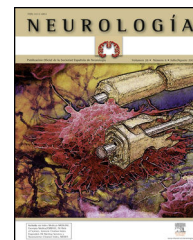




NEUROLOGÍA

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ORIGINAL ARTICLE

Correlation between demyelinating lesions and executive function decline in a sample of Mexican patients with multiple sclerosis[☆]

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Received 27 May 2012; accepted 4 October 2012

Available online 21 September 2013

KEYWORDS

Multiple sclerosis;
Cognitive
impairment;
Executive functions;
Demyelinating
lesions;
Neuropsychology;
Mexico

Abstract

Background: Multiple sclerosis (MS) is characterised by several neurological symptoms including cognitive impairment, which has recently been the subject of considerable study. At present, evidence pointing to a correlation between lesion characteristics and specific cognitive impairment is not conclusive.

Objective: To investigate the presence of a correlation between the characteristics of demyelinating lesions and performance of basic executive functions in a sample of MS patients.

Material and methods: We included 21 adult patients with scores of 0 to 5 on the Kurtzke scale and no exacerbations of the disease in at least 3 months prior to the evaluation date. They completed the Stroop test and the Wisconsin Card Sorting Test (WCST). The location of the lesions was determined using magnetic resonance imaging (MRI) performed by a blinded expert in neuroimaging.

Results: Demyelinating lesions were more frequently located in the frontal and occipital lobes. The Stroop test showed that as cognitive demand increased on each of the sections in the test, reaction time and number of errors increased. On the WCST, 33.33% of patients registered as having moderate cognitive impairment. No correlation could be found between demyelinating lesion characteristics (location, size, and number) and patients' scores on the tests.

Conclusion: Explanations of the causes of cognitive impairment in MS should examine a variety of biological, psychological, and social factors instead of focusing solely on demyelinating lesions.

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[☆] Please cite this article as: Aldrete-Cortez VR, Duriez-Sotelo E, Carrillo-Mora P, Pérez-Zuno JA. Correlación entre las lesiones desmielinizantes y el deterioro de las funciones ejecutivas en una muestra de pacientes mexicanos con esclerosis múltiple. Neurología. 2013;28:394–399.

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PALABRAS CLAVE

Esclerosis múltiple;
Deterioro cognitivo;
Funciones ejecutivas;
Lesiones
desmielinizantes;
Neuropsicología;
México

Correlación entre las lesiones desmielinizantes y el deterioro de las funciones ejecutivas en una muestra de pacientes mexicanos con esclerosis múltiple

Resumen

Antecedentes: La Esclerosis Múltiple (EM) se caracteriza por una gran diversidad de síntomas neurológicos de entre los cuales el deterioro cognitivo recientemente ha cobrado una especial relevancia. Hasta el momento la evidencia acerca de una correlación entre las características de las lesiones y el deterioro cognitivo específico aún no es concluyente.

Objetivo: Analizar si existe una correlación entre las características de las lesiones desmielinizantes y el desempeño de las funciones ejecutivas básicas en estos pacientes.

Pacientes y Métodos: Se incluyeron 21 pacientes adultos con puntaje de 0-5 en la escala de Kurtzke, sin exacerbaciones de la enfermedad en los 3 meses previos a la evaluación. Se les aplicaron las pruebas de Stroop, y el Wisconsin Card Sorting Test (WCST). La localización de las lesiones fue determinada por Resonancia Magnética por un observador experto y cegado

Resultados: Las lesiones desmielinizantes se distribuyeron con mayor frecuencia en los lóbulos occipitales y frontales. En el Stroop se observó que, a medida que se incrementa la demanda cognitiva en cada sección de la prueba, aumentan el tiempo de reacción y el número de errores. En el WCST, un 33.33% presentó un deterioro medio a moderado. No se encontró una relación entre la lesiones desmielinizantes – localización, tamaño y suma total – y los puntajes de las pruebas aplicadas.

Conclusión: En la explicación del deterioro cognitivo en la EM, se deben considerar no sólo a las lesiones desmielinizantes sino también otros factores biológicos, psicológicos y sociales.

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Introduction

Multiple sclerosis is a chronic demyelinating autoimmune disease of the central nervous system (CNS) characterised by the relapsing appearance of multiple demyelinating lesions in the white matter. Lesions show mild axonal damage at onset and severe damage in advanced stages of the disease.^{1,2} MS is clinically characterised by episodes of very diverse types of neurological dysfunction, including motor, sensory, visual, cerebellar, and other deficits.² Among its many clinical manifestations, cognitive and psychiatric symptoms have recently attracted attention due to their involvement in the disability associated with this disease.^{3,4}

Studies indicate that between 40% and 65% of patients with MS experience neuropsychological alterations.⁵ Changes are considered to be severe in 6% to 10% of all cases, and contribute significantly to patients' levels of disability.⁶ Although neuropsychological alterations are more common in the later stages of secondary progressive MS, researchers have also described cognitive impairment in early stages of relapsing MS.^{4,7} The most frequently affected cognitive functions in this disease are attention, long-term memory, verbal information processing speed, and executive functions (EF).^{1,5}

It is especially interesting to analyse EF performance, since EFs are tertiary cognitive processes that regulate the more basic cognitive functions involved in patients' activities of daily life. These processes are often impaired in patients with MS.^{8,9} Some authors have even stated that inhibition is perhaps the most frequently altered function in these patients.¹⁰ Defining the cognitive processes involved in EFs is a theoretical problem, since EF is usually understood as an umbrella category including all higher-level processes. On the other hand, authors such as Miyake et al. propose a model in which EF has 3 main components: inhibition,

flexibility, and working memory.¹¹ The inhibition of pre-ailing responses or irrelevant stimuli has been widely and effectively examined using the Stroop test.¹² In addition, the Wisconsin Card Sorting Test (WCST) is considered a useful tool for assessing cognitive flexibility.^{8,11} Working memory may also be analysed by using modified versions of the Stroop Test requiring temporary retention of information. We therefore propose this brief evaluation with the aim of assessing basic EF performance.

Researchers have previously attempted to correlate cognitive deterioration in MS patients with such different clinical variables as progression timeline, educational level, age, sex, depressive symptoms, etc. However, many authors found no significant relationships.^{13–16} At the same time, other studies have searched for a link between neuropsychological deterioration and different characteristics of demyelinating lesions including location, size, number of lesions, and total lesion area, but no conclusive results have been found to date.^{17,18} Identifying any correlations between the location of demyelinating lesions and the neuropsychological deterioration of specific processes (such as basic EFs) will enable us to predict the clinical behaviour of MS patients. This will help researchers establish cognitive rehabilitation measures designed to reduce the disability stemming from this process.

Patients and methods**Patients**

We included 21 patients from Hospital CIMA (Monterrey, Nuevo León, Mexico) with a definitive diagnosis of relapsing remitting MS according to the revised McDonald criteria¹⁹; patients were recruited consecutively. Included patients

scored between 0 and 5 on the Expanded Disability Status Scale (EDSS). They were clinically stable at the time of evaluation (no exacerbations during the 3 months prior to recruitment) and their brain MRIs presented demyelinating lesions. Each imaging studies was performed in the 3 months prior to the patient's neuropsychological study. At time of inclusion, patients were required to have good visual acuity (20/20) in at least one eye. Additionally, they had to be undergoing treatment with subcutaneous interferon (beta-1b) dosed at 12 or 8 million units, 3 times weekly, at time of inclusion. All patients had been treated with interferon since being diagnosed with MS. Exclusion criteria were as follows: history of alcohol or drug abuse; concomitant illnesses such as epilepsy, psychiatric disorders, or other autoimmune diseases; difficulty understanding basic instructions (as shown by results from the Barcelona subtest)²⁰; and a score of more than 11 on the Beck Depression Inventory.²¹ The research project and the informed consent statement were approved by the Ethics Committee at Hospital CIMA in Monterrey, Nuevo León.

Procedure

The presence of lesions was determined by MRI scans, which were completed in the 3 months prior to the study and interpreted by a blinded neuroimaging expert. MRI scans were performed using a Siemens Magnetom 1.5 tesla scanner. We employed the fast spin echo technique in order to obtain T1-weighted, T2-weighted, or FLAIR images along the axial, sagittal, and coronal planes. The neuropsychological evaluation was first carried out using the Stroop Color and Word Test, then the WCST, and lastly the Beck Depression Inventory.

Instruments

Instruments for the neuropsychological evaluation included the modified version of the Stroop Color and Word Test and the WCST.

We used the version of the Stroop test designed by Valdez-Ramírez, which not only evaluates inhibition as a cognitive process determining performance on the test (according to instruction sets 3 and 4),²² but also requires patients to use working memory. This is also stated in the description published by Flores-Lázaro et al.²³

Valdez-Ramírez's version of the Stroop Color and Word Test employs a page-size card listing 48 words (Arial font, size 28). Words were limited to 4 colour names in Spanish (*azul, café, rojo, verde*) with each word printed in a colour other than that named.²² Participants are asked to produce answers as quickly as possible according to 4 sets of instructions: reading words while ignoring their print colour; naming ink colour without reading the word; reading those words marked with a dot to the left and naming the ink colour for words lacking a dot; and lastly, reversing the third procedure, that is, naming ink colour for words with a dot to the left and reading words lacking a dot. The variables included were completion time and number of errors for each of the 4 instruction sets.

For the WCST,^{24,25} we took into account the standardised score from the age-adjusted table, errors, perseverative

Table 1 Demographic data for the 21 patients with MS.

Sex	8 men 13 women
Age	33 years (20–57)
Education	15.14 ± 3.13, 9 to 21 years
Marital status	Married: 12 (57%) Single: 8 (38%) Divorced: 1 (5%)
Occupation	Students: 2 (9.5%) Professionals: 11 (52.3%) Business owners: 3 (14.3%)
Progression timeline	3.9 months (between 4 months and 19 years)

responses, perseverative errors, and non-perseverative errors.

Statistical analysis

We used the Spearman rank correlation to calculate the association between cognitive performance on the Stroop/WCST tests and total number and localisation of the lesions. Correlations between lesion size, the WCST, and the Stroop tests were analysed using the chi-square test. Likewise, we used the Spearman rank correlation to examine the association between lesion size/location and the demographic variables. Values of $P < .05$ were considered statistically significant.²⁶ SPSS software version 19.0 was used for data analysis.

Results

Table 1 shows general demographic data for the 21 patients included in the study. Regarding demyelinating lesions, the largest percentage of patients (23%) presented 2 lesions. The next largest percentage, 14%, was a 3-way tie between patients with 4, 7, or 9 lesions (Fig. 1). The areas most affected by demyelinating lesions were the subcortical

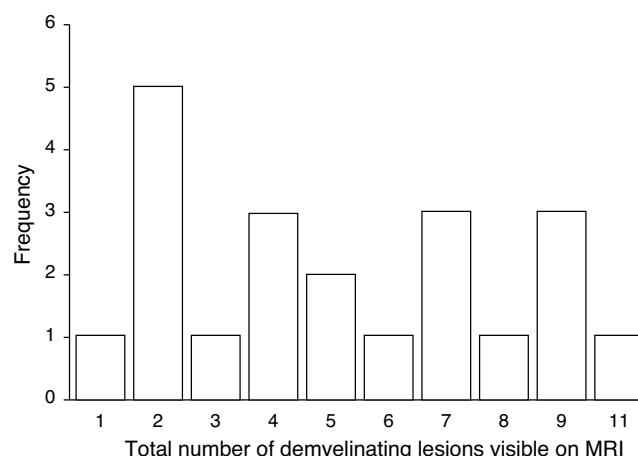


Figure 1 Total number of demyelinating lesions in MS patients according to the MRI scan. The MRI showed only 2 lesions in most patients.

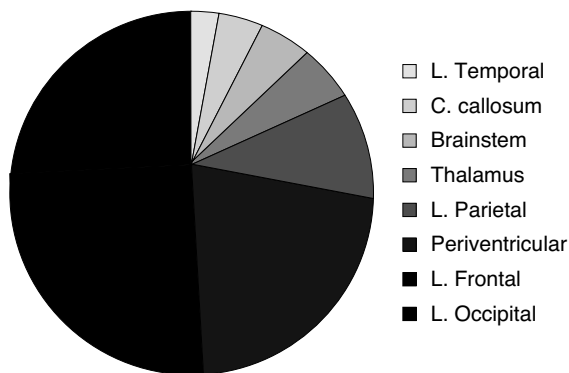


Figure 2 Distribution of the anatomical localisations of the demyelinating lesions identified by the MRI. Most of the patients' demyelinating lesions were located in the subcortical white matter of the occipital/frontal lobes, or in the periventricular region.

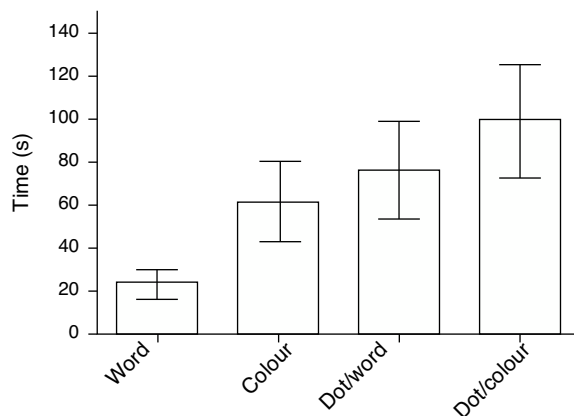


Figure 3 Completion time for each section of the Stroop test.

white matter of the frontal and occipital lobes, and the periventricular region (Fig. 2). Lesions were classified as smaller and larger than 2.5 cm; of the total lesions, 87% were smaller than 2.5 cm and only 13% were larger than 2.5 cm. As was to be expected, most of the lesions larger than 2.5 were located in the white matter of the cerebral hemispheres; brainstem lesions were quite rare.

In the modified Stroop test, the mean period of time was 23.52 ± 6.72 for the word reading section, 61.57 ± 18.68 for the colour naming section, 76.76 ± 22.34 for the dotted word section, and 99.19 ± 26.30 for the dotted colour section (Fig. 3). The mean number of errors was 0 for the word section, 2.43 ± 3.4 for the colour section, 3.48 ± 3.487 for the dotted word section, and 8.19 ± 11.90 for the dotted colour section (Fig. 4). We observed that as cognitive demand increased on each of the sections, reaction time and number of errors also increased.

The mean number of errors on the WCST was 85.6 ± 17.9 (89.4 ± 18.4 for perseverative responses; 86 ± 17.6 for perseverative errors; and 94.1 ± 20.1 for non-perseverative errors). According to the WCST manual, subjects from a clinical sample can be further classified in each dimension as moderate to severe impairment, moderate impairment, mild to moderate impairment, and mild impairment. In a normal sample, subjects' performance may be classified as

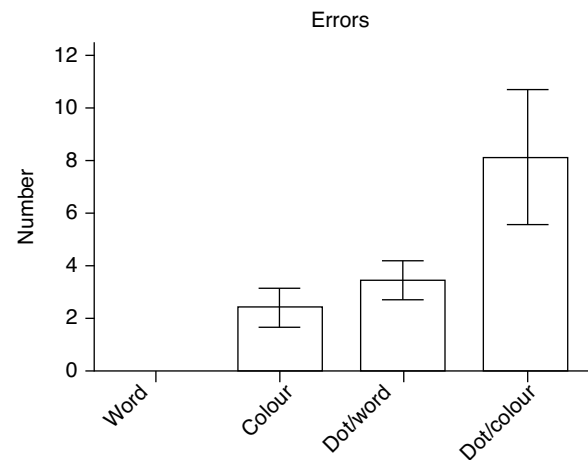


Figure 4 Number of errors for each section of the Stroop test.

below the mean, at the mean, and above the mean. Based on the scoring parameters from the WCST manual mentioned above, most MS patients were at the mean or showed mild impairment on the different dimensions of the WCST test. This means that, according to the WCST test, basic EFs were slightly affected in most patients (Table 2).

The Spearman correlation only showed an association between the total number of lesions and the fourth dimension, dotted colour, on the Stroop test ($r^2 = 0.459$, $P = .036$). Regarding the location of the lesion, we found a correlation between the frontal region and the dotted colour dimension on the Stroop test ($r^2 = 0.437$, $P = .048$), and also between the occipital region and the dotted colour dimension ($r^2 = 0.543$, $P = .011$). Regarding lesion size, the chi-square test was significant for perseverative errors $\chi^2 = 0.221$, $P = .045$.

Discussion

MS is considered to be the leading cause of disability in young adults from developed countries.²⁷ It is estimated that up to 60% of all MS patients in Mexico present some degree of disability.²⁸ The location, number, and size of the demyelinating lesions in our patients correspond to the results from the international and Mexican literature; the predominant lesions are those smaller than 2.5 cm and those located in the periventricular and hemispheric white matter.¹⁸

The presence of cognitive impairment has traditionally been underestimated as a fundamental symptom of MS; Mexican literature reports a frequency of cognitive impairment of only 25%.²⁸ On this subject, few Mexican studies have focused on analysing cognitive impairment in MS patients. Hernández et al. published a neuropsychological analysis of 9 patients with relapsing remitting MS and low scores on the Kurtzke Disability Status Scale. In this group, researchers found abnormal values for memory, efficiency in information processing and visuospatial tasks, and the process of creating concepts.²⁹ Nevertheless, they did not report analysing the basic EF processes which necessarily affect more complex EFs and therefore patients' activities of daily living as well. The present study evaluated patients with similar characteristics to those described by Hernández

Table 2 Number of patients classified in each dimension of the WCST according to typical scores.

WCST dimensions	Moderate to severe impairment	Moderate impairment	Mild to moderate impairment	Mild impairment	Below the mean	At mean	Above the mean	Total number
Errors	2	3	0	5	4	4	3	21
Perseverative responses	2	1	1	3	5	6	3	21
Perseverative errors	3	0	2	6	2	5	3	21
Non-perseverative errors	2	0	1	4	1	7	6	21

According to typical scores. Source: Daniels.²⁴

WCST: Wisconsin Card Sorting Test.

et al. (low scores on the EDSS and low number of lesions). We found that 33.33% had mild to moderate impairment in the area of flexibility according to the WCST test, which is especially observant of perseverative responses. In addition, more errors and a longer reaction time were observed on the Stroop dimension requiring inhibition and working memory; this was the only dimension to correlate with the total number of lesions and with those located in the frontal and occipital regions. However, we should note the correlation between the occipital region and the total number of lesions.

Some authors have found a correlation between total number of lesions (particularly those located in the frontal region) and WCST scores, and especially with perseverative responses on the test. Nevertheless, their analysis describes the WCST as an abstract and conceptual reasoning test, without mentioning flexibility.^{16,17,30–32} In addition, they suggest an association between demyelinating lesions and working memory only.¹⁸ We have no knowledge of any studies examining the relationship between demyelinating lesions in MS and basic EFs. Likewise, these kinds of studies may present certain limitations, especially with regard to their methods. For example, patient samples were heterogeneous, including 2 or more types of MS, in various studies.^{15,17,18,33} Also, some patients were in the active phase of the disease and undergoing different types of treatment.¹⁵ EDSS scores presented a wide range from 0 to 8.5 points.^{15,16,31,33} Some studies, including our own, did not include a control group.^{15,16,18,31}

While this study found no correlations, this may result from the methodological deficiencies mentioned above. Correlations do not seem to be consistent with the dimensions we assessed. We should also note that structural MRI, used to calculate the number of lesions in the study, does not always provide information about the anatomical pathology and functional profile of the lesions. It is also well known that MRI shows some types of impaired tissue as if it were normal. In addition, chronic active plaques extend through the cerebral parenchyma beyond the visible limits (which may determine deafferentation between several regions), while some demyelinating lesions become chronic and silent.^{34,35} As a consequence, a single MRI scan does not seem to offer a good enough picture to be used as a predictor of cognitive performance in MS.³⁶ Based on the above, demyelinating lesions cannot reliably be used as predictors of cognitive impairment.

While their effects on the patient's daily life may not be obvious, their impact is clearly detrimental. Since it is not

feasible to use the total number of lesions as the only predictor, a neuropsychological assessment seems recommendable in these stages of the disease. Completing such an assessment will promote use of cognitive training and the design of programmes to stimulate processes including basic EFs, flexibility, working memory, and inhibition.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to thank María Eugenia Mendoza González, professor and neuropsychologist at Universidad Nacional Autónoma de Nuevo León; Dr Gerardo Palacios-Saucedo, researcher at hospital no. 25, Instituto Mexicano del Seguro Social; and María de la Cruz Cortés Sobrino, professor at Universidad Autónoma de Yucatán, for her valuable comments and contributions to the drafting of this text.

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