

Cognitive status in patients with multiple sclerosis in Lanzarote

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Objectives: Cognitive impairment is a common feature in multiple sclerosis affecting ~43%–72% of patients, which involves cognitive functions such as memory, processing speed, attention, and executive function. The aim of this study was to describe the extent and pattern of the involvement of cognitive impairment and psychological status in all patients with multiple sclerosis on a small Spanish island.

Patients and methods: In all, 70 patients and 56 healthy controls were included in the study between February 2013 and May 2013. All participants were assessed using the Brief Repeatable Battery of Neuropsychological Test. The patients also completed instruments to evaluate the presence of fatigue, perceived cognitive dysfunction, and symptoms of anxiety and depression. All procedures were performed in a single session.

Results: Cognitive impairment, defined as a score <1.5 standard deviation on two subtests of the battery, was present in 35% of the participants. The most frequently affected domain was working memory, followed by verbal memory and processing speed. Disease duration showed a moderate correlation with visuospatial memory and processing speed. The Expanded Disability Status Scale score correlated with verbal and processing speed. Verbal memory was correlated with depression symptoms and fatigue.

Conclusion: Cognitive impairment was present in 35% of the study population. The most affected domains were working memory and verbal memory. Working memory and verbal fluency deficit are independent factors of disease evolution. Cognitive decline is related to clinical variables and psychological measures such as fatigue or depression but not to anxiety.

Keywords: cognitive status, cognitive impairment, Lanzarote, multiple sclerosis

Introduction

Neurodegenerative conditions, such as dementia, multiple sclerosis (MS), Parkinson's disease, and Huntington's disease, are often characterized by significant neuropsychological deficits that interfere significantly with patient's abilities and quality of life.^{1–4}

Cognitive impairment is a common feature in MS affecting ~43%–72% of patients^{5,6} and is characterized as other signs and symptoms of the disease by variability and heterogeneity. However, dementia is rare, and the more common clinical presentation is one of the specific and subtle cognitive deficits.⁷

The most frequently affected cognitive functions are attention, speed of information processing, memory, executive functions, and visuospatial abilities,⁸ although new domains such as theory of mind have also been identified.⁹ Involvement of cognitive functions such as language, praxis, and gnosis is rare and less well studied.

The influence of the duration of the illness on cognitive functioning is still a matter of controversy. As regards clinical presentation, the progressive forms of MS

(both secondary progressive MS and primary progressive MS) are more involved in both degree and altered domains as compared to relapsing-remitting multiple sclerosis (RRMS).^{10,11}

Some authors point out that impairments are almost invariably a complication of the later stages of the disease when there is axonal loss with the involvement of large areas of white matter, disconnection between several cortical areas of association, and disconnection between cortical and subcortical areas, but impaired cognitive function appears to be present even in the early stages of the disease. Studies with long-term follow-up indicate that cognitive function decreases as the disease progresses.^{12,13} The degree of neurological impairment is shown as a predictor of cognitive decline in the follow-up studies.¹⁴

In the case of fatigue, this can interfere negatively, especially in tasks that require sustained mental effort such as working memory tests or sustained attention.¹⁵

Neuropsychological dysfunction severely affects the patients' lives¹⁶ in terms of their ability to keep their jobs,¹⁷ and they require greater assistance with daily living activities. Cognitively compromised patients are also more likely to have problems with socialization than cognitively intact MS patients.¹⁸ Cognitive impairment has been associated with nonsomatic symptoms of depression in RRMS, and this finding supports the importance of evaluating depressive symptoms when cognitive impairment is suspected in patients with RRMS.¹⁹ Anxiety has been less studied than depression in MS patients, although there is evidence that high levels of anxiety are associated with poor performance in cognitive tasks, especially processing speed, working memory, and visual-spatial memory.^{20,21}

This study was conducted in Lanzarote, the easternmost landmass of the Canary Islands, Spain (Figure 1). The only study of the prevalence of MS on this island was published in 1980s, which reported a low prevalence of 15/100,000.²² The population of the island at that time was 60,000 inhabitants, and the authors concluded that the rate was higher than expected because of the geographical situation of the island. More recently, a study presented at the LXV Annual Meeting of the Spanish Society of Neurology identified a total of 70 patients with MS on the island. This figure gives a prevalence of 49/100,000.²³

Other epidemiological studies conducted in the region have found that the Canary Islands is a medium-to-high risk area like Spain and other Mediterranean countries.^{24,25} Thus, the Canary Islands, despite being closer to the equator, are still a medium risk area.

The aim of this study was to describe the extent and pattern of the involvement of cognitive impairment and the psychological status in all patients of a MS cohort. A study of the full MS population, which rules out a possible selection bias, should provide a more comprehensive view of the cognitive impairment spectrum in MS.

Patients and methods

The study protocol was approved by the Ethics Committee for Clinical Research of the University Hospital of the Canary Islands and the Medical Director of Hospital Doctor José Molina Orosa. The study was conducted in accordance with the Declaration of Helsinki.²⁶ All patients signed written informed consent. The study was performed between February and May 2013.

Participants

Seventy patients with MS or clinically isolated syndrome (CIS) treated at the Doctor José Molina Orosa Hospital in

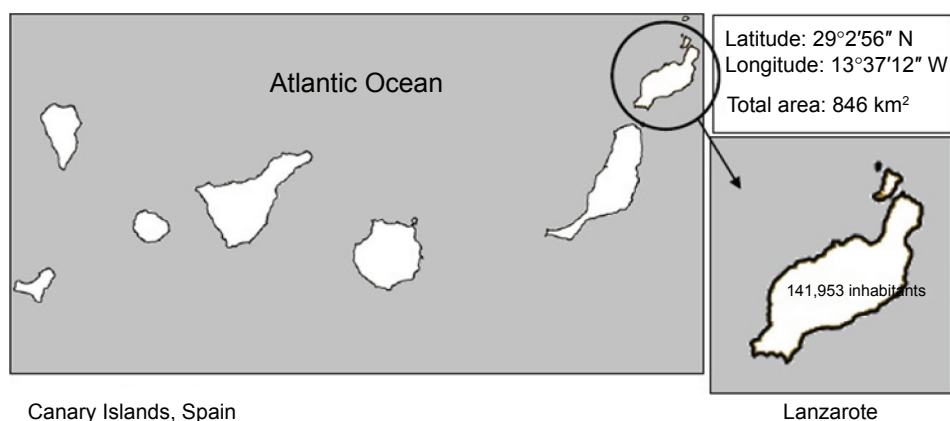


Figure 1 Study area.

Abbreviations: N, north; W, west.

Lanzarote (the hospital sees all the MS or CIS patients on the island) and 56 healthy controls (HCs) matched by sex, age, and schooling were included in the study.

The inclusion criteria for the patients were as follows:

- willing and able to sign written informed consent;
- MS diagnosed according to the McDonald criteria 2005²⁷ or CIS; and
- neurologically stable MS (with no evidence of relapse or steroids treatment in the last 4 weeks preceding the enrollment).

The inclusion criterion for the control group (CG) was willing and able to sign the written informed consent.

The exclusion criteria for the CG were as follows:

- no history of psychiatric or neurological disorders and
- no history of drug abuse or any major medical illness.

Six patients did not participate in the study: three patients were not on the island at the time, one patient could not attend due to severe physical disability, and two patients refused to participate in the study.

Measurement instruments

The Spanish version of the Brief Repeatable Battery of Neuropsychological Test (BRB-N)⁶ is used to assess the cognitive status of all the participants. The BRB-N includes the following tests:

- Selective Reminding Test (SRT)²⁸ as a measure of verbal learning and delayed recall. This test gives three different scores: SRT-Long-Term Storage (SRT-LTS), SRT-Consistent Long-Term Retrieval (SRT-CLTR), and SRT-Delayed (SRT-D).
- 10/36 Spatial Recall Test (SPART), an extended version of the original form the 7/24 SPART to assess visuospatial learning and delayed recall.²⁹ This test gives two scores: SPART-Total and SPART-Delayed (SPART-D).
- Symbol Digit Modalities Test (SDMT)³⁰ as a measure of complex attention and processing speed.
- Paced Auditory Serial Addition Test (PASAT)³¹ as a measure of sustained attention and working memory.
- Controlled Oral Word Association Test³² as a measure of verbal fluency.

The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ),³³ the Hospital Anxiety and Depression Scale,³⁴ and the Fatigue Severity Scale³⁵ were administered to the patients.

Procedure

All evaluations were performed by a neuropsychologist who was an expert in MS and familiar with the administration of

all tests. These tests were administered in a single session of ~1 hour.

A *z* score (direct score mean/standard deviation [SD]) was created for each cognitive domain according to standard practice to obtain a global cognitive-performance score. The different subtests were weighted by their *z* score to balance the tasks.

$$\text{Verbal memory} = \frac{z\text{-LTS} + z\text{-CLTR} + z\text{-SRT-D}}{3} \quad (1)$$

$$\text{Visuospatial memory} = \frac{z\text{-SPART total} + z\text{-SPART-D}}{2} \quad (2)$$

$$\text{Processing speed} = z\text{-total correct responses of SDMT} \quad (3)$$

$$\text{Working memory} = \frac{z\text{-total correct responses of PASAT 3''} + \text{PASAT 2''}}{2} \quad (4)$$

$$\text{Verbal fluency} = \frac{z\text{-semantic} + z\text{-phonetic total correct responses}}{2} \quad (5)$$

Finally, a global cognitive function score (*z*-Global) was obtained by calculating the mean of the *z* scores from the five cognitive domains.

Cognitive impairment definition

Different cognitive impairment criteria were used: <1.0 SD, <1.5 SD, and <2.0 SD (compared to the CG) in one, two, or three subtests of the battery, respectively.

Interviews were also conducted with family members about their level of functionality (food preparation, medication management, use of money, travel outside home) in the case of patients with suspected dementia.

Dementia was diagnosed following the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, text revised (*DSM-IV-TR*).³⁶

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean ± SD. Normality was tested using the Kolmogorov–Smirnov test. All the variables analyzed followed a normal distribution except PASAT 3'', and the scores were log transformed before analysis of covariance.

Table 1 Clinical and demographic characteristics of both HC and MS patients

	HC (n=56)	MS patients (n=60)	P-value
Sex (female), n (%)	40 (71.4)	36 (60)	0.19
Age (years)	42.1±9.38	43.9±11.54	0.36
Schooling (years)	11.2±2.87	11.5±3.10	0.93
Educational level, n (%)			
Primary	22 (39.3)	22 (36.7)	
Secondary	19 (33.9)	20 (33.4)	
University	15 (26.8)	18 (30.1)	
MS course, n (%)			
RR		49 (81.7)	
SP		5 (8.3)	
PP		4 (6.7)	
CIS		2 (3.3)	
Disease duration (years)		13.5±10.9	
EDSS		2.4±2.13	

Note: Data presented as mean ± standard deviation unless otherwise stated.

Abbreviations: HC, healthy control; MS, multiple sclerosis; RR, relapsing remitting; SP, secondary progressive; PP, primary progressive; CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale.

Analysis of covariance was performed, including cognitive domains such as dependent variables and controlling for age and schooling.

Correlation between the cognitive domains and the patient's clinical variables and questionnaires were assessed using the Pearson's correlation test.

Statistical analysis was performed with SPSS v20.0 software (IBM Corporation, Armonk, NY, USA). *P*-values were corrected for multiple testing problem using the Bonferroni correction method (α/k : 0.05/6=0.008), considering *P*-values <0.008 as statistically significant.

Results

Four patients met the diagnostic criteria for dementia. These patients were excluded from the analysis.

Table 1 shows the clinical and demographical characteristics of HC (n=56) and patients (MS; n=60; both groups had similar distributions of sex, age, and schooling).

The patients scored less than controls, in the controlling for age and schooling, on all variables of the BRB-N except visuospatial memory (Table 2).

A high prevalence of cognitive impairment (75.0%) was obtained when using a lenient criterion (<1.0 SD in one subtest). The prevalence was 35.0% with a moderately stringent criterion (<1.5 SD in two subtests), and the prevalence was 16.6% when using the most stringent criterion of cognitive impairment (<2 SD in three tests; Table 3). These percentages include patients with dementia.

The most frequently affected domain was working memory with an impairment in 43.8% of the patients (28 patients), followed by verbal memory in 21.7% (13 patients), processing speed in 15.0% (nine patients), verbal fluency in 13.3% (eight patients), and finally, visuospatial memory in 11.7% (seven patients). Nine patients had a lower global impairment index.

When clinical variables were analyzed, disease duration had a moderate correlation with visuospatial memory and processing speed ($r=-0.400$ and $r=-0.370$, $P<0.008$). The Expanded Disability Status Scale (EDSS) score showed correlations with verbal memory, processing speed, and global cognitive index ($r=-0.344$ to -0.395 , $P<0.008$; Table 4).

The questionnaire scores are listed in Table 5. Symptoms of anxiety were present in 18.3% of patients, and depression symptoms were present in 33.3% of patients. Fatigue (scores >4.1) was present in 22 patients. MSNQ score and anxiety symptoms were not associated with performance in any of the cognitive domains. Verbal memory correlated with

Table 2 Cognitive measures of both HC and MS patients (controlling by age and schooling)

	HC (n=56)	K-S (P-value)	MS patients (n=60)	K-S (P-value)	F	P-value
SRT						
LTS	43.6±15.48	0.49	32.1±16.43	0.98	15.69	<0.001
CLTR	35.6±17.00	0.98	24.8±16.98	0.77	11.27	0.001
SRT-D	8.8±2.91	0.11	5.9±2.97	0.28	31.69	<0.001
10/36 SPART						
SPART-Total	21.1±4.83	0.31	20.3±5.87	0.61	0.22	0.64
SPART-D	7.3±2.18	0.17	7.5±2.38	0.06	0.53	0.46
SDMT	52.4±13.51	0.27	46.6±14.74	0.68	5.02	0.02
PASAT						
PASAT 3"-correct	40.5±14.09	0.40 ^a	29.2±17.56	0.24	14.50	<0.001
COWAT	36.2±11.15	0.08	31.7±11.18	0.62	4.47	0.03
Semantic fluency (animals)	21.8±4.45	0.22	19.4±5.16	0.52	6.78	0.01

Notes: Data are expressed as mean ± standard deviation. ^aPASAT 3"-correct scores were log transformed before ANCOVA analysis.

Abbreviations: HC, healthy control; MS, multiple sclerosis; K-S, Kolmogorov-Smirnov test; SRT, Selective Reminding Test; LTS, Long-Term Storage; CLTR, Consistent Long-Term Retrieval; SRT-D, SRT-Delayed; SPART, Spatial Recall Test; SPART-D, SPART-Delayed; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; COWAT, Controlled Oral Word Association Test; ANCOVA, analysis of covariance.

Table 3 BRB-N results in patients according to different strength criteria

MS patients (n=60)	Criteria		
	≤1.0 SD	≤1.5 SD	≤2.0 SD
Abnormal subtest, n (%)			
≥1 subtest	45 (75.0)	39 (65.0)	36 (60.0)
≥2 subtest	30 (50.0)	21 (35.0)	12 (20.0)
≥3 subtest	23 (38.3)	11 (18.3)	10 (16.6)

Abbreviations: BRB-N, Brief Repeatable Battery of Neuropsychological Test; MS, multiple sclerosis; SD, standard deviation.

symptoms of depression ($r=-0.415$, $P=0.001$) and fatigue ($r=-0.383$, $P=0.003$).

MSNQ correlated with depression ($r=-0.405$, $P=0.001$) and anxiety ($r=-0.255$, $P=0.049$).

Discussion

The aim of this study was to describe the extent and pattern of cognitive impairment in all the population affected by MS on a small island located in the southwest of Europe. Lanzarote is an interesting place for MS study because its geographical location confers a high exposure to UV radiation for most of the year and patients probably have an optimal vitamin D serum level. Low vitamin D status is a possible environmental risk factor for MS development and outcome.^{37,38}

Table 4 Correlations between cognitive domains, clinical variables, and questionnaire results

	VM	VSM	PS	WM	VF	GCS
Disease duration						
<i>r</i>	-0.210	-0.400	-0.370	-0.074	-0.312	-0.330
<i>P</i>	0.114	0.002*	0.005*	0.579	0.017*	0.012*
EDSS score						
<i>r</i>	-0.344	-0.296	-0.395	-0.151	-0.262	-0.355
<i>P</i>	0.008*	0.023*	0.002*	0.253	0.045*	0.006*
Anxiety score						
<i>r</i>	-0.062	0.066	0.086	-0.004	0.193	0.061
<i>P</i>	0.642	0.617	0.520	0.976	0.142	0.650
Depression score						
<i>r</i>	-0.415	-0.217	-0.256	-0.129	-0.113	-0.279
<i>P</i>	<0.001*	0.100	0.053	0.328	0.392	0.034*
MSNQ						
<i>r</i>	-0.236	-0.097	-0.068	-0.105	0.035	-0.130
<i>P</i>	0.072	0.466	0.613	0.431	0.793	0.331
Fatigue						
<i>r</i>	-0.383	-0.110	-0.239	-0.245	-0.068	-0.272
<i>P</i>	0.003*	0.408	0.071	0.062	0.609	0.039*

Note: *Significant *P*-value corrected for multiple testing using the Bonferroni correction method (α/k : 0.05/6=0.008).

Abbreviations: VM, verbal memory; VSM, visuospatial memory; PS, processing speed; WM, working memory; VF, verbal fluency; GCS, global cognitive score; EDSS, Expanded Disability Status Scale; MSNQ, Multiple Sclerosis Neuropsychological Questionnaire.

Table 5 Questionnaires results

	MS patients (n=60)
MSNQ	15.4±10.23 (0–47)
FSS	3.4±1.82 (1–10)
HADS	
Anxiety	4.7±3.21 (0–14)
Depression	4.8±3.81 (0–16)

Note: Results are expressed as mean ± SD (min–max).

Abbreviations: MS, multiple sclerosis; MSNQ, Multiple Sclerosis Neuropsychological Questionnaire; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; min, minimum; max, maximum.

Severe cognitive impairment, with clear criteria for dementia (*DSM-IV-TR*), was found in four patients in the study sample (6.3% of the total). All these four patients had an obvious neuropsychological deficit, and they were unable to perform all the selected tests. Interviews with family members revealed significant functional impairment with an impact on activities of daily living. The mean age of the dementia patients was 71 years (60–78 years), and they obtained an EDSS score between 6.0 and 8.0 as well as had progressive forms of the disease.

The remaining nondementia patients formed a population with a low–moderate degree of disability (<3.0 on the EDSS), and most patients had an RRMS.

The patient group underperformed the (demographically equivalent) CG in most of the battery tests after controlling the results for age and schooling, suggesting an overall performance deficit.

The range of variability observed in the prevalence of cognitive impairment is possibly associated with the methodological differences between the studies such as the study design and setting, as well as the neuropsychological tests selected for the study. However, the biggest difference could be due to the consideration of the concept of cognitive impairment. For example, a performance <1.0 SD in one subtest may reflect the fluctuant nature of the disease and does not necessarily reflect the real pattern of cognitive impairment. The concept of cognitive impairment proposed by Amato et al¹² as a failure in two or more BRB-N subtests with scores at least 1.5 SD below the scores of HC is suggested for use here.

Using the aforementioned criterion for defining abnormality showed that 35.5% of the patients had impairment. Similar figures were found by Nogales-Gaete et al³⁹ with a sample of Chilean patients with RRMS, but the finding here differs from other studies conducted in Oslo (Norway) and the UK and from another study in Spanish speaking patients in Argentina,⁴⁰ where the prevalence of cognitive impairment was >45%.

The pattern of involvement found suggests that working memory and verbal memory are the most affected areas. Physical disability has been associated with cognitive impairment in some studies,^{6,14} while others found no such association.⁴¹ In the present work, a negative correlation between EDSS score and verbal memory, processing speed, and a global cognitive index was found. The association was strongest for processing speed. These data could indicate that deficit in processing speed might be a good predictor of disease progression and, therefore, constitutes a key deficit in time monitoring. However, the involvement of other domains such as working memory or verbal fluency could start in any stage of the disease and does not evolve in parallel with other symptoms of this disease.

MSNQ-Self report (as opposed to MSNQ-Informant report) is not considered a sensitive screen for neuropsychological impairment in MS, and indeed, no correlation with this test was found here, suggesting that it is not an effective screening method for detecting cognitive impairment.

Depressive symptoms were less (present in 33.3% of the sample) than those found in the literature,⁴² and higher scores on the depression scale were correlated with poorer performance in verbal memory. This finding has been associated with the mineralocorticoid expression in the brain that diminishes during depression, especially in the hippocampus and the prefrontal cortex, which are critical brain areas for memory.⁴³ Anxiety (present in 18.3% of patients) was not associated with cognitive performance.

Fatigue was present in 36.7% of the sample and only correlated with verbal memory. This confirms findings of another study that has linked cognitive functioning with the state of fatigue in patients with MS⁴⁴ and more specifically with memory.⁴⁵

As a limitation of the study, the use of a more extensive evaluation protocol could provide more information about the true neuropsychological profile of studied patients.

Conclusion

At least 35% of the study population had mild-to-moderate cognitive impairment relative to a control sample. The results of this study confirm the high prevalence of cognitive impairment in an MS cohort. The most affected domains were working memory and verbal memory. Working memory, verbal memory, and verbal fluency did not deteriorate as the disease progressed, and therefore could not be used as a means of monitoring it. Cognitive decline was frequently related to clinical variables (disease duration and EDSS score). Verbal memory was associated with depression

and fatigue, but none of the cognitive domains showed a strong correlation with anxiety and subjective perception of cognitive impairment.

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Disclosure

The authors report no conflicts of interest in this work.

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