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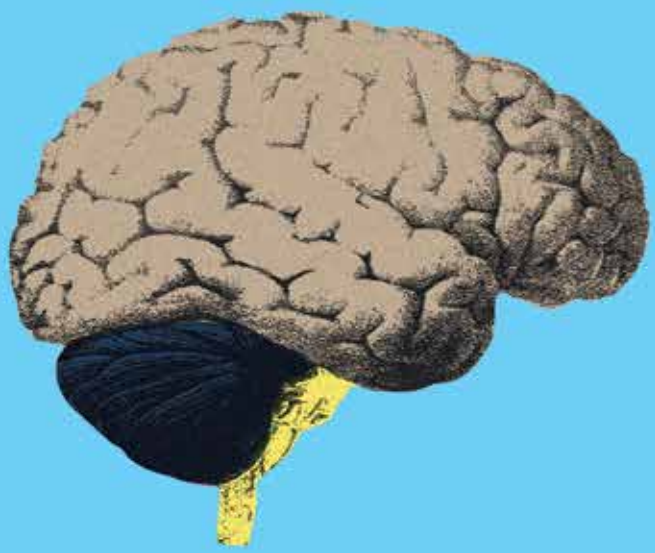

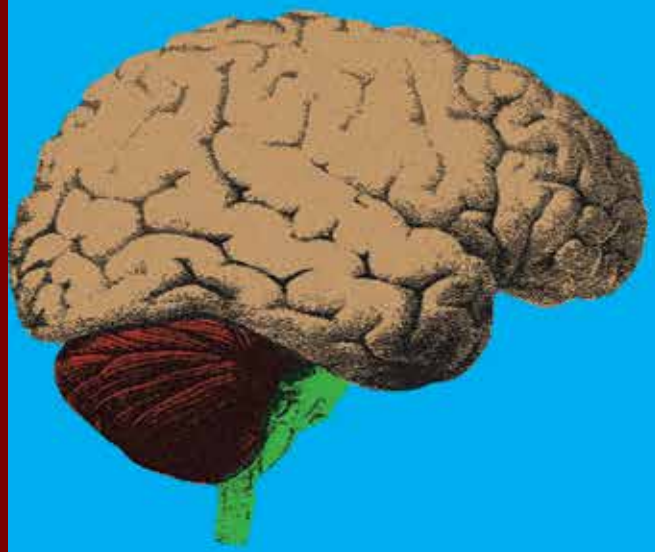

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Esclerosis múltiple en América Central y el Caribe: Estado actual y recomendaciones clínicas

Multiple Sclerosis in Central America and the Caribbean: Current Status and Care Recommendations

Resumen

Introducción: La esclerosis múltiple (EM) es una enfermedad altamente discapacitante y costosa. El manejo médico de la EM es complejo y en regiones y países donde existen sistemas de salud con escasos recursos y limitaciones para el acceso a salud el impacto en de la EM en la salud y la sociedad es alto.

Métodos: Para comprender de una forma más adecuada las situaciones particulares relacionadas al manejo de la EM en Centroamérica y el caribe, un grupo de expertos de la región y países aledañas se reunieron para valorar el estatus de la EM y emitir recomendaciones sobre su manejo a nivel clínico e institucional.

Resultados: Posterior a una extensa revisión de la literatura, el panel concluyó que se deben de reforzar las actividades de vigilancia epidemiología en cada país de la Región debido a que la EM en muchas ocasiones está infradiagnosticada o mal diagnosticada. Además, es importante fortalecer los programas de farmacovigilancia, mejorar los programas educativos para los clínicos, mejorar el acceso a la referencia a Neurología en las comunidades y el desarrollo de guías clínicas relevantes para la Región que estén en sintonía con las recomendaciones internacionales para el diagnóstico y manejo de la EM. Adicionalmente, la disponibilidad y uso apropiado de los medicamentos modificadores de la enfermedad aprobados localmente debe de mejorar con un abordaje basado en políticas públicas.

Conclusiones: Las sociedades médicas e instituciones deben de dedicar una mayor cantidad de recursos a la educación de profesionales de la salud y a la población general sobre los aspectos de la EM. Se recomienda dedicar una mayor cantidad de recursos para mejorar el acceso a medicamentos para la EM.

Palabras clave

Esclerosis Múltiple, tratamiento, Centroamérica, Caribe, recomendaciones

Abstract

Background: Multiple Sclerosis (MS) is a very serious, highly debilitating and costly disease. The medical management of MS is complex and in regions and countries with relatively limited health care systems and reduced financial resources, the impact of MS on individuals and society can be alarming.

Method: To better understand the issues related to MS management in Central America and the Caribbean, a group of experts from the Region and nearby countries were assembled to assess the status of MS and provide recommendations to government, organizations and practitioners.

Results: Based on an extensive review of the literature and their personal experiences, the Panel concluded that surveillance and epidemiology efforts within and between each country in Central America and the Caribbean needs substantial improvement and that MS is clearly mis- or undiagnosed to a great extent in the Region. Also, there is a need for comprehensive pharmacovigilance programs, better continuing education programs for clinicians and out-reach to communities, and the development of clinical guidelines relevant to the Region that stress the internationally accepted criteria to diagnosis MS, and its progression and treatment. In addition, the availability and appropriate use of approved medications, and more community-based, public-service programs focused on MS are also urgently needed.

Conclusions: Medical societies and government should devote more resources toward educating health professionals and the public on all aspects of MS, and government should provide and support all necessary and well-grounded treatments.

Keywords

Multiple Sclerosis, treatment, Central America, Caribbean, recommendations

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Practice points

1. It is mandatory to use the internationally established and accepted criteria to diagnosis MS. It is also important to initiate treatment at the earliest possible moment after diagnosis. Practitioners should be aware of the criteria for the identification of disease activity and progression.
2. MS patients should be referred to a local neurologist, and patient support groups or organizations focused on MS patients.
3. Patients with poor prognostic factors and aggressive MS should be evaluated for receiving higher potency anti-inflammatory agents, such as fingolimod, natalizumab or alemtuzumab at any time during the course of MS.

The goal of the Americas Health Foundation (AHF) is to improve the health of individuals living in the Americas. Since MS has such an adverse effect on health, the AHF sought to determine the status of MS management in Central America and the Caribbean, a Region in the Americas that has often been singled out for study and analysis. To gain a better understanding of the issues related to MS in this Region, the AHF assembled a group of MS experts to review published information and discuss the current state of MS management in the Region. Their deliberation resulted in this manuscript and it is hoped that the recommendations made will result in MS patients leading longer and healthier lives.

1. What is the epidemiology of multiple sclerosis in Central America and the Caribbean and what are the relevant genetic, environmental and risk factors?

MS is a chronic, inflammatory, immune-mediated demyelinating and neurodegenerative disease of the central nervous system affecting mainly young adults aged 20-40 years. It affects a wide array of neurological functions: sensory, motor, autonomic and cognitive.[1,2] The etiology of multiple sclerosis is multifactorial: both genetic and environmental factors contribute to disease risk. However, the precise etiology is unknown and there is no defined way to prevent the disease.[3]

A report of the MS International Foundation[4] indicated that the prevalence of MS in North America and Europe is approximately 100-250 cases per 100,000 inhabitants, which contrasts with the reported prevalence in Latin American countries of approximately 1-22 cases per 100,000 inhabitants[5].

In Central America and the Caribbean (comprising up to 84 million inhabitants), the prevalence of MS varies. The Central American Region is geographically defined as countries south of Mexico and north of Colombia and is comprised of seven countries: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama *(Figure 1)*. Information related to the epidemiology of MS is limited in the Central American region. Published studies suggest that the prevalence of MS in Central America is "low" or "very low", from 1.0 to 7.1.[4-7,5], cases per 100,000 inhabitants.

In the Caribbean, which is comprised of 28 countries, only very few have reported any prevalence data, with rates ranging from 8.5 to 21.0 cases per 100,000.9,11. The reason for the higher prevalence of MS in the Caribbean compared to Central America is unclear. The incidence of MS has not been reported for most of the countries in the Region.

Environmental risk factors influence the incidence of MS and the severity and progression of the disease. In a recent study, of 44 presumed risk factors only three were shown to be strongly associated with MS3: previous infection with Epstein-Barr virus, infectious mononucleosis and smoking. Risk factors with suggestive evidence included appendectomy or tonsillectomy before 20 years of age and traumatic injury. Vitamin D levels, often considered to be important, were only weakly associated with MS3. Promotion of smoking cessation could be one of the most effective public health interventions to reduce the incidence of MS.

Figure 1: Map depicting Central America and The Caribbean

Some studies have shown that the frequency of MS is related to latitude, with a higher prevalence being associated with northern latitudes and a lower prevalence in countries near the equator. This hypothesis may explain the lower prevalence of MS in Central America. On the other hand, the higher reported prevalence of MS in some Caribbean countries and the fact that no gradient has been found in Latin America itself, raises doubt about the validity of the north-south gradient hypothesis[10-12].

Although environmental factors seem to play a role in the development of MS, genetic factors are also very important. In a review by Melcom et al.[10] and others,[11,13] protection from MS has been reported in indigenous populations worldwide. Another review also reported that the prevalence of MS varies according to the racial characteristics of the population;[14] the rate of MS in Latin America is higher in people with Caucasian ancestry, Mestizos and Afro-Americans than in individuals native to their country[15]. However, the low prevalence rates found in Central America seem not to be related to ancestry because the populations in most of the Central American countries are primarily Mestizo, yet the prevalence rates are low.

The importance of other genetic factors in susceptibility to MS has been shown by genetic epidemiologic studies.[16] The relationship between HLA types and the development of MS is well established[15]. The strongest relationship has been observed among patients with HLA-DRB1*15, mainly in individuals with Caucasian ancestry[15]. Unfortunately, there is a paucity of data on the distribution of HLA haplotypes in Central American and Caribbean populations with MS. In addition, HLA types in different populations may be positively or negatively associated with the disease[17,18].

Approximately 15-20 percent of MS patients have an affected relative, with the highest risk of concurrence being observed in patients' siblings[19-21]. The case for heritability is also supported by studies of twins in whom one of each pair is known to have MS. In the most extensive of these studies,[19] the diagnosis was verified in 12 of 35 pairs of monozygotic twins *(34 percent)* and in only 2 of 49 pairs of dizygotic twins *(4 percent)*. The concordance rate in dizygotic pairs is similar to that in non-twin siblings.[19-21]

Despite these findings, no consistent pattern of mendelian inheritance has emerged. Of course, not all diseases with an increased familial incidence are hereditary, given that instances of the same condition in several members of a family may reflect an exposure to a common environmental agent.[22] One factor that could contribute to the low prevalence of MS in the Region is related to the so-called hygiene hypothesis. That is, individuals more frequently exposed to infectious agents early in life have a diminished risk of developing allergic or autoimmune diseases. Since many countries in the Region have such conditions, this might explain the reduced prevalence observed.[23,24] However, there are no conclusive data demonstrating that other autoimmune diseases in the Region have a lower than expected prevalence.

A Collaborative Central American and Caribbean Multiple Sclerosis Registry was established in 2012. A total of 613 cases, all from Central America, had been entered into the registry at the time of this meeting. This collaborative registry should eventually provide Regional information regarding the demographic and clinical characterization of MS patients, as well as treatment-related issues.

On the assumption that the prevalence numbers for Central America are correct, there should be about 2500 cases of MS in Central America. However, based on anecdotal data only, about 1200 patients have been diagnosed *(though not all have been entered into the registry)*, suggesting that a large proportion of MS patients are undiagnosed. These preliminary data also lend support to the need for a region-wide effort to register all MS patients.

The likely high rate of undiagnosed MS lends support for alternative hypotheses to explain the relatively low prevalence of MS in the Region. That is, it may be due to relatively insufficient

access to healthcare, a relative deficiency of health personnel trained in identifying MS patients, the lack of a major public awareness effort about the disease and the relative lack of appropriate diagnostic technology. All these reasons could conspire to provide a misclassification of MS and many undiagnosed cases, resulting in an artificially low prevalence rate.

Future studies on the genetic and environmental factors that influence the development of MS are critically important for the Region. In addition, in order to be confident that epidemiological data on MS in Central America and the Caribbean is accurate, standardized diagnostic criteria must be utilized in all studies[25] and a greatly increased surveillance effort must be undertaken.

Recommendations:

1. NGOs with an interest in MS should actively participate in public awareness efforts to reduce the prevalence of smoking.
2. Government and NGOs throughout the Region should actively support the Collaborative and Central American MS Registry.
3. A task force with Region-wide participation should be established to facilitate surveillance and epidemiology efforts within and between each country in The Region.
4. Government, private institutions and the pharmaceutical industry should increase their support of academic centers performing research on MS.

2. What are the clinical features of MS in Central America and the Caribbean and how should the disease be diagnosed?

Diagnosis of MS based solely upon clinical examination and history should be discouraged. It is mandatory to use the internationally established and accepted diagnostic criteria.[25]

Prior to diagnosing MS, patients may present with "clinically isolated syndrome" (CIS), which is now recognized as the first clinical presentation that shows characteristics of inflammatory demyelination that could eventually convert to MS, but has yet to fulfill the criteria for diagnosis. Evidence obtained from longitudinal follow-up of CIS patients has shown that up to 80% of such patients will eventually develop relapsing-remitting MS *(RRMS)*.[26] Patients at greater risk are those with MRI lesions suggestive of MS and oligoclonal bands in cerebrospinal fluid.[27]

The most frequent form of presentation of MS is RRMS. The most common clinical symptoms from a study performed in the Region are motor dysfunction *(48%)*, optic neuritis *(31%)*, and sensory disturbances *(27%)*.[6] RRMS is characterized by unpredictable relapses followed by periods of months to years of relative stability (remission) with no new signs of disease activity *(e.g. relapses and MRI worsening of T2 lesions or gadolinium enhancing lesions)*. Neurological deficits that occur during relapse may either resolve or leave residual effects, especially in patients with a longer MS duration. Current definitions sub-classify MS patients into those who have evidence of disease activity and those with inactive disease. By definition, a patient with a CIS who presents with evidence of disease activity has converted to MS.[28]

MS phenotypes can be categorized as relapsing or progressive in the context of current medical status and history, but these categories do not provide temporal information about the ongoing disease process. The MS Phenotype Group *(a consortium of MS experts)* proposed that disease activity should be detected by clinical relapses or imaging changes.[28] An additional modifier of the course of MS is whether or not there is clinical evidence of disease progression, independent of relapses over a given period of time. That is why it is important to ascertain disability scores throughout the course of the disease.

Secondary Progressive MS *(SPMS)* is diagnosed retrospectively by a history of gradual worsening after an initial relapsing and remitting disease course, with or without acute exacerbations during the progressive phase. This occurs in up to 80% of RRMS patients after an average period of 10 years disease duration. In contrast, Primary Progressive MS (PPMS) is diagnosed in patients who undergo

a progressive worsening from disease onset without clear evidence of relapses and remission before the progressive phase. All progressive forms of MS should be sub-classified according to disease activity and evidence of progression.

Sub-classification allows for a patient with progressive forms of MS to be classified as (1) active and progressing; (2) active but without progression; (3) not active but with progression; or (4) inactive and without progression (stable disease), based on whether the patient has worsening physical disability (defined as "progression") and/or has relapses or gadolinium-enhancing lesions on MRI.[28]

The fundamental criteria for establishing the diagnosis of MS virtually always comprises the concept of "dissemination in space and time," in an appropriate clinical context, as demonstrated by MRI and laboratory tests as supportive diagnostic tools.[28-30] Therefore, an MRI is essential to rule out diseases masquerading as MS, such as neuromyelitis optica *(NMO)* and other demyelinating conditions.[31,32] Rates of MS misdiagnosis vary considerably with ranges of up to 35%.[29] A careful history and physical examination remain the crux of neurological diagnosis, rather than cranial MRI reports suggesting the presence of demyelinating disease, which itself is insufficient for diagnosis. Over-reliance on MRI without the appropriate clinical context should be avoided in diagnosing MS. In situations where the diagnostic findings are ambiguous or inconclusive, it is important, especially in the Central American and Caribbean Region, to rule out NMO and human lymphotrophic virus type 1 *(HTLV-1)* infection, primarily in patients with non-specific demyelinating lesions on MRI and predominant spinal dysfunction.[29]

The latest diagnostic criteria made it possible to establish the diagnosis earlier, even on a single examination that combines clinically compatible findings with a positive MRI scan.[25] The early initiation of disease-modifying therapy *(i.e. before a second attack)* has shown to reduce the likelihood of converting to MS and even MS-associated disability[27,33] and mortality.[34] Therefore, early treatment of CIS patients may interrupt the progression to MS.

To achieve early diagnosis of MS, patients who present with signs and symptoms suggestive of the disease should be promptly referred to a neurologist for a definitive evaluation.[35] In addition, the availability and utilization of MRI facilities are necessary. Continuing medical education on the clinical signs and symptoms of MS is also important to ensure early detection and appropriate referral. Relevant NGOs have an important role to play in educating physicians and the public on the clinical signs and symptoms of MS.

Recommendations:

5. Medical societies in the Region should disseminate information on the signs, symptoms and the diagnostic criteria of MS to health professionals who are likely to have patients at higher risk for MS.
6. National MS Societies should be more active in developing public awareness regarding the signs and symptoms of MS so as to facilitate early diagnosis of CIS and MS.
7. Governments should support the establishment of the necessary facilities and equipment to diagnose MS.
8. It is mandatory to use the internationally established and accepted criteria to diagnosis MS. It is also important to initiate treatment at the earliest possible moment after diagnosis. Practitioners should be aware of the criteria for the identification of disease activity and progression.

3. How should MS be treated in Central America and the Caribbean?

The correct diagnosis and proper classification of MS is essential prior to beginning treatment. Before initiating MS-specific drug therapy, it is necessary to conduct a careful risk assessment for factors that will influence the choice of therapeutic modalities. Such an assessment includes the presence or risk of infections, co-

morbidities, as well as the patient's ability to adhere to the treatment regimen. In addition, the physician treating MS must be fully aware of the safety and efficacy of the drugs to be prescribed.

Periodic clinical monitoring is essential in order to recognize a suboptimal response to therapy and drug-related complications. Latin American algorithms for the treatment of MS have been published.[35] The ultimate goal of therapy in MS is to achieve "no evidence of disease activity" or "NEDA," which is defined as the absence of relapses, no disability progression, no new radiological activity *(absence of gadolinium-enhancing T1 lesions and new or newly enlarged T2 lesions)* and brain parenchymal loss of no more than 0.4% annually.[36,37] In the future, NEDA may also encompass no evidence of increasing cognitive impairment.

Healthcare systems should provide or pay for medications for the clinical subtype of MS for which they were approved. So far, the only indications for disease-modifying therapy are for RRMS, CIS at high-risk of converting to MS, and SPMS with clinical activity.[38] Pharmacovigilance programs should be established in each treatment center and should be responsible for the documentation of adverse drug-related events.

It is also important to discuss with the patient and his/her family the risks associated with the prescribed medications, potential side effects to be aware of, as well as the critical importance of adherence to therapy. Patients with poor prognostic factors and aggressive MS should be evaluated for receiving higher potency anti-inflammatory agents, such as fingolimod, natalizumab or alemtuzumab at any time during the course of MS.[35] Poor prognostic factors include age above 40 years at the time of diagnosis, male gender, African descent, motor or autonomic dysfunction, frequent relapses, absence of recovery from relapses, rapid development of disability, high lesional load on MRI, lesions in the posterior fossa or spinal cord, gadolinium-enhancing lesions and chronic T1 black holes.[39,40]

In non-aggressive MS or for patients with a better prognosis, treatment with interferons, teriflunomide or fingolimod is recommended. Glatiramer acetate is not widely available in the Region, but is also appropriate. Dimethyl fumarate, also used for the treatment of non-aggressive MS, is yet to be licensed for use in the Region. The choice of therapeutic agent for both aggressive and non-aggressive MS should be individualized and based on co-morbidities, patient preference, cost, and the risk of patient-specific adverse reactions. Combination therapy is not recommended for treatment of any form of MS.[35,41]

Another aspect related to drug choice is the observation that individuals of African descent may have a diminished response to interferons.[42] In patients with established MS receiving disease-modifying therapies, the early identification of predictors of suboptimal response should guide the decision of treatment escalation (optimization) in order to diminish the likelihood of disability progression.[43] Therapy resulting in a less than optimal response *(e.g. occurrence of relapses, new MRI activity and disability progression)*,[39,43,44] may warrant escalation. As mentioned above, treatment algorithms for RRMS and CIS have been published for Latin America. *Figure 2* is a summary treatment algorithm for patients with RRMS in the Region.

Treating acute relapses to shorten their duration and limit residual effects is indicated.[45-46] Irrespective of baseline therapy, relapses must be treated with the administration of intravenous doses of methylprednisolone. The dosage ranges from 500-1000 mg per day for three to five days.[28,47]

Since MS is a disease that takes a significant psychological toll , virtually all patients benefit from support by family, friends and other affected individuals. This support is often most effectively obtained from organized support groups or organizations.

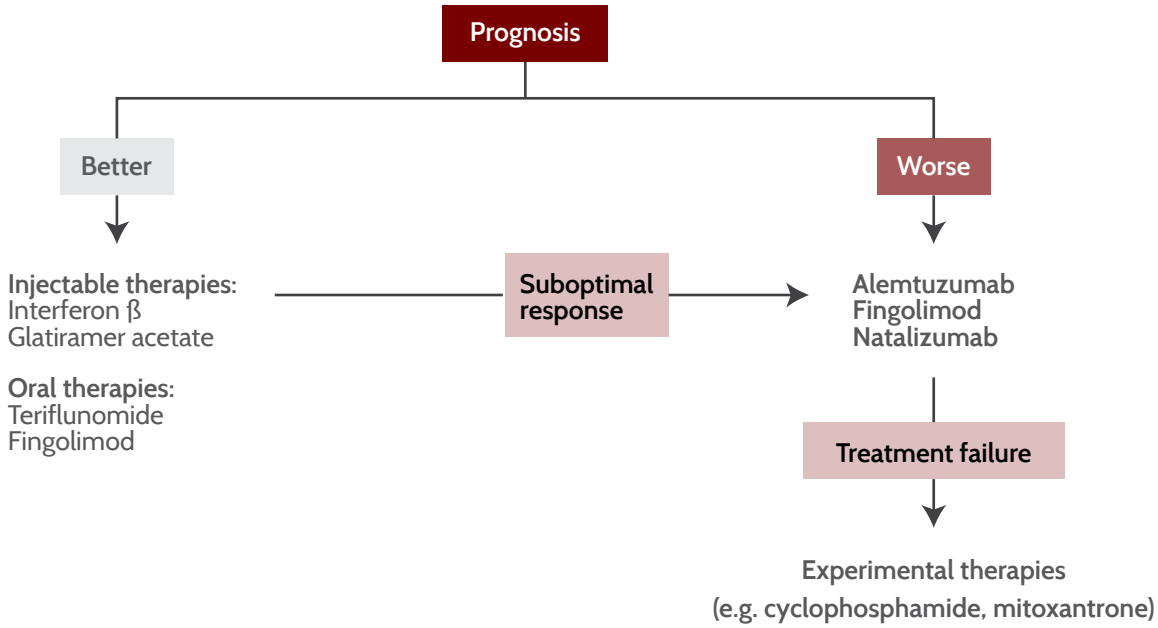

Figure 2: Summary treatment algorithm for relapsing remitting MS. Adapted from reference 35

All drugs approved for the treatment of MS by the Food and Drug Administration and the European Medicines Agency should be approved and available for prescription to all MS patients in every country in Central America and the Caribbean.

Recommendations:

9. Pharmacovigilance programs should be established in each treatment center and should be responsible for the recognition and documentation of all cases of MS and adverse drug-related events.
10. MS patients should be referred to a local neurologist, and patient support groups or organizations focused on MS patients.
11. All approved drugs for the treatment of MS should be readily available for prescription in every country in Central America and the Caribbean.
12. Continuing medical education programs should stress the appropriate use of all appropriate medications for the treatment. The use of established treatment guidelines is recommended and treatment decisions should be individualized.
13. Patients with poor prognostic factors and aggressive MS should be evaluated for receiving higher potency anti-inflammatory agents, such as fingolimod, natalizumab or alemtuzumab at any time during the course of MS.

4. What is the role of government and NGOs in the management of MS?

Heath professionals treating individuals with MS know firsthand the severity and impact of the disease on their patients and society. With this knowledge comes the responsibility to educate government officials on the "price" of MS. Because of the relatively low prevalence rate, it could easily be assumed that MS is much less consequential than other chronic diseases - this would be an erroneous belief. It is widely recognized that more than half of the costs derived from MS care are due to disability and that the early administration of disease modifying therapies has a positive impact in this issue.

Governments can ease the impact of MS by efficiently allocating public resources towards the management of the disease. This adverse impact should be shared by NGOs, which are defined as any non-profit, voluntary citizens' group.. In a study of 20 Latin American countries, all of them had patient-family focused Multiple Sclerosis Associations.[48] Such an

organization should represent the ideal partner with Government to support and maintain the health of MS patients. Each country in this Region also has medical societies that should provide essential services (e.g. continuing medical education, public awareness) to support physicians who treat patients with MS.

In a review of the global economic impact of MS across 15 countries *(no Central American or Caribbean countries were included)* the average weighted cost per patient per year was **$41,335 USD**.[49] This high cost is perhaps one of the main obstacles to providing comprehensive care in most countries within the Region where the GDP per capita is substantially lower than in North America and Europe [50,51]. The high cost of MS can be illustrated in Trinidad, one of the more advanced countries in the Caribbean, where anecdotal evidence suggests that the cost of disease modifying therapy per patient per year is approximately **$16,000 USD**, in an island where the GDP per capita is **$18,373 USD**.[50]

Moreover, the prices of newer drugs are 25-60% higher than for first generation agents.[52] Of note,it is estimated that MS-specific disease modifying therapy represents only about 50% of the total health care cost related to MS. Additional direct costs include other pharmacologic agents for MS-related symptoms and co-morbidities, hospitalizations, emergency room visits, physical therapy, mental health, and other tests and procedures. Therefore, Government, in partnership with NGOs, should take a more active role in advocating for a reduced cost of MS-specific therapies. A reduction in the cost of comprehensive MS management would facilitate availability and patient access to needed health care.

Government and other health-related agencies play an important role in improving health outcomes. One of their most important roles is the education and training of health care professionals, particularly the training and support of a greater number of neurologists.

Currently, most health care provided to patients with MS is provided by physicians alone. However, it is well known that much better outcomes can be obtained when a multi-disciplinary team is utilized. Partnership with academic centers and professional societies to facilitate development of comprehensive multidisciplinary teams for the treatment of MS is recommended.[53] The establishment and maintenance of a MS registry within each country is recommended.

Recommendations:

14. The focus of governments in the Region should be on the provision of necessary medications, promotion of education across the entire population, an improvement in the number and training of health care professionals and multi-disciplinary teams who treat MS, and the creation and maintenance of local and regional MS registries.
15. Government, in partnership with NGOs, should take a more active role in advocating for a reduced cost of MS-specific disease-modifying therapies.
16. Community-based rehabilitation services, such as physiotherapy and occupational therapy, should be encouraged and supported.

Conflicts of interest declaration

The authors declare that there are no conflicts of interests economic related with this scientific report.

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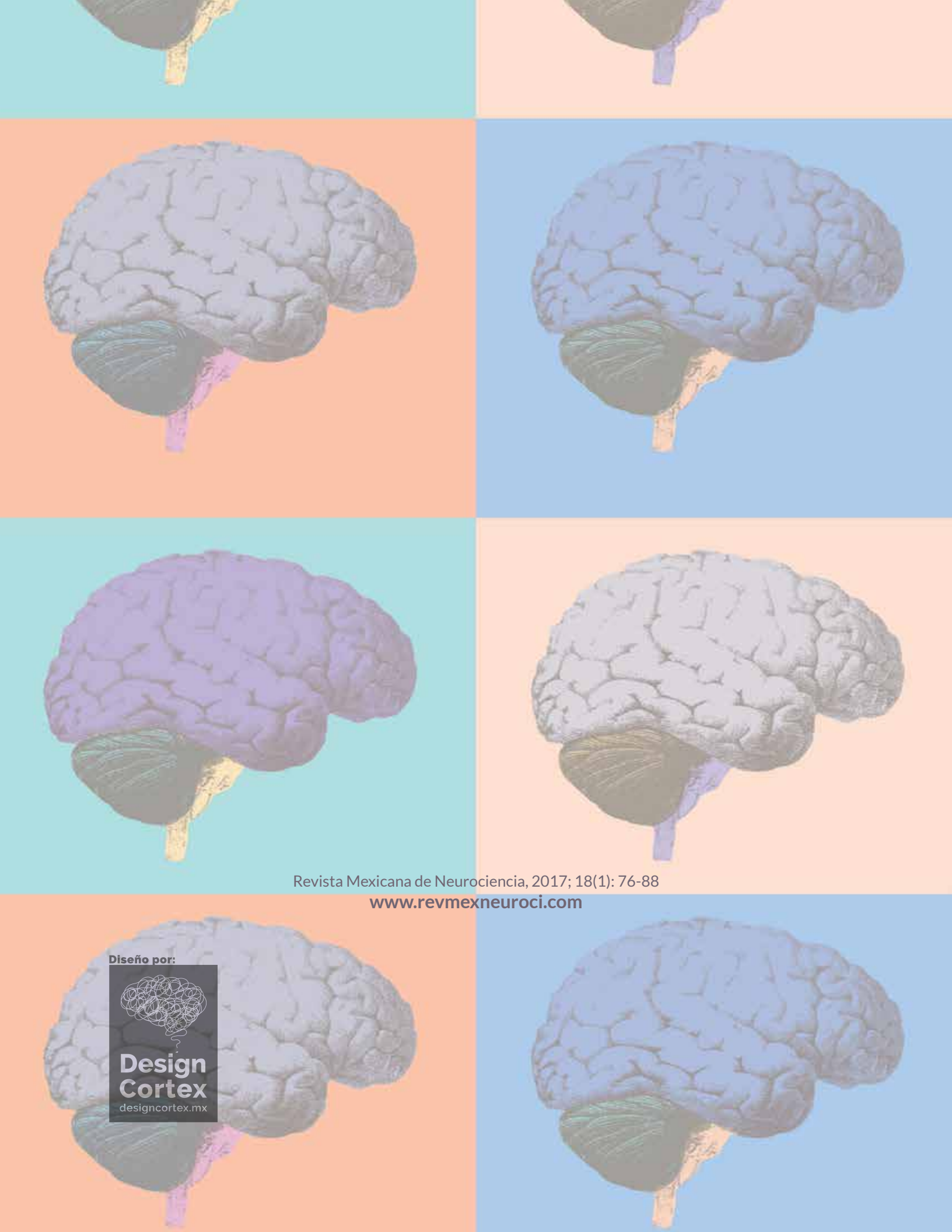

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