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Cognitive and neuropsychiatric disorders among multiple sclerosis patients from Latin America: Results of the RELACCEM study

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Abstract

Background: Cognitive impairment and psychiatric symptoms impact many aspects of the lives of people with multiple sclerosis [MS]. This literature is based largely on North American and Western European samples, and little is known about these aspects of MS disability in Latin America.

Objective: RELACCEM is a longitudinal, multicenter study including MS centers in Argentina, Chile, Columbia, Venezuela, Uruguay and Mexico. The goal is to determine the prevalence of cognitive impairment (two or more cognitive domains under the 5th percentile of healthy controls performance) and the full range of neuropsychiatric symptoms in these regions, and how these symptoms relate to caregiver burden and employment.

Methods: Participants were 110 patients with relapsing-remitting [RR] course and less than five years of disease duration. Thirty-four healthy controls were also recruited. All participants were evaluated in one of 14 specialized centers.

Results: In additional to overall neurological disability, both cognition and neuropsychiatric symptoms distinguished patients and controls. The prevalence of cognitive impairment was 34.5% and 20.9% presented with clinically significant neuropsychiatric symptomatology. Cognitive impairment was a significant predictor of employment status.

Conclusions: This is the first multicenter epidemiological study of MS-associated cognitive and neuropsychiatric symptoms in Latin America. Results indicate that cognitive dysfunction and psychiatric decline symptoms, fatigue, depression and caregiver burden are already apparent at an early stage of the disease. The presence of neuropsychiatric abnormalities indicates the need for appropriate interventions as early as possible to mitigate psychosocial consequences of caregiver burden.
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1.   Introduction

MS causes marked impairments in cognitive function as well as neuropsychiatric symptoms, both of which have adverse impact on quality of life (QoL) (Langdon, 2011). Epidemiological studies further show that these symptoms can appear in early stages of the disease and are greatly varied, including not only cognitive disorder, but also neurobehavioral signs, fatigue and depression (Amato et al., 2001; Benedict and Zivadinov, 2011).

For the most part, these conclusions are based on many studies from North America and Western Europe. Few studies are available from other regions of the world, notably Latin America. An exception is the Cáceres et al. (2011) study showing significant cognitive impairment using a Spanish translation of conventional neuropsychological (NP) tests. This study was limited by inclusion of just a single country, Argentina, and restriction of outcomes to the domain of cognition. Little is known about cognitive and especially neuropsychiatric manifestations of MS in Latin America, more generally speaking.

Herein we present the results of the first multicenter study of persons with MS from Argentina, Chile, Colombia, Mexico, Uruguay and Venezuela. The study was designed to be a longitudinal, prospective assessment of consecutively enrolled MS patients from clinics affiliated with the RELACCEM Study group (Spanish acronym for Cognitive and Behavioral Survey of MS patients from Latin America). Our goal was to widen the scope of assessment to the domains of cognition and neuropsychiatric symptoms, and then determine their impact of caregiver distress and employment.

2.   Methods

2.1.   Study design and participants

The RELACCEM study is in progress and herein we report on baseline data from 110 MS patients and 34 healthy controls (HCs). The study was approved by the local Ethics Committee of each center and the independent institutional review board. All participants provided signed informed consent. Enrollment commenced in February 2010 and was closed in October 2010.

All patients had a confirmed diagnosis of MS and relapsing-remitting course (Polman et al., 2005). Other inclusion criteria were $\geq$ 18 years old, disease duration <5 years, patient stable on disease modifying treatment for at least 3 months, not in a relapsing phase or under corticosteroid therapy during or 2 months before the evaluation, and absence of any other neurological or psychiatric illness. Fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp et al., 1989) Self- and informant-report of overall neuropsychological status was quantified using the MS Neuropsychological Screening Questionnaire [MSNQ] (Benedict et al., 2004) validated in Spanish (Vanotti et al., 2009). Neurological disability was assessed with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and The Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999).

The HCs group was well matched to the patient group except that they were on average five years younger. As a result, age was controlled statistically in subsequent analyses. Exclusion criteria for this group were history of neurological illness, head trauma, or alcohol or drug abuse. At least 3 Hcs were enrolled in each center

2.2.   Measures

Cognitive status was assessed using a Spanish translation of the Rao Brief Repeatable Battery for MS, implemented in prior research (Rao, 1991; Cáceres et al., 2011). The Selective Reminding Test (SRT) (Buschke and Fuld, 1974) was used to measure verbal learning and memory, yielding a sum of recalled words on the learning trails and the number of words recalled after a 25 min delay. The 7/24 Spatial Recall Test (Barbizet and Cany, 1968) was employed to measure visual memory. The 7/24 also included a measure of total learning and delayed recall. The Brief Visuospatial Memory Test Revised [BVMTR] (Benedict, 1997) was also administered because it was more sensitive than an adapted version of the 7/24 called the 10/36 Spatial Recall Test (Strober et al., 2009), and we hypothesized that it may also be more sensitive than the 7/24 in this Spanish study. BVMTR scores were total recall over all learning trials and recall after a delay interval, similar to SRT and 7/24. The Paced Auditory Serial Addition Test (Gronwall, 1977) administered using the Rao adapted 2- (PASAT-2) and 3-second (PASAT-3) inter-stimulus interval (Rao, 1991) was applied. Likewise, the oral version of the Symbol Digit Modalities Test [SDMT] (Smith, 1982) was administered. Finally, a word list generation task (WLG) (Benton et al., 1994) was administered.

The Beck Depression Inventory Second Edition (BDI2) (Beck et al., 1996) was employed to quantify depression symptoms. The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), an informant report structured interview, was used to evaluate a wide range of neuropsychiatric symptoms. The NPI has well-established reliability and validity, and has been employed in numerous studies of dementia of varying etiology (Litvan et al., 1996; Mega et al., 2000) including MS (Fishman et al., 2004). This structured interview yields a score for severity [0=mild to 3=severe] and the frequency [0=none to 4=daily] for each of 10 symptom domains [hallucinations, delusions, sleep disturbance, agitation, euphoria, depression, anxiety, disinhibition, lability, apathy]. Total scores for each domain are derived by multiplying severity $\times$ frequency.

We also used Zarit's Caregiver's Burden Scale (Martín et al., 1996) which has been used in Alzheimer's disease (Hébert et al., 2000) and MS studies (Rivera-Navarro et al., 2009). The Zarit Scale is a self-administered tool, which consists of 22 statements regarding stress and burden of care, with ratings from "never" (score 0) to "almost always" (score 4). The total sum is from 0 to 88, with higher totals reflecting greater burden.

Employment status was coded in three categories: full and part time employment, unemployment or retired, and housekeepers and students. These data were reported by patients and confirmed via informant interview.

2.3.   Procedure

The project commenced with an investigator meeting including neurologists, neuropsychologists and psychiatrists from the diverse set of countries noted above. Consensus on