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Multiple Sclerosis and the Evolution of its Treatments

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ABSTRACT

Multiple sclerosis is an autoimmune disease that demyelinates the nerves, the damage to the nerves interrupts communication between the brain and the body. Although it is a disease that has no cure, it has been studied for a long time to try to find a treatment to stop the progression of the disease. Currently there are many drugs that can help reduce the effects caused by the disease, but it is necessary to evaluate which one is given because of the adverse effects that these may have, even so, the research of new treatments has not stopped until finding one that benefits completely or its risks are minimal.

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INTRODUCTION

"Multiple sclerosis (MS, multiple sclerosis) is an autoimmune disease of the central nervous system (CNS) characterized by the triad of inflammation, demyelination and gliosis (plaques or scarring) and neuronal loss; its evolution may be relapsing-remitting or progressive. The lesions usually occur at different times and in different locations of the CNS (i.e. they are scattered in time and space). It affects nearly 900,000 Americans and millions of people worldwide. The clinical course can be extremely variable, ranging from a benign disease to a rapidly progressive and disabling disorder requiring notable lifestyle adjustments." (Cree & Hauser, 2016).

The oldest description of a probable Multiple Sclerosis (MS) is found in "Saga Island" by Saint Torlakr (1133-1193), patron saint of Iceland, where the blindness and speech disturbances of Hala, a Viking woman who would have recovered after some days of prayer and sacrifices, are mentioned (Torres, 2015).

There is reason to believe that MS appears in Scandinavian individuals before the 11th century and that it was spread by the Vikings in Europe. The earliest known diary of a possible case of MS is that of St. Lidwina of Scheidam, a 14th century Dutch nun (1380-1433), who recorded the symptoms she suffered from the onset of the disease at age 16 until her death at age 53.

His disorders included difficulty in walking, lancinating pains, weakness in the right arm, blindness, sensory disturbances and dysphagia. His suffering is well documented by the church and was instrumental in consecrating his sainthood. The two Margaret's, Auguste, the poet Heine and Alan Stevenson. Richard Gough, in "Antiquityes and Memoyres of the Parish of Myddles, County of Salop" (1700), recounted the case of Margaret Davies, who presented with pregnancy-associated lameness and progressive deficit over a period of 30 years. She was examined and treated by physicians, surgeons and apothecaries.

Augustus Frederick d'Este (1749-1848), illegitimate grandson of George III, King of Great Britain, narrated his illness in a diary that he wrote rigorously for 26 years. He recounts how he began in 1822 with loss of vision while attending the funeral of a friend. He recovered after ten months and later manifested new symptoms such as paraparesis with episodes of relapse-remission and gradual worsening.

Numerous British physicians were aware of his illness, among them the legendary Sir Astley Cooper, Sir Benjamin Brodie and Sir Richard Bright. Among the therapeutic alternatives recommended were mineral water, baths with zinc sulfate, valerian, various types of herbs and flowers, strychnine, quinine, silver nitrate, hydrotherapy, electrical stimulation, bloodletting, massage and equine therapy.

However, d'Este reports that he only obtained some relief when he traveled in Scotland and was "embraced and invigorated by the highland air".

The German poet of Jewish origin, Heinrich Heine (1797-1856), presented a clinical picture characterized by progressive visual deficit and visual impairment; however, the presence of ptosis, an uncommon finding in MS, raises doubts about its true diagnosis.

This chronic disease, which affects nerve transmission, injures nerves, inflames and degenerates neurons, producing a lack of recognition by the immune system of its own components, unleashing an erroneous inflammatory process of defense.

There are worldwide reports that the current number of patients with Multiple Sclerosis is approximately 2.5 million. For example, a new case is diagnosed every four hours in countries such as Spain.

It is a disease that affects more women than men, in a ratio of 2.3 to 1, and the peak age of presentation is 25 years old. It is also the most studied neurological disease and with more achievements and better scientific advances in recent decades.

In our country it is estimated that there are about 20 thousand patients diagnosed with Multiple Sclerosis, since it is known that the prevalence of the disease in the national territory is approximately 15 to 17 patients per 100 thousand inhabitants, which represents a low figure compared to other nations. The initial presentation of Multiple Sclerosis varies according to the location of the lesions and affected sites within the Central Nervous System, and that is why it is called "the disease of the thousand faces", due to this polymorphism in its manifestation.

Warning signs are: loss of visual acuity with pain in one eye (optic neuritis), spinal signs (transverse myelitis), alterations in sensitivity and fine movements, gait, balance and motor strength, etc.

This disease is very active if treatment is not started once it is detected, that is, it will progressively advance to become a factor of disability due to the number of injuries and acute activity that this entails.

The diagnosis of Multiple Sclerosis requires several studies, both clinical and laboratory; likewise, treatment must be specific in each of the symptoms and signs for new outbreaks. In addition, this condition requires physical rehabilitation and an adequate management of disease-modifying drugs (AME) to reduce the affectations.

Multiple Sclerosis is a disease that is increasingly detected in all countries and requires significant multidisciplinary management, however, it also needs strategies and resources for research to attend to the affected population.

CLINICAL MANIFESTATIONS

MS may begin suddenly or insidiously. Symptoms may be pronounced or so insignificant that the person may not see a doctor for months or years. In fact, the necropsy of nearly 0.1% of people who had no symptoms throughout their lives has unexpectedly been found to have MS. Similarly, an MRI scan done for some unrelated cause may reveal signs of asymptomatic MS. The manifestations of the disease are very varied and depend on the CNS site of the lesions. Signs of neurological dysfunction are usually identified on examination, often at asymptomatic sites. For example, a person may initially have symptoms in one pelvic extremity and signs in both.

Sensory symptoms are diverse and include paresthesia (such as prickling, itching, tingling, pruritus or painful burning) and hypoesthesia (decreased sensation, numbness or a feeling that the area is "dead"). Unpleasant sensations (e.g., that parts of the body are edematous or moist, crusty or tightly wrapped) are also common. Sensory deficits of the trunk and pelvic limbs below a horizontal line on the trunk (sensory level) suggest that the spinal cord is the point of origin of the sensory disturbance. It is usually accompanied by a banded sensation and constriction around the trunk. Pain is a common symptom of MS and is present in more than 50% of patients. It can arise at any site of the body and change over time to other sites (Fernandez, 2022).

Optic neuritis (ON, optic neuritis) includes decreased visual acuity, visual penumbra or decreased color perception (desaturation) in the central field of vision. Symptoms may be mild or progress to severe visual loss. Rarely, light perception is completely lost. Visual symptoms are usually monocular, but may affect both eyes. Periorbital pain (aggravated by eye movements) is often present before or at the same time as visual loss. An afferent pupillary defect may be identified. Fundus examination data may be normal or indicate optic disc edema (papillitis). Pallor of the optic disc (optic atrophy) is often a consequence of ON. Uveitis is rare and should raise the possibility of other pathologic entities in the diagnosis such as sarcoidosis or lymphoma.

Limb weakness may manifest in the form of loss of power, speed or dexterity, fatigue or gait disturbances. Exercise-induced weakness is a characteristic manifestation of MS corresponding to the upper motor neuron type and is often accompanied by other pyramidal signs such as spasticity, hyperreflexia and Babinski's sign. Occasionally a tendon reflex is lost (which appears to be some lower motor neuron lesion) if a MS lesion disrupts afferent reflex fibers in the spinal cord.

Facial weakness is a consequence of the lesion in the pons and may have manifestations similar to idiopathic Bell's palsy. Unlike Bell's palsy, facial weakness in MS is not associated with loss of ipsilateral taste sensation or with retroauricular pain.

Spasticity is often accompanied by spontaneous and movement-induced muscle spasms. More than 30% of subjects with MS have spasticity ranging from moderate to severe, particularly in the pelvic limbs. It is often accompanied by painful spasms and interferes with the ability to move about, work, or self-care. Occasionally, spasticity

represents support of body weight during movement. In these cases, measures to combat spasticity may do more harm than good.

Epidemiology

MS is three times more frequent in women than in men. The age of onset is usually between 20 and 40 years (slightly later in males than in females), but the disease can occur at any time of life. About 10% of cases begin before the age of 18 years and a smaller percentage begin before the age of 10 years.

Geographical gradients in the distribution of DM have been repeatedly observed and its highest known prevalence (250 cases per 100,000 persons) was localized in the Orkney Islands, located in northern Scotland. In other temperate zones (e.g., northern North America, northern Europe, and southern Australia and New Zealand), the prevalence of DM is 0.1% to 0.2%. In contrast, in the tropics (such as Asia, equatorial Africa, and the Middle East), the prevalence is typically 10 to 20 times lower. Much of this geographic variation appears to be stimulated by exposure to ultraviolet light.

The prevalence of DM has increased steadily (and impressively) in some regions of the world, and over the last 50 years reflects the influence of some environmental displacement. Moreover, the fact that the increase has been observed mainly in women indicates that they are more reactive to such environmental change.

Well-established risk factors for DM include vitamin D deficiency, exposure to Epstein-Barr virus (EBV, Epstein-Barr virus) after early childhood, and smoking. Vitamin D deficiency is associated with increased risk of DM and data suggest that continued deficiency may increase activity once DM has begun. The immunoregulatory effects of vitamin D may explain this apparent relationship. Exposure of the skin to ultraviolet-B (UVB) radiation from the Sun is essential for vitamin D biosynthesis and this endogenous production is the most important source of vitamin D in most individuals; a diet rich in fatty fish represents another source of vitamin D. At high latitudes, the amount of UVB radiation reaching the earth's surface is often insufficient, particularly during the winter months, and consequently low serum vitamin D concentrations are common in temperate zones. The common practice of avoiding direct sun exposure and the widespread use of sunscreens, which with sun protection factors (SPF) greater than 15 block 94% of UVB radiation, could exacerbate vitamin D deficiency in a large population.

There are data supporting that distant EBV infection has some involvement in DM, which is supported by numerous epidemiological and laboratory studies. An elevated risk of infectious mononucleosis (associated with relatively late EBV infection) and elevated concentrations of antibodies to latent EBV nuclear antigen have been repeatedly associated with risk of DM, although the causal involvement of EBV has not yet been established. (Marínez- Altarriba, 2015)

A history of smoking has also been associated with MS risk. In animal models of MS, the lung was identified as a critical site of pathogenic T lymphocyte activation causing autoimmune demyelination.(Cree & Hauser, 2016).

Diagnosis.

For the diagnosis of multiple sclerosis it has to be based on the Mcdonald 2010 criteria, for the relapsing remitting subtype it is required at least one incidence of an attack and a lesion with disseminations shown in the MRI in space and time. For the progressive subtype, neurological deterioration of at least one year is required. These criteria are 80 to 85% effective. Darwin.R (2019)

There are complementary studies to diagnose this disease, such as blood tests, this test is used to rule out other pathologies with symptoms similar to those of multiple sclerosis. The lumbar puncture test, in this test a small sample of cerebrospinal fluid is extracted to analyze the anomaly of the antibodies in the disease. Another very effective test is the evoked potentials test, which records the electrical signals produced by the nervous system in response to certain stimuli, usually this test is used in progressive multiple sclerosis.

Treatment.

There is no treatment that cures this disease, but the treatments used in these patients are aimed at improving their symptoms. The most common symptoms are pain, abnormal or reduced sensation, visual disturbances, fatigue and sudden loss of bladder control.

Pain is classified into two, nociceptive pain and neuropathic pain. In patients with multiple sclerosis, nociceptive pain is related to musculoskeletal changes, i.e. joint pain, myalgia, bladder spasms, dyskinesia, etc. Likewise, neuropathic pain is caused by damage to axons and myelin. Medications used to manage pain include non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants, steroids and antispasmodics. Thus, the "Pain and Cognition Multiple Sclerosis" study was conducted with 171 patients of whom 91 had MS, the use of non-steroidal anti-inflammatory drugs, analgesics (naproxen, ibuprofen, diclofenac and paracetamol), anticonvulsants and antidepressants (pregabalin, gabapentin, carbamazepine) were reported and have been considerably accepted to manage neurogenic pain. Likewise, the use of baclofen and tizanidine treat pain caused by tonic spasms. Other alternatives for pain management are cannabinoids and transcutaneous stimulation, as a study of 19 patients diagnosed with MS showed a significant reduction in pain after administration of Sativex.

For the symptom of fatigue, it is necessary to rule out other possible causes of the symptom because it is necessary to take into account the real context of fatigue to avoid further worsening the symptoms associated with the pathology. It has been shown that amantadine sulfate moderately improves the

symptom of fatigue, however some patients who consume it become resistant to its effect over time, another drug used is Pemoline, its activity is similar to amphetamines and methylphenidate but with minimal sympathomimetic effects. L-Carnitine showed great tolerance and effectiveness for fatigue management.

A study made with 30 people suffering from MS concluded an improvement on the symptom of spasticity with the administration of baclofen, although, due to its side effects there is another alternative, intrathecal baclofen, which is through the implantation of a pump that releases it successively and is administered in severe cases of this symptom. On the other hand, a study made with 187 people suffering from MS announced a great improvement after the use of another drug, tizanidine, whose effectiveness is similar to the aforementioned drug, but its side effects are minimally reported. Likewise, cannabinoids have announced an improvement in the management of spasticity.

For bladder dysfunction, a common condition in MS patients, treatment is focused on easing and improving the symptomatology derived from the condition. Medications to treat neurogenic bladder are anticholinergic drugs such as oxybutynin and tolterodine, both of which cause bladder smooth muscle relaxation and thus reduce urgency, incontinence and bladder hyperactivity. In addition, there are studies with darifenacin and solifenacin (anticholinergics) that announce positive results on bladder urgency and other related symptoms, as well as acceptable side effects they may cause. However, neuromodulation and surgical interventions such as tibial nerve stimulation or sacral neuromodulation are considered in cases where patients have a poor therapeutic response to drugs, for example, a study of 9 women, 5 of whom suffered from MS, announced relevant improvement in incontinence, increased bladder capacity and increased volume in the first non-inhibited contraction after implantation of a cable to stimulate the sacral nerve and connection of a subcutaneous neurostimulator. (Arteaga-Noriega A, 2020)

Regarding disease-modifying treatments, glatiramer acetate has been the most prospectively studied drug in RRMS, showing a good level of efficacy. On the other hand, the pharmacological treatments approved for progressive forms of MS are ocrelizumab, siponimod and cladribine, which have less evidence.

Dimethyl fumarate: this treatment was used in a study of 55 patients, this drug helps to reduce inflammation and prevent relapses to some degree, the study was conducted from 2015 to 2019. The form of administration is orally, in the first week 120 mg was administered every 12 hours and then increased to 240 mg every 12 hours. Despite obtaining good results it was found that this drug has several side effects such as lymphopenia or gastrointestinal diseases. Increasing the dose may cause grade III lymphopenia in patients with multiple sclerosis. In order to administer this treatment, blood studies should be requested from the patient every two to three months to evaluate the lymphocyte levels.

There are other drugs such as monomethyl fumarate which is modified release, as the release is slow and steady there is expected to be a decrease in side effects.

On the other hand there are drugs that are still in the approval phase such as Bruton's tyrosine kinase inhibitor (BTK) is a new treatment under study for relapsing remitting multiple sclerosis and for secondary progressive multiple sclerosis. It acts primarily by modulating B lymphocytes and microglia, which are immune cells of the central nervous system. Stem cell transplantation is a treatment that destroys the immune system of a person with multiple sclerosis and replaces it with transplanted healthy stem cells, the latter is even more experimental and is expected to decrease inflammation and help reboot the immune system.

Rehabilitation.

In this sense, neuropsychological rehabilitation works on the altered brain functions and the emotional impact they entail, seeking to improve the patient's functional capacity. López Gutiérrez (2021)

A study was conducted in a patient with multiple sclerosis and disorganization/apathy, rehabilitation consists of 12 sessions, one per week, 1 hour per session, the patient had to do exercises with pencil and paper where the caregiver helped her, after the sixth week improvements in her behavior were noticed, so the study showed that psychological support is also a tool to help patients with this disease.

DISCUSSION

Treatments for multiple sclerosis are improving over time, but there is still no treatment that cures the disease, the only thing that has been achieved is the damage limitation of this disease, different drugs have been tested for the treatment of this disease but so far one of the most approved is dimethyl fumarate, However, it can have adverse effects, that is why blood studies must be done from time to time, to measure the levels of lymphocytes and thus prevent lymphopenia, for this reason there is still more research to discover drugs that have fewer side effects such as stem cell transplantation studies to restart the immune system and thus combat the disease.

Multiple sclerosis is a disease that is increasing over time the number of cases, so it is very important to know what are the best measures and drugs to combat this disease, slow diffusion drugs are the best response have been proven that these drugs have fewer side effects and therefore their use is more recommended, even so it is recommended to use a treatment depending on the patient and the diseases you have.

CONCLUSIONS

Although the manifestations of the disease are very varied and depend on the CNS site where the lesions are located. For the diagnosis of multiple sclerosis it has to be based on the Mcdonald 2010 criteria, for the relapsing remitting subtype at

least one incidence of an attack and a lesion with disseminations shown on MRI in space and time is required.

There are complementary studies to diagnose this disease, such as blood tests, this test is used to rule out other pathologies with symptoms similar to those of multiple sclerosis. The lumbar puncture test, in this test a small sample of cerebrospinal fluid is extracted to analyze the abnormality of the antibodies in the disease.

MS is three times more frequent in women than in men. The age of onset is usually between 20 and 40 years (slightly later in men than in women), but the disease can occur at any time in life. Vitamin D deficiency is associated with increased risk of DM, and data suggest that continued deficiency may increase activity once DM has begun. There are data supporting that distant EBV infection has some involvement in DM, which is supported by numerous epidemiologic and laboratory studies.

A history of smoking has also been associated with MS risk. In animal models of MS, the lung has been identified as a critical site of activation of pathogenic T lymphocytes causing autoimmune demyelination.

Although there is currently no treatment that cures this disease, but the treatments used in these patients are aimed at improving their symptoms. It has been shown that amantadine sulfate moderately improves the symptom of fatigue, however some patients who consume it eventually become resistant to its effect, another drug used is Pemoline, its activity is similar to amphetamines and methylphenidate but with minimal sympathomimetic effects.

L-Carnitine showed great tolerance and effectiveness for fatigue management. A study made with 30 people suffering from MS concluded an improvement on the symptom of spasticity with the administration of baclofen, although, due to its side effects there is another alternative, intrathecal baclofen, which is through the implantation of a pump that releases it successively and is administered in severe cases of this symptom. For bladder dysfunction, a common condition in MS patients, treatment is focused on facilitating and improving the symptomatology derived from the condition. In relation to disease-modifying treatments, glatiramer acetate has been the most prospectively studied drug in RRMS, showing a good level of efficacy.

Approved drug treatments for progressive forms of MS are ocrelizumab, siponimod and cladribine, which have less evidence. Dimethyl fumarate: this treatment was used in a study of 55 patients, this drug helps reduce inflammation and prevent relapses to some degree, the study was conducted from 2015 to 2019. The form of administration is orally, in the first week 120 mg was administered every 12 hours and then increased to 240 mg every 12 hours. To administer this treatment, blood studies must be requested from the patient every two to three months to evaluate the lymphocyte levels. On the other hand, there are drugs that are still in the approval phase, such as the Bruton's tyrosine kinase inhibitor (BTK), a new treatment under study for relapsing remitting multiple sclerosis and for secondary progressive multiple sclerosis.

Stem cell transplantation is a treatment that destroys the immune system of a person with multiple sclerosis and replaces it with transplanted healthy stem cells, the latter is even more experimental and is expected to decrease inflammation and help reboot the immune system.

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