Narrative review

Multiple sclerosis: from demyelination to neurodegeneration

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Esclerosis múltiple: de la desmielinización a la neurodegeneración.

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Abstract
Multiple sclerosis is a chronic autoimmune demyelinating inflammatory disease of the central nervous system, characterized by demyelination and subsequent neurodegeneration secondary to neuronal damage due to axonal loss. Currently, it is still a disease of unknown etiology that affects more than 2 000 000 people, is associated with various genetic and environmental factors that increase susceptibility, and occurs mainly in the 20-40 age group. For the preparation of this article, a review of the literature available in databases such as PubMed and SagePub. Original articles, bibliographic reviews, systematic reviews, and meta-analyses in English and Spanish were selected in order to review multiple sclerosis, its background, epidemiology, clinical manifestations, classification, diagnostic criteria and available therapy. Advances in treatment have improved the quality of life by reducing the frequency and severity of flares. However, the etiology of the disease remains uncertain, and its neurodegenerative effects are poorly prognosed.

Keywords
Multiple Sclerosis, Nervous System Diseases, Autoimmunity.

Resumen
La esclerosis múltiple es una enfermedad inflamatoria desmielizante, autoinmune y crónica del sistema nervioso central, caracterizada por la desmielinización y la posterior neurodegeneración secundaria al daño neuronal por pérdida axonal. Actualmente, sigue siendo una enfermedad de etiología desconocida que afecta a más de 2 000 000 personas. Se asocia a diversos factores genéticos y ambientales que aumentan su susceptibilidad y ocurre principalmente en el grupo de edad de 20 a 40 años. Para la elaboración de este artículo, se efectuó una revisión de la bibliografía disponible en bases de datos como PubMed y SagePub. Se seleccionaron artículos originales, revisiones bibliográficas, revisiones sistemáticas y metaanálisis en inglés y español, con el objetivo de realizar una reseña de la esclerosis múltiple, sus antecedentes, epidemiología, manifestaciones clínicas, clasificación, criterios diagnósticos y terapia disponible. Los avances en el tratamiento han logrado mejorar la calidad de vida al reducir la frecuencia y severidad de los brotes, pero la etiología de la enfermedad sigue siendo incierta y sus efectos neurodegenerativos de mal pronostico.

Palabras clave
Esclerosis Múltiple, Enfermedades Del Sistema Nervioso, Autoinmunidad.

Introduction

Multiple sclerosis (MS) is currently a chronic autoimmune demyelinating inflammatory disease of the central nervous system (CNS), characterized by demyelination and subsequent neurodegeneration secondary to neuronal damage due to axonal loss.[i] The etiology remains unknown and has been associated with factors that increase susceptibility. Its pathogenesis is mediated mainly by T lymphocytes (LT) and B lymphocytes (LB), which initiate the cycle of inflammation and demyelination, followed by partial remyelination, neurodegeneration and gliosis in the white matter of the CNS[ii].

Diagnosis is based on an initial clinical evaluation supported by laboratory and neuroimaging studies. Therapy is multidisciplinary. The drugs used can be divided according to their target in the course of the disease.[ii] MS occurs mostly between the ages of 20 and 40 years, and is more frequent in women.[iii,iv]

For this review, a search was carried out in databases such as PubMed and SagePub. Original articles, literature reviews, systematic re-

views and meta-analyses in English and Spanish were selected, with the aim of describing MS, presenting new guidelines on its pathogenesis and establishing the current context in terms of epidemiology, clinical features, classification, diagnostic criteria and available therapeutic options, which may be relevant for the future understanding of this disease.

Discussion

Historical background and current context

The clinical features of MS were first described by Jean-Martin Charcot, who distinguished between the tremor of agitated paralysis (later termed Parkinson's disease) and that of MS. The three most reliable indicators of MS (intention tremor, nystagmus and scandid speech) became known as the Charcot triad[i].

In parallel, new treatments have emerged, including disease-modifying therapies that have demonstrated efficacy in reducing relapses and disability progression. Despite these advances, MS remains a disease without a cure, with an unpredictable clinical course that varies between different manifestations, underscoring the need for further research to improve patient management and quality of life.

Etiology

The origin of MS is multifactorial, related to genetic and environmental factors. These include living in latitudes far from the equator, vitamin D deficiency, exposure to ultraviolet B rays, herpes virus infection (Epstein-Barr, herpes simplex and varicella-zoster), mycoplasma pneumonia, obesity, diet and smoking[ii-iv].

The risk of developing MS in relatives is related to the susceptibility of genetic traits. The genetic risk ratio in monozygotic twins with 100 % genetic similarity is 25 %. In cases of 50 % similarity, such as dizygotic twins and first-degree relatives, the risk decreases to 2-5 %. Similarly, in second-degree relatives with 25 % genetic similarity, the risk is 1-2 %, while in third-degree relatives with 12. 5 % genetic similarity it is less than 1 %.[v] In the human leukocyte antigen (HLA) region of chromosome 6, a group of genes associated with an increased risk of MS has been identified. The main genes involved reside in the HLA-DRB1*15 gene; however, more than 200 independent genetic associations have now been identified[vi,vii]

Microorganisms, such as viruses and bacteria, may have antigens structurally homologous with myelin components, such as proteolipid protein, myelin basic protein and/or myelin-associated glycoprotein. Thus, when these pathogens activate immune cells, parallel myelin lesions could develop.[viii]

Other hypotheses postulate that vitamin deficiency, especially D and B12, is a risk factor. It has recently been shown that obesity may be related to MS by three theories. The first is the inflammatory theory, where it is postulated that the hypertrophy involved and subsequent hyperplasia of adipocytes in obesity is characterized by low-grade inflammation, in which high levels of proinflammatory mediators are produced. The second is the hormonal theory, in which excess adipose tissue is accompanied by altered secretion of adipokinesix. The third is related to vitamin deficiency; obesity also leads to lower vitamin D availability, which correlates with a proinflammatory state.[x]

Another possible etiology is the association between changes in the intestinal microbiome and CNS alterations. Blood-brain barrier (BBB) selectivity is related to a favorable gut microbiota that can activate microglia. In MS, there is an abundance of certain bacterial species such as Archaea, at the same time as a decrease or absence of other types such as the Firmicutes and *Bacteroidetes* phyla. Associations of certain microbiota profiles have been associated with increased risk of relapse.[xi]

Dietary and lifestyle factors may participate in MS symptoms by modulating the inflammatory state[xii]. Components such as fatty acids, polyphenols, and high-carbohydrate or high-fat diets can trigger a number of inflammatory reactions. The persistence of this diet promotes cell metabolism towards biosynthetic pathways, including the production of proinflammatory molecules such as tumor necrosis factor, interleukins, matrix metalloproteinases, prostaglandins and leukotrienes, which contribute to systemic inflammation and oxidative stress.[xii] In contrast, exercise and low-calorie diets based on vegetables, fruits, legumes, fish, prebiotics and probiotics act on nuclear receptors and enzymes that up-regulate oxidative metabolism and down-regulate the synthesis of proinflammatory molecules.[xiii]

Finally, numerous evidence suggests that smoking, due to the production of nitric oxide and carbon monoxide, could play an important role in the etiology of MS[xiv-xvi].

Pathophysiology

This autoimmune disease is mainly mediated by activated LT; however, recent evidence has shown contribution of LB to the

pathogenesis. The immune response is initiated by peripheral activation of autoreactive LT following decreased self-tolerance to myelin or different CNS antigens. The trigger may be an environmental antigen (virus), a cross-reaction between endogenous proteins (myelin basic protein) or an exogenous pathogenic protein (viral antigen); by molecular mimicry. After activation of myelin-reactive LTs, they cross the BBB facilitating the expression and positive regulation of adhesion molecules, chemokines and matrix metalloproteins.

Upon entering the CNS, autoreactive LTs can be reactivated by antigen presenting cells, triggering an inflammatory cascade by local release of cytokines and chemokines, recruitment of additional inflammatory cells such as monocytes, LBs and LTs, and persistent activation of macrophages. This results in myelin damage and loss of oligodendrocytes caused by the inflammatory response against myelin, as well as axonal loss that may occur during early inflammatory phases or when repair mechanisms are exhausted by persistent macrophage and complement activation and indirect effects of proinflammatory cytokines such as tumor necrosis factor alpha, nitric oxide and matrix metalloproteinases.[vii]

The pathological features of MS are inflammation, demyelination followed by remyelination or neurodegeneration, and gliosis. These features occur focally or diffusely in the white and gray matter of the CNS. These features are present in most MS subtypes, although they vary over time and between individuals.[xvii]

Epidemiology

The prevalence of MS varies, being highest in North America and Europe, with 140 and 108 cases per 100 000 population, and lowest in sub-Saharan Africa and East Asia, with 2. 1 and 2. 2 per 100 000, respective.[vii] It is estimated that MS affects more than 2, 000,000 people worldwide, has a 3:1 female predilection, occurs most frequently in people aged 20-40 years, and is the most common non-traumatic cause of neurological disability in young adults.[ii,xviii,ixx]
Its prevalence varies according to geography and ethnicity, and increases with latitude.[xx,xxi]

The incidence of MS appears to have increased over the past 100 years, primarily in women and populations traditionally considered low risk, such as Hispanics, Asians, and African Americans. Despite difficulties in surveillance, the incidence of MS is very low in Africans and native populations of Latin America and Oceania.[xxii,xxiii] Migration studies support the fact that MS may result from contact with environmental risk factors early in life (before the age of 15 years). It has been shown that adult immigrant patients to Europe from low-risk countries have a low risk of developing MS, while children of immigrants to Europe have a higher risk of developing the disease.[xxiv]

Clinical manifestations

Clinical signs and symptoms are variable depending on the location of damage, and may affect sensory, motor, visual and brainstem pathways. The most frequent lesion areas are the periventricular, optic nerve, brainstem, cerebellar peduncles and spinal cord.[xxv] At onset, most patients debut with recurrent remitting episodes of symptoms and neurological dysfunction lasting more than 24 hours, defined as flare-ups.[xxvi]

Signs and symptoms in the early stages

Clinically isolated syndrome

Considered as the first demyelinating clinical event compatible with MS. It usually occurs in young adults and affects the optic nerves, brainstem or spinal cord (Figure 1). Although patients usually recover from the presenting episode, the course of MS following a clinically isolated syndrome is variable. After 15-20 years, one-third of patients have a benign course with minimal or no disability and half will develop secondary progressive MS with increasing disability.[xxvii,xxviii.]

Optic neuritis

Optical neuritis is the first clinical manifestation in 20 % of patients with MS, there is a progressive unilateral loss of vision in the first days. There may be retroocular pain that worsens with eye movements, as well as decreased visual acuity and alterations in color perception, especially red. These symptoms may be accompanied by relative afferent pupillary defect and central scotoma.[xxix] The optic disc may appear normal (retrobulbar neuritis) or acutely inflamed, may become pale and atrophic, some time after the attack. After an episode of unilateral optic neuritis, ipsilateral or contralateral relapses are frequent.[xxx]

Acute myelitis

Acute myelitis is usually partial and manifests subacutely. Lesions are usually small, located in the periphery of the spinal cord and usually do not extend for more than two lon-

gitudinally contiguous vertebral segments. The lesions are cervical or dorsal in location in most cases.[xxxi]

Partial acute symptoms appear within hours or days, and consist of sensory and motor disturbances that may be associated with sphincteric involvement. Spinal cord damage at the cervical level may cause L'hermitte's sign (brief sensation similar to an electric shock provoked by cervical flexion).[xxxii] The appearance of a band-like sensation of tension around the chest or abdomen (the so-called "hug" of MS) is a characteristic symptom of myelitis and suggests involvement of the posterior columns of the spinal cord.[xxix.]

Brainstem syndromes

Brainstem syndromes may manifest with symptoms such as diplopia, oscillopsia, loss of facial sensation, vertigo and dysarthria. Characteristic signs include isolated sixth cranial nerve palsy, gaze-induced nystagmus or internuclear ophthalmoplegia. Bilateral internuclear ophthalmoplegia is considered a pathognomonic clinical sign of EM.[xxix]

Signs and symptoms in the established stages of the disease

Spasticity

The cumulative prevalence of spasticity in MS patients is approximately 47. 5 %,[xxxiii] also the most common symptoms associated with MS spasticity are muscle stiffness, spasms and mobility restrictions, which may include fatigue, pain and bladder dysfunction.[xxxi]

Sensory disorders

Symptoms such as numbness and paresthesias are common in most patients during the course of MS. These symptoms may suggest an acute demyelinating lesion when their duration persists for hours or days. Pain is a symptom present in up to 54 % of patients with established or newly diagnosed MS (within the last 12 months). Pain in MS can be both nociceptive and neuropathic. Neuropathic pain can be central or peripheral and may be caused by brain or spinal cord lesions.[xxxiv]

Subtypes of MS

Relapsing-remitting multiple sclerosis

This is the most common clinical course of the disease, occurring in approximately 85 % of cases. It is characterized by alternating periods of neurological dysfunction, known as relapses, followed by partial or complete recovery, and periods of relative clinical stability without new neurological symptoms, known as remissionsi.[xxx,xxxi,xxxv] The frequency of relapses differs from case to case, but usually does not exceed 1. 5 relapses per year.

During relapse, various neurological symptoms may occur, such as weakness, altered sensation, impaired balance, impaired visual acuity and color perception, or double vision, lasting at least 24 hours in the absence of infection or metabolic disturbance.[xxxvi] This disease phenotype must meet a diagnostic criterion of dissemination in time and space, i.e., the presence of multiple clinically distinct events affecting different parts of the CNS separated by at least one monthxxxvii (Figure 2).

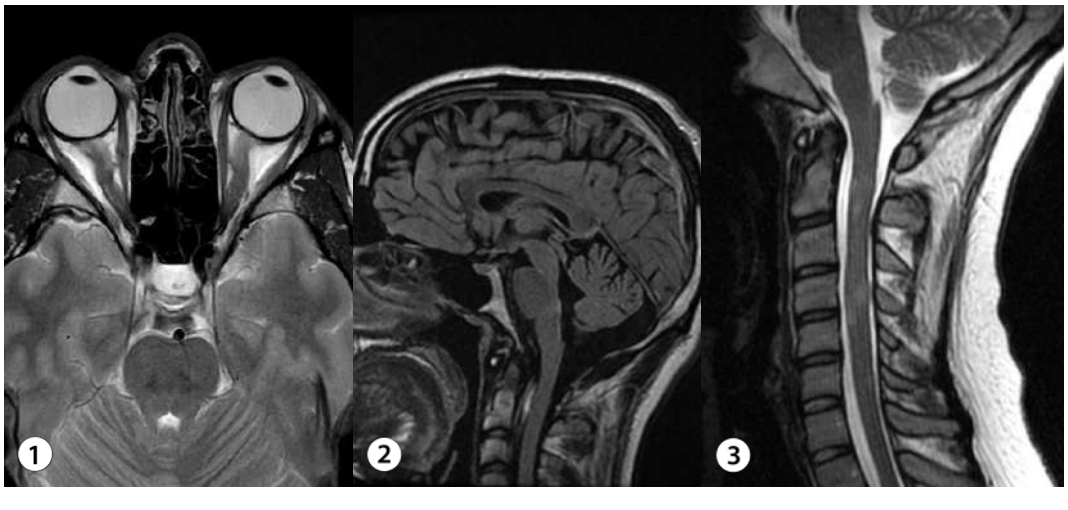

Figure 1. Demyelinating lesions in T2 MRI images. 1. Optic nerve. 2. Encephalic trunk. 3. Spinal cordl.
Sources: 1) Case courtesy of Nicole Tamara Nudelman, Radiopaedia.org, rID: 160621; 2) Case courtesy of Andrew Dixon, Radiopaedia.org, rID: 38552; 3) Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 2635

Primary progressive multiple sclerosis

Between 10 and 20 % of patients present this form of MS, it is characterized by a steady progression of neurological symptoms with no obvious remissions since onset.[xxxi] The progression is not uniform throughout the course and there may be overlapping relapses as well as periods of relative stability. The apparent absence of a relapse-remission phase in patients with PPMS could possibly be attributed to individual lesions that localize to clinically silent regions, which aggregate to ultimately induce disability (Figure 2).[x,xxvi,xxxviii]

Secondary progressive multiple sclerosis

It starts as relapsing-emitting MS and, after ten to 15 years of disease, 50 % of untreated patients present progressive clinical deterioration.[xxxix] The age at onset is the most important predictive factors for conversion to the secondary progressive form (the older the patient, the shorter the time to progression). Female gender has been associated with a longer time to progression. In addition several studies have reported that visual or sensory symptoms, and occasionally brainstem-related symptoms, are associated with a longer time to secondary progression, whereas spinal cord-related symptoms are associated with a shorter time to progression (Figure 2).[xl]

Progressive-recurrent multiple sclerosis

It was considered a subtype of primary progressive MS that could present with infrequent relapses superimposed on slow progression. In 2013, the National Multiple Sclerosis Society eliminated the clinical classification of progressive-recurrent MS. Previously diagnosed individuals were reclassified as either active, in the presence of relapses or new lesions on magnetic resonance imaging (MRI), or nonactive primary progressive MS.[xxxv,xxxvi] (Figure 2).

Diagnosis

Diagnosis is based on clinical presentation, neuroimaging findings, cerebrospinal fluid (CSF) analysis and evoked potential studiesxli. Currently, the McDonald criteria are the diagnostic standard. These combine clinical data, MRI, and CSF analysis to establish a diagnosis with greater accuracy. The criteria have been revised several times since their introduction in 2001, with the most recent update in 2017 by the International Panel on Diagnosis of Multiple Sclerosis.[xlii,xliii]

These criteria propose that, for diagnosis, it is necessary to demonstrate two fundamental principles: dissemination in space (DIS) and dissemination in time (DIT), ruling out any other more probable diagnostic cause.

DIS refers to evidence of demyelinating lesions present in different areas by detecting MRI lesions in at least two of the four classic regions: periventricular, cortical or juxtacortical, infratentorial and medullary.

DIT, on the other hand, is established by demonstrating that the lesions occurred at different times, which can be evidenced by the simultaneous presence of gadolinium- and non-gadolinium-absorbing lesions, or by

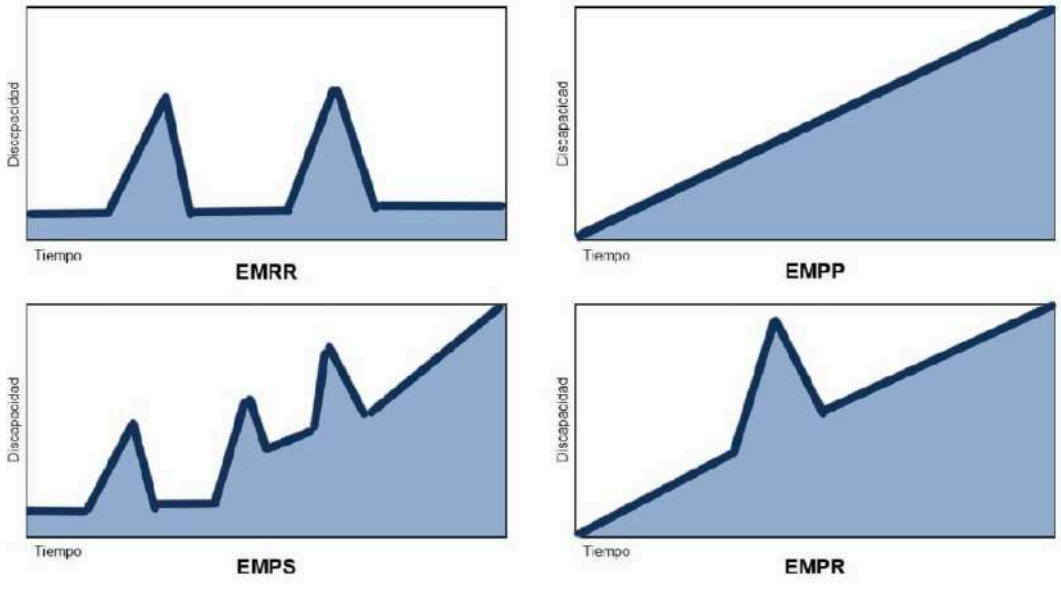

Figure 2. Subtypes of multiple sclerosis [xxix,xxxi] . RRMS relapsing-remitting multiple sclerosis, PPMS primary progressive multiple sclerosis, SPMS secondary progressive multiple sclerosis, progressive-remitting multiple sclerosis.

Table 1. Definition of the McDonald Criteria for the diagnosis of MS.[xlii-xliv].

Criterion	Description
DIS	Evidence of at least 2 lesions in characteristic CNS regions: periventricular, cortical/juxtacortical, infratentorial or spinal cord.
DIT	Lesions at different points in time, identified by MRI or new lesions on follow-up MRI. Alternatively, the presence of single BOCs in cerebrospinal fluid.
Exclusion of other diagnoses	It should not be better explained by other diseases.
CIS	First clinical manifestation suggestive of CNS inflammation and demyelination, which may or may not progress to MS.
Compatible MRI findings	Typical lesions in characteristic regions of the CNS. Gadolinium enhancement to determine recent activity.
CSF OCB	Presence of unique OCBs in the cerebrospinal fluid, indicating immune-mediated inflammation of the CNS.

OCB: oligoclonal bands, CIS: clinical isolated syndrome, DIS: dissemination in space, DIT: dissemination in time, MS: multiple sclerosis, CSF: cerebrospinal fluid, MRI: magnetic resonance imaging, CNS: central nervous system.

the appearance of new lesions in follow-up MRI studies.[xliii,xliv]

If the postulated criteria are met (Table 1) and there is no better explanation for the clinical presentation, the diagnosis is MS. However, if the disease is suspected, but the criteria are not fully met, it is classified as possible MS. And if during the evaluation another diagnosis that better explains the clinical presentation is proposed, the diagnosis is not MS.[xliii]

Evaluation of MS: Expanded Disability Status Scale

In order to objectively assess the physical and cognitive disability status of patients, tests have been designed to represent the impact of the clinical course of the disease. In 1954, Kurtzke developed the first scale to assess physical disability in MS patients, called the Disability Status Scale. Originally, the scale was composed of eight functional systems, including pyramidal, cerebellar, brainstem, sensory, bladder-gut, visual, cerebral or mental, and others. Each functional system has a weighting ranging from "0", indicating normal findings on neurological examination, to "5", reflecting clear findings of neurological injury; subsequently, the maximum score was replaced by "6". Currently, the Expanded Disability Status Scale is based on the results of the clinical interview and neurological examination. It consists of 20 steps, with a score starting at "0" as an indication of normal neurological status. The first score after 0 is 1, and thereafter the score has increments of 0. 5 in proportion to increasing neurological deterioration, where "10" is the maximum score and represents death from ME.[xlv]

Prognosis

There are no established prognostic factors for MS; however, risk variables for disease severity have been associated. These include some demographic components, such as being male, over 40 years of age, of African or Latin American origin. Clinical factors include severity of relapse, defined as: an increase of one point or more in the Expanded Disability Status Scale score, an increase of two points or more in one functional system area, or an increase of one point or more in two functional system areas; steroid use; hospitalization; multifocal seizure with partial and incomplete recovery; and motor, cerebellar, sphincteric and cognitive effects of the seizure. In addition, the frequency of relapses in 2-5 years, short intervals between attacks, and disease course with rapidly progressive disability. On imaging, onset with: high T2 lesion burden, more gadolinium enhancing lesions, T1 lesions, infratentorial lesions (Figure 3). On follow-up: new T2 lesions, one or more gadolinium enhancing lesions.[xlvi]

Therapeutics used in the treatment of MS

Effective treatment of MS requires a multidisciplinary approach to control acute

attacks, manage progressive worsening, and treat associated symptoms.[xl,xlvii] The drugs used can be divided according to their target in the course of the disease, and treatments for MS can be classified into three categories: treatment of acute relapses, disease-modifying treatments (DMTs), and symptomatic treatments (Table 2).

Acute exacerbations are episodes of focal neurological disturbances lasting at least 24 hours, preceded by periods of clinical stability of at least 30 days.[xxvi] These are the result of new white matter lesions; gadolinium binding to white matter lesions has been demonstrated by MRI in patients with relapses.

The goal of treatment in patients with MS relapses is to decrease the duration and intensity of neurological dysfunction. To achieve this, they mainly use corticosteroids (methylprednisolone) and some alternative techniques such as plasmapheresis.[xlix] Treatment Description Corticosteroids As for long-term treatment, DMTs such as beta interferons, glatiramer acetate, sphingosine-1-phosphate modifiers and monoclonal antibodies such as natalizumab, modify the course of MS due to suppression or modulation of various effects of immune function, exert anti-inflammatory activity mainly in the relapsing phases. MSDs reduce the relapse rate and decrease the accumulation of lesions observed on MRI. In addition, they stabilize, delay and in some cases, modestly improve long-term disability. However, they are not curative.[xl,l]

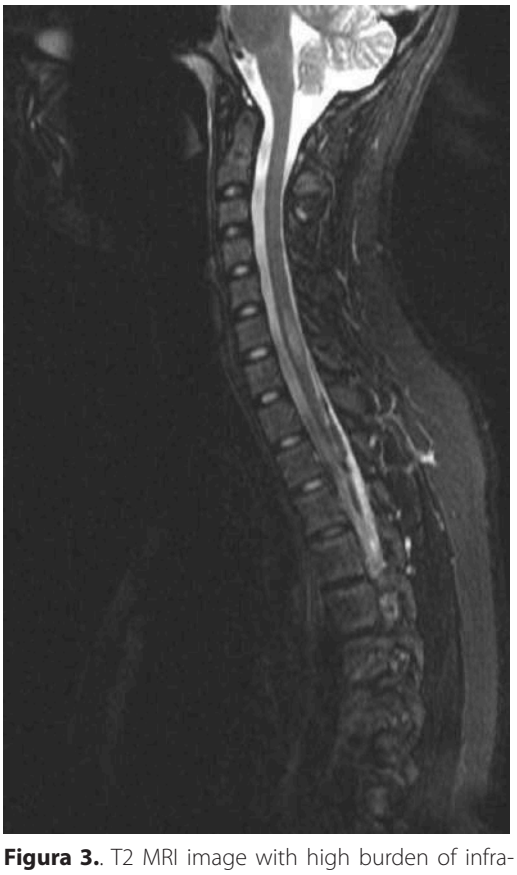

Figura 3.. T2 MRI image with high burden of infratentorial lesions (in spinal cord). Case courtesy of Sandeep Bhuta, Radiopaedia.org, rID: 5483.

Conclusion

MS is a complex and multifactorial disease that affects the world population, with distinctive geographic, ethnic and demographic patterns. It is more prevalent in young women in regions far from the equator. Since its initial description, advances in the knowledge of its pathophysiology, diagnosis and management have led to the development of therapies that improve quality of life by reducing the frequency and severity of outbreaks. However, the etiology of the disease remains uncertain, and its neurodegenerative effects have a poor prognosis.

The future of MS management is moving towards precision medicine that integrates genomic, proteomic and microbiome data, enabling early diagnosis and personalized treatments.

Research on associated genetic loci, such as HLA-DRB1*15, and their interaction with environmental factors could revolutionize understanding of the disease and risk prediction. Likewise, modulation of the gut microbiota and dietary factors offer new therapeutic possibilities by influencing immune regulation.such as HLA-DRB1*15, and their interaction with environmental factors could revolutionize disease understanding and risk prediction. Likewise, modulation of the gut microbiota and dietary factors offer new therapeutic possibilities by influencing immune regulation.

In the therapeutic arena, advances in immunomodulation, specifically targeting T and B cells, together with the use of biomarkers to assess disease activity and response to treatments, will allow for more effective management. In addition, regenerative and neuroprotective strategies, such as remyelination using stem cells and biological modulators, present promising potential for addressing progressive neurodegeneration. Finally, nanotechnology for targeted drug delivery and the identification of specific biomarkers could transform current treatment.

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Table 2. Available treatments for Multiple Sclerosis and their targets.[xlvii-l]

Objective	Treatment	Description
1. Modify the course of the disease	Disease-modifying drugs (DMARDs)	They reduce the frequency of relapses and slow progression.
	- Interferones beta (IFN-β)	Immune modulators that decrease inflammation.
	- Glatiramer acetate	Mimics myelin, promoting immune tolerance.
	- Natalizumab-	Monoclonal antibody that blocks lymphocyte migration to the CNS.
	- Ocrelizumab	Monoclonal antibody that depletes CD20+ B cells, indicated in recurrent and primary progressive forms.
	- Fingolimod	Sphingosine-1-phosphate receptor modulator, retains lymphocytes in lymph nodes. Inhibits proliferation of activated lymphocytes.
	- Teriflunomide	Inhibe la proliferación de linfocitos activados.
	- Dimethyl fumarate	Reduces inflammation and oxidative stress in the CNS.
	- Siponimod	Similar to fingolimod, specific for secondary progressive active MS.
	- Cladribine	Induces transient lymphopenia, decreasing autoimmune activity.
	- Alemtuzumab	Depletes T and B cells, rebooting the immune system.
2. Acute outbreak management	- Conrticosteoroids	Control inflammation during outbreaks.
	- Intravenous methylprednisolone	First line in severe acute flare-ups.
	- Oral Prednisone	Option for mild to moderate outbreaks.
	- Plasmapheresis	Used in severe corticosteroid-resistant outbreaks.
	- Intravenous immunoglobulin (IVIG)	Alternative in refractory cases.
3. Symptom management	Spasticity	Baclofen, tizanidine, diazepam, botulinum toxin.
	Neuropathic pain	Pregabalin, gabapentin, amitriptyline.
	Fatigue	Amantadine, modafinil.
	Urinary disorders	Anticholinergics (oxybutynin), alpha-blockers (tamsulosin).
	Depression and anxiety	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), cognitive-behavioral therapy.
	Cognitive dysfunction	Neuropsychological rehabilitation.
	Gait disturbances	Dalfampridine (improves nerve conduction in demyelinated axons).

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