GENERAL AND NEUROPSYCHOLOGICAL CHARACTERISTICS IN THE ASSESSMENT AND INTERVENTION OF MULTIPLE SCLEROSIS

CARACTERÍSTICAS GENERALES Y NEUROPSICOLÓGICAS EN LA EVALUACIÓN E INTERVENCIÓN DE LA ESCLEROSIS MÚLTIPLE

Diana Alejandra Delgado Anguiano. dianaalejandradelgado@psicología.unam.mx. Universidad Nacional Autónoma, México. ORCID: https://orcid.org/0009-0004-7107-2148
Kevin Fernando Gervacio Flores. fernandogervacio94@hotmail.com. Universidad Nacional Autónoma, México. ORCID: https://orcid.org/0009-0007-8402-5780
Gabriela Orozco Calderón. gabrielaorozco@psicología.unam.mx. Universidad Nacional Autónoma, México. ORCID: https://orcid.org/0000-0002-4978-1667

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ABSTRACT

The description of the general characteristics of Multiple Sclerosis (MS), its comorbidity, predictors of development, findings from neuropsychological assessment and intervention, and psychosocial factors that can affect the course of this condition was the objective of this research, since in recent decades there has been an increase in the global prevalence of the disease. Methods such as historical-logical and analysis-synthesis, among others, were used in the study. It is evident that with pharmacological and rehabilitation options, the frequency and severity of relapses can be reduced, and patients' quality of life can be improved.

KEYWORDS: multiple sclerosis; findings; evaluation; neuropsychology

RESUMEN

La descripción de las características generales de la Esclerosis Múltiple (EM), su comorbilidad, predictores de desarrollo, hallazgos de evaluación e intervención neuropsicológicos y factores psicosociales que pueden afectar el curso de este padecimiento, constituyó el objetivo de la presente investigación, pues en las últimas décadas, se produjo un aumento en la prevalencia mundial de la enfermedad. En el estudio fueron utilizados métodos tales como el histórico-lógico, análisis-síntesis, entre otros. Se evidencia que con opciones farmacológicas y de rehabilitación se pueden reducir la frecuencia y gravedad de los brotes y mejorar la calidad de vida de los pacientes.

PALABRAS CLAVE: esclerosis múltiple; hallazgos; evaluación; neuropsicología

INTRODUCTION

Multiple Sclerosis (hereinafter MS) is an inflammatory and degenerative disease of the central nervous system that primarily affects the young adult population. It is an autoimmune, demyelinating neurological disorder that has a wide range of signs and symptoms; including physical symptoms, such as motor, visual, and sensory alterations, as well as symptoms related to cognitive and emotional processes.

It is considered a chronic multifocal inflammatory demyelinating disease associated with neurodegeneration. It is mediated by an abnormal autoimmune response in genetically predisposed individuals, upon whom various environmental factors may influence the development and progression of the disease. Genetic predisposition is primarily mediated by the major histocompatibility complex; among the studied risk factors, those with the strongest evidence include association with Epstein-Barr virus infection, smoking, low levels of vitamin D, and a high body mass index during adolescence.

Some of these factors, such as vitamin D levels and smoking, can influence the course of MS. More than 80% of the costs caused by multiple sclerosis are related to disability rather than therapies.

All these processes occur from the early stages of the disease and lead to a progressive accumulation of disability. MS is a chronic demyelinating disease of the Central Nervous System (hereinafter CNS), with a multifactorial and complex etiology involving a series of interactions between genetics and the environment (Bravo & Álvarez, 2019; Correa et al., 2018; Cuevas, Segura & Herrera, 2018; Custodio, Montesinos & López, 2018; Margarit, et al., 2019). The epidemiology of Multiple Sclerosis is heterogeneous worldwide, with the highest prevalence in Europe and North America, while being low or intermediate in Latin American countries. In Spain, the disease prevalence is 47,000 people (Pérez, Fernández & Sempere, 2019).

Recent data from systematic reviews, longitudinal studies, and national or regional registries indicate an increase in the global prevalence of the disease in recent decades. This growth seems partly justified by improvements in healthcare or the wide availability of magnetic resonance imaging tests, and there is data suggesting a real increase in disease prevalence. The highest prevalence in the world have been documented in regions traditionally considered at high risk for MS, such as southern Canada, the northern United States, the British Isles, and Scandinavia (Pérez, Fernández & Sempere, 2019).

The presence of this disease is higher in cities, such as Quito and Cuenca where there is a smaller indigenous population and higher white and mestizo populations, suggesting the influence of European ancestry. It affects genetically predisposed individuals in whom an environmental factor triggers an abnormal immune response (Bravo & Álvarez, 2019).

In summary, epidemiological data point out that MS has a heterogeneous geographical distribution worldwide, with a global increase in its prevalence during recent decades, although its causes are not fully understood.

It affects genetically predisposed individuals, and it is believed that an environmental factor causes an abnormal immune response (Custodio, Montesinos & López, 2018; Margarit, et al., 2019). It is supposed that the interaction of different genetic susceptibility factors and various environmental factors causes an abnormal activation of the immune system against self-antigens of the CNS. Autoreactive T cells, likely CD4, Th1 and Th17 T cells, are activated in the periphery by a systemic or local trigger that go through the blood-brain barrier, and reach the CNS. There, they are reactivated by antigen-presenting cells, causing the production of different proinflammatory mediators and chemokines originating massive cell recruitment, increasing the initial inflammatory response (González, 2018).

Efforts have been made to identify the environmental factors involved in this entity, with disagreements regarding the findings. A North-South gradient in MS prevalence in the Northern Hemisphere, and a South-North gradient in the Southern Hemisphere, strongly suggests a latitude effect on this condition, maybe related to solar radiation incidence in these regions. Although a specific environmental factor as a single cause has not yet been identified, it is believed that a combination of genetic and environmental factors can trigger this autoimmune disease (González, 2018).

Geographical and climatic factors sit an advantaged position among possible disease causes. Variables, such as altitude, latitude, room temperature, ultraviolet radiation exposure, and soil composition have been postulated as risk factors (Margarit, et al., 2019). In particular, it has been showed that people living in cold, high-latitude environments have a higher risk of developing MS; this is due to the interaction between genetic and environmental variables. Also, the geographical risk factor would be acquired up to 15 years old, meaning eventual migration after that moment would not reduce the risk to match that of the new geophysical environment (González, 2018).

Other authors suggest that respiratory tract infections and nutritional habits can reduce the effect of geographical conditions. Areas have been observed where the disease prevalence is significantly lower than theoretically predictable, which could be due to vitamin D, obtained through food, and prior history of infectious diseases (Margarit, et al., 2019).

Although the exact environmental factors that cause Multiple Sclerosis are not known with certainty, there is evidence suggesting that geography, temperature, and nutritional habits can influence its origin. Therefore, it is important to continue research in this area to prevent and treat the disease.

RESULTS AND DISCUSSION

MS is characterized by the formation of plaques (lesions) in the CNS accompanied by inflammation, demyelination, axonal damage, and axonal loss. It is an autoimmune disease caused by autoreactive immune cells that go through the blood-brain barrier and attack the CNS. Plaques are located in the brain and spinal cord, primarily affecting the white substance surrounding the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts, midbrain, and gray substance.

These plaques are expressed in all forms of MS (primary, secondary, recurrent-remitting); however, expression is heterogeneous over time in the immunohistopathological patterns of demyelination and oligodendrocyte degeneration between the recurrent-remitting course and progressive forms (Dighriri et al., 2023). Relapsing MS is characterized by acute inflammatory activity associated with disruption of the blood-brain barrier, evidenced by lesions. Acute lesions begin with infiltrates of B, T inflammatory cells, plasma cells, and macrophages surrounding central veins. Additionally, there is demyelination, axonal, and neuronal damage in acute lesions.

On the other hand, MS progressive forms may involve intrinsic autoimmune processes in the CNS, after a so-called intact blood-brain barrier. Active lesions can occur in progressive types, but studies reveal the presence of slowly expanding, inactive plaques, remyelinated shadow plaques, and more abundant cortical lesions. Other mechanisms related to degeneration include chronic microglial activation, mitochondrial injury, and meningeal inflammation. Spinal cord injury is more frequent in progressive types, combined with spinal cord gray substance atrophy, correlating with the severity of disability in progressive Multiple Sclerosis.

While recurrent-remitting MS and progressive MS are characterized by distinct clinical phenotypes, research shows that inflammatory and degenerative processes are in parallel across disease subtypes. The diagnosis of Multiple Sclerosis is made using the modified McDonald criteria from 2010, which unify clinical and radiological findings. These criteria are the most widely accepted worldwide for diagnosing multiple sclerosis. For the recurrent-remitting subtype, clinical evidence of at least an attack and magnetic resonance images (MRI) lesions with dissemination in space and time are required. For the progressive subtype, sustained neurological deterioration for at least one year is additionally required. Sensitivity and specificity have been estimated at 84% and 80%, respectively, in a South American population (Correa et al., 2018).

In patients with a first acute or subacute episode with neurological clinical symptoms suggestive of inflammatory demyelinating disorders, with magnetic resonance images (MRI) also suggestive of demyelinating lesions, it is a clinically isolated syndrome (CIS). This syndrome can be an early manifestation of Multiple Sclerosis (Correa et al., 2018).

It is important to note that it is not common for multiple sclerosis to have a progressive course, but it occurs in about 10% of cases. Therefore, early diagnosis is essential to initiate appropriate treatment and avoid future complications (Correa et al., 2018). The Multiple Sclerosis treatment is complex and must take into account whether the patient is in a relapse and disease

modification. Treatment can be disease-modifying or symptomatic; additionally, there is the option of prescribing non-pharmacological treatment, such as rehabilitation. In cases of very severe relapses, administration of methylprednisolone 1 g IV/day for three to five days is recommended depending on the severity of the relapse. Plasmapheresis or immunoglobulin may also be required (Aguilar et al., 2019).

Evidence has shown the importance of early treatment. Disease-modifying treatments include interferon beta 1a, intramuscular interferon beta 1a, interferon beta 1b, glatiramer acetate, natalizumab, fingolimod, newly reformulated interferon beta 1a, and teriflunomide in 2018 (Aguilar et al., 2019).

The presence of comorbid diseases is a critical problem for healthcare professionals due to the adverse impacts associated with them. Comorbidity is associated with a delay between symptom onset and diagnosis, more severe disability at diagnosis, greater disability progression, need for healthcare, and mortality (Marrie, 2016). Up to 50% of patients may have at least a comorbid condition. Hypertension, depression, and anxiety are the main comorbid diseases in the MS population. Fatigue and loss of quality of life are closely related to patient comorbidity (Diržiuvienė & Mickevičienė, 2022), with lower quality of life and long-term disability.

Depression, anxiety, cardiovascular disease, epilepsy, metabolic disease, and autoimmune diseases are the most common. Diabetes, hypertension, and hyperlipidemia increase sedentary behavior, lower levels of physical activity, weight gain, obesity, and poorer general health. Psychiatric comorbidities are a concern in MS as they are associated with fatigue and lower quality of life, impacting treatment adherence. Mood dysfunction (depression, anxiety, bipolar disorder) is common in MS.

Some studies indicate that an inflammatory component involving inflammatory cytokines (interferon gamma and tumor necrosis factor alpha) is associated with mood disorders. Another common comorbidity is epilepsy, which is more

prevalent in the MS population than in the general population. Among other common comorbidities are migraine, fibromyalgia, ocular and olfactory comorbidities, autoimmune diseases, cancer, and pulmonary diseases (Hauer, Perneczky & Sellner, 2021).

To study the MS progression, the terms benign and malignant are often used; however, they are not a classification standard, but severity indicators along the time. The term benign refers to few relapses and absence or reduced disability after 20 evolution years, while the term malignant refers to disabling attacks with incomplete recovery, resulting in rapid disability progression. The «Expanded Disability Status Scale» is proposed to assess the neurological condition of a patient with MS. This has disability level indicators, progression index, and disease duration (Pinto et al., 2020).

Being female, with a family history of MS, parenchymal brain fraction, early onset, optic neuritis, and sensory symptoms are associated with a favorable course, while those with pyramidal involvement, higher T2 lesion volume on neuroimaging, are characteristics for worse progression (Pinto et al., 2020).

Cognitive predictors are required in MS; previously, cognitive impairment was used as an indicator of progression, but currently the approach is to assess multiple cognitive domains, such as attention, executive function, verbal fluency, and information processing speed. It is also proposed to assess the presence of depression and anxiety in these patients. Assessing and monitoring motor and cognitive symptoms in parallel is crucial to providing correct treatment.

Annual screenings are proposed for those primarily with subjective cognitive complaints. Disease duration, progressive phenotypes, adult, lower education (associated with lower cognitive reserve) are well-known predictive factors of physical and cognitive decline over time (Virgilio et al., 2023).

Neuropsychological findings

Cognitive impairment (CI) is common in patients with MS, with a prevalence between 34% and 65%, depending on multiple factors, such as disease duration and onset age (Cortese et al., 2021). CI can progress gradually, insidiously, or abruptly during relapses. Isolated cognitive relapses with purely cognitive involvement have already been described. The CI frequency and severity tend to increase over time and become more pronounced in progressive courses (Portaccio & Amato, 2022).

The main marker of cognitive alteration in imaging is atrophy of the retinal nerve fiber layer (RNFL), associated with brain atrophy; this, along with inflammatory markers as oligoclonal bands and cerebrospinal fluid, were related to cognitive decline. On the other hand, the brain-derived neurotrophic factor Val66Met may play a protective role against cognitive alteration. Thalamic atrophy may also represent an ideal biomarker for studying neuroprotective strategies or restorative therapies for cognition (Cortese et al., 2021).

It is still unknown what mechanisms contribute to the conversion from preserved cognition or mild or severe cognitive impairment and who is at risk. Damage to gray and white matter correlates with cognitive impairment. The main cause of these deficits is thought to reside in dysfunction of a functional neural network, the DMN (default-mode network). This is normally suppressed during cognitive tasks, but in MS, it becomes stuck in a hyperconnected state and it is not suppressed efficiently.

The most affected domains in MS are processing speed, complex attention, working memory, visuospatial ability, and executive functions with a predominance of dysexecutive disorders in progressive forms and an amnestic profile in recurrent-remitting MS. The presence of cognitive impairment at diagnosis is considered a marker of a worse prognosis. If there are difficulties in verbal memory and processing speed in the early stages, it is predictive of greater long-term disability (Meca et al., 2021).

Recently, five phenotypes of cognitive functioning have been identified through latent profile analysis: preserved cognition, mild involvement of verbal memory and semantic fluency, mild multidomain impairment, severe executive-attentional impairment, and severe multidomain impairment. General intelligence and language, preserved in adults, may be altered in pediatric onset (under 18 years old). On the other hand, as it was already mentioned, those with late onset (50 years old or older) have alterations in memory, verbal fluency, and visual learning (Portaccio & Amato, 2022).

Cognitive deficits are associated with a greater lesion burden. The location of lesions in white substance, microstructural injury, gray substance lesions, cortical and subcortical gray substance atrophy, and discrepant patterns of brain activation are important for their contribution to cognitive impairment. Longitudinal studies have been related to risk of CI, including brain atrophy, microstructural damage, and cortical lesions (Sumowski et al., 2018).

MS can have a significant impact on patients' quality of life. In addition to physical symptoms, the disease can also impact patients' mental and emotional health. Therefore, it is important to understand the psychosocial factors associated with MS (Mateu, 2018). Psychosocial factors are those related to the individual's social and psychological environment. In the case of MS, these factors may include clinical and sociodemographic variables, such as age, sex, symptoms associated with the disease, tobacco use, and exposure to stressful situations. Personality characteristics, such as neuroticism and extraversion that can modulate the response to this disease are also analyzed (Mateu, 2018).

Several psychosocial factors related to MS have been analyzed; clinical and sociodemographic variables include age, sex, tobacco use, and exposure to stressful situations. Age is an important factor in the MS development. Most people are diagnosed between 20 and 40 years old.

Symptoms associated with the disease can also impact psychosocial factors. Symptoms may include fatigue, muscle weakness, balance and coordination problems, vision and cognitive problems. These symptoms can affect the patient's quality of life and his ability to perform daily activities (Mateu, 2018).

Particularly, the evidence addresses case and group studies with consistent results primarily in attentional domains, processing speed, and executive functions. For example, Achiron et al., (2005) conducted a longitudinal study in patients with recurrent-remitting MS to verify that cognitive alteration is actually progressive. Patients were divided into 2 groups: short-term group (duration <5 years) and long-term group (>5 years). Annual neuropsychological assessments were performed.

After five years from disease onset, patient performance on cognitive tests decreased by 10% (visual learning, sustained attention, working memory, and processing speed).

Language skills and retrospective memory were already impaired in the first 5 years after diagnosis and did not show progression. Cognitive Impairment was reported in patients (53.7%) at an early stage of motor symptom onset. It is an integral part of the disease and should be thoroughly assessed from diagnosis (Achiron et al., 2005).

Neurorehabilitation is crucial in the MS treatment. Neuroplasticity has been documented in patients with MS, influencing a variety of functions such as memory, cognition, and motor function. Following rehabilitation programs, resting-state MRI revealed improvement in brain synchronization patterns and cognitive performance, involving areas in the right medial orbitofrontal gyrus and the medial visual circuit of the cerebellar region, which agrees with clinically observed improvements.

Within cognitive rehabilitation, it is recommended to include psychological therapy, cognitive reassessment, cognitive enhancement, and stress management. Nowadays, cognitive rehabilitation can benefit from technological tools, retraining residual neurological capacity through cognitive models (Sîrbu et al., 2022).

Benedict et al., (2020) reveal three case reports. The first is a 15-year-old girl, she is a ninth grade and when she was 13 years old, she was diagnosed with MS. Initial symptoms were dysesthesias in the region of the right trigeminal nerve; 6 months later, psychiatric interview showed the patient had low self-esteem and difficulties in social integration. School performance was low; at that time, she did not present physical disability. When she was 13 years old, impairment was detected in processing speed, memory, and linguistic skills in the neuropsychological assessment. This case showed a dissociation between physical and cognitive alterations in a pediatric patient with MS, meaning cognitive alteration can occur in the absence of physical disability (Benedict et al., 2020).

The second case discusses a woman with 14 years of schooling diagnosed with primary progressive MS when she was 45 years old, presenting for cognitive assessment at 84 years old. Main neurological signs included bilateral weakness in lower limbs, balance impairment, and recurrent falls.

The neuropsychological assessment at 84 years old reflected impairment in visuospatial processing and memory; the assessment coincided with a dementia consultation, and the patient was diagnosed with amnestic mild cognitive impairment. At 85 years old, substantial deficits were found in memory, processing speed, episodic memory, and verbal fluency.

PET reflected increased focal uptake in right occipital gray matter. In the 5-year follow-up, there was brain volume loss (5%), a 25% increase in lateral ventricular volume, and a 10% decrease in hippocampal volume. This case

shows comorbidity between two alternative neurodegenerative disorders (Benedict et al., 2020).

Staff, Lucchinetti & Keegan (2009) also state a series of cases having early fulminant cognitive impairment. A 43-year-old man with no history of neurological disease developed subacute memory impairment, aphasia, and apraxia over a 2-week course. Gait and other neurological functions were normal. T2 MR showed consistent lesions with MS; cerebrospinal fluid showed oligoclonal bands. It was begun immediate treatment, but despite this, the patient continued with relapses and within 2 years developed dementia, coexisting with mild depression (Staff, Lucchinetti & Keegan, 2009).

Cognitive assessment

It is highlighted that up to 40-60% of patients with MS experience cognitive impairment, even in early stages of the disease. Neuropsychological assessment is important to establish a pattern of cognitive impairment and to implement a specific cognitive rehabilitation program for each patient. Cognitive impairment is influenced by different clinical and psychological variables (Hernández & Orozco, 2020).

Although there are some studies reporting contradictory results, neuropsychological assessment is considered clinically useful for early diagnosis in MS (Abreu et al., 2023).

Neuropsychological assessment is an important tool for developing the neuropsychological profile of the MS patient. A cognitive profile can be obtained through the use of standardized instruments, to determine which cognitive abilities are impaired or preserved, as well as possible emotional and behavioral alterations (Mamaladze, 2022).

In the specific case of patients with MS, the aim is to compensate or restore cognitive, emotional, and behavioral functions affected by the disease. To achieve this, preserved skills are activated, and attentional skills, memory,

processing speed, executive functions, and concentration are worked on (Abreu, et al., 2023). Neuropsychological assessment in patients with MS must be done by a professional specialized in this area. It is important for the professional to have specific knowledge about the disease and its neuropsychological implications to do a satisfactory assessment (Mamaladze, 2022).

Among the instruments used for neuropsychological assessment in patients with MS are: the Visual-Spatial Memory Test (TVMS), the Card Sorting Test (TCT), the Wisconsin Card Sorting Test (WCST), among others (Abreu, et al., 2023).

The most commonly used instruments for neuropsychological assessment in patients with MS are:

1. Visual-Spatial Memory Test (TVMS): This test assesses the patient's visual and spatial memory. It involves presenting the patient with a series of geometric figures he must remember and reproduce later.

2. Card Sorting Test (TCT): This test assesses the patient's ability to change his cognitive strategy in changing situations. It involves presenting the patient with a series of cards with different shapes and colors, which must be classified according to different criteria.

3. Wisconsin Card Sorting Test (WCST): This test assesses the patient's ability to change his cognitive strategy in changing situations and to inhibit automatic responses. It involves presenting the patient with a series of cards with different shapes and colors, which must be classified according to changing criteria throughout the test.

4. Stroop Test: This test assesses the patient's ability to inhibit automatic responses and control selective attention. It involves presenting the patient with words written in different colors, but whose meaning does not match the color they are written in.

5. Hospital Anxiety and Depression Scale (HADS): This scale assesses the patient's levels of anxiety and depression. It consists of a series of questions the patient must answer according to his emotional state.

The instruments chosen for assessing cognitive domains in the MS population must be performed considering the specific characteristics the disease may do in each patient; this will define the neuropsychological implications (Mamaladze, 2022). Similarly, it is relevant to understand that empathy plays an important role in the neuropsychologist's work, as MS can have a great emotional impact on patients and their families, so the professional must have skills to handle these situations and provide emotional support to patients; the most effective techniques have been shown to be behavioral therapies (Abreu, et al., 2023).

Although immunomodulatory medications are the main treatment for MS, they have not been shown to prevent the decline of cognitive impairment produced by the disease. Therefore, it is relevant to implement neuropsychological rehabilitation in patients with MS. Neuropsychological rehabilitation focuses on restoring cognitive functions and preventing cognitive impairment produced by the disease. To achieve this, the mechanism underlying the alteration must be identified, a neuropsychological diagnosis established, and a rehabilitation program developed to bring about positive changes in the patient's lifestyle. The use of cognitive strategies and techniques for rehabilitation focuses on recovering lost cognitive functions through specific exercises. Another strategy is compensation, which teaches the patient to use alternative strategies to perform tasks that were previously simple. Adaptation focuses on modifying the environment to enable daily tasks (Acosta, 2021).

Cognitive reserve is an essential guideline for neuropsychological diagnosis and intervention in patients with MS. Leisure cognitive activities in lifestyles are core indicators for approaching the cognitive reserve index and favoring neuroplastic capacities, as well as brain reorganization processes. The value of early intervention in MS, through a rehabilitation program, is a pathway to preserve brain functioning and prevent cognitive impairment produced by the disease

(Acosta, 2021). Neuropsychological rehabilitation is an important strategy to improve the quality of life of patients with MS. The aim is to restore cognitive functions and prevent cognitive impairment produced by the disease through different techniques and strategies. Also, it is emphasized the importance of cognitive reserve (Acosta, 2021).

CONCLUSIONS

The MS diagnosis is a challenge due to the variety of symptoms that may be shown, but advances in neuroimaging techniques and cerebrospinal fluid analysis have significantly improved its early detection. This disease treatment has also evolved in recent decades, with pharmacological and rehabilitation options that can reduce the frequency and severity of relapses and improve patients' quality of life. Neuropsychological assessment helps identify cognitive and emotional deficits in patients, while psychological interventions can improve their emotional well-being and adaptation to the disease. Physiotherapy and occupational therapy are also important for keeping or improving motor and functional skills.

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