely, this would not strictly represent the educational level of the population all MS patients in Argentina.

From a methodological point of view, this epidemiological study has been carried out in MS specialized centers ("center-based study"). It has not been carried out as a "community-based study." There could exist a selection bias as regards the population of patients analyzed, which could be reflected in the educational level. CI in Argentinean patients with MS was 46%. Unfortunately, we were not able to compare our results with other Latin American countries due to the lack of neuroepidemiological research performed in the region.

Within the past 25 years, it became evident that 40–70% of MS patients present CI. The range of variability observed in the prevalence of CI is due to the methodological differences among the studies such as study design and setting, the neuropsychological tests selected for the study, and the criteria for determining CI (Beatty, Blanco, et al., 1995; Mcintosh-Michaelis et al., 1991; Peyser et al., 1990). Our estimate of CI among MS patients agrees with those found by Rao, Leo, Bernardin, et al. (1991) and Solari et al. (2002) who reported a prevalence of CI of 43%; however, they assessed the subjects with a more exhaustive neuropsychological battery (i.e., 32 tests were used) and used a more astringent criterion to determine CI (i.e., a patient had CI if 4 or more tests were below the 5th percentile of the control's scores). On the other hand, Solari et al. reported the results of a multicenter study using a slightly shorter version of the BRB-N than the one used in this study. Considering the design, Solari et al.'s study would be more comparable to our study except for the fact that they found a 16% prevalence of CI when they considered the same CI criterion. When they relaxed the criterion (i.e., 1 or more tests below the 5th percentile of the control group scores), their estimate of CI was 43%.

The BRB-N is a sensitive and valid screening battery to predict cognitive impairment in MS outpatient populations (Boringa et al., 2001). It has been successfully used not only in the clinical setting but also as a research tool (Aupperle et al., 2002) and in cases where the test should be repeatedly administered (Aupperle et al., 2002). This study provided useful parameters for measuring CI in a Latin American population, as well as serving as a validation of the BRB-N batteries in the region.

We found no differences between the MS patients with and without CI when we compared gender composition and age. Disease duration did not influence cognitive performance. Solari et al. (2002) and Rao, Leo, Bernardin, et al. (1991) reported similar results.

We found the highest percentage of cognitive impairment in PP MS (87.5%), followed by SP MS (60%) and RR MS (37.6%). Huijbregts et al. (2004) found similar results when they included 108 patients with RR MS, 71 with SP, and 55 with PP. Participants of this study completed the BRB-N. The authors found greater deficits in patients with SP, followed by PP and, to a lesser extent, RR MS.

In the study performed by Aupperle et al. (2002), the authors compared three neuropsychological screening batteries and combined primary and secondary progressive MS in a single group. They found statistically significant differences in the performance of each battery, RR MS being the form of the disease that showed better cognitive performance. In addition, Rao, Leo, Bernardin, et al. (1991) found a tendency for the relapsing–remitting patients to fail fewer cognitive tests than those with the progressive forms of the disease. Benedict et al. (2006) also showed that all tests are successful at discriminating between RR and SP patients.

We obtained large effect sizes for the tests of episodic memory, processing speed, and working memory. The effect sizes reported here are similar to those from previous studies (Benedict et al., 2006). Strober et al. (2009) reported that the SRT Delay, the PASAT–2 version, and the SDMT showed high effect sizes, comparable to our results.

In a logistic regression model, PASAT–3 and 7/24 Delay were the only significant predictive variables to detect CI.

When assessing the disability level of our population with the EDSS, we observed an association between the severity of the physical disability and CI. Our results are similar to those described in other studies (Rao, Leo, Bernardin, et al., 1991; Solari et al., 2002). Physical disability was higher in MS patients with CI. An unexpected result of this study was that there was not a statistically significant correlation between the MSFC and CI.

Our study also validated the oral version of the SDMT, which prevents biases in the performance of the test due to MS-related physical impairments. This test is easy to administer and reliable. This test showed a large effect size in agreement with the findings of Beatty, Paul, et al. (1995) and Benedict et al. (2006). In the study conducted

by Sepulcre et al. (2006), the SDMT showed the strongest correlation with the EDSS and the MSFC.

Our results are consistent with those obtained in other studies performed in Europe and North America. Also, the validation of this instrument is a very useful tool not only for clinical practice but also for future research studies to assess cognitive function in MS patients to be performed in Latin America.

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