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NEW DIAGNOSTIC AND THERAPEUTIC CRITERIA FOR NEUROIMMUNE DISEASES

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ABSTRACT

Neuroimmune diseases, such as multiple sclerosis (MS), ataxia, and myasthenia gravis (MG), are inflammatory disorders of the central nervous system (CNS) in which the immune system attacks the brain, causing a pathological state. Neurological dysfunctions can affect both white and grey matter and often involve inflammatory pathways. Immune-mediated neurological diseases are very complex, involving demyelization and inflammation with different clinical manifestations. The therapeutic treatment of neuronal pathologies caused by neuroimmune dysfunction can include both psychiatric and immunotherapeutic drugs. In the non-infectious cerebral inflammatory response, corticosteroids are used for therapy, but immunoglobulins can also be used through intravenous administration. These treatments cause immunosuppression and are often beneficial for the patient. In recent years, much progress has been made in the diagnosis and therapy of neuroimmune diseases, however many pathologies still remain obscure. More in-depth studies should be done on the pathological markers and the immune and inflammatory pathogenic mechanisms.

KEYWORDS: *Neuroimmune disease, CNS, inflammation, antibody, immune therapy, brain, neurology*

INTRODUCTION

Neuroimmune diseases are inflammatory disorders of the central nervous system (CNS) that can occur at any age. These diseases are diverse and include multiple sclerosis (MS), ataxia, and myasthenia gravis (MG) (1), which are discussed in this article. In the interaction between the immune and nervous systems, the immune system can attack the brain, causing a pathological state which can manifest with various neuroimmune disorders, depending on the affected area (2). Often, before neurological disease is acquired, the patient may present warning symptoms such as fever, psychiatric symptoms, headache, and fatigue, which can lead to a pathology focused in one part of the brain or generalized in the CNS.

Immune-mediated diseases of the CNS are often chronic pathologies that are unpredictable and can affect young adults, leading to disabilities and negatively influencing their quality of life, including professional life. Neuroimmune diseases are very complex and involve demyelization and inflammation with different clinical manifestations, often due to the dysregulation of the immune system. For this reason, an update on the study of these disorders certainly helps to improve the clinical pathogenetic aspects. The study of biological markers, genetics, and pathological mechanisms is important in addressing neurological disorders involving the immune response. For these reasons, international

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researchers in this field should join together to exchange information in order to achieve new diagnostic and therapeutic goals.

DISCUSSION

Neuronal damage is often due to a chronic innate immune response, where immune cells such as macrophages, microglia, and activated lymphocytes produce highly inflammatory proteins such as cytokines which contribute to the pathological state of the disease (3,4). Immune dysfunction affecting neurons, astrocytes, and the CNS in general, participates in mediating damage, regeneration, and repair (5), and could be a target for new therapeutic approaches. In the CNS, the activation of the immune response against external insults or against the self, can cause neuroinflammation. This process in the brain is driven by glial cells, which provide support for neurons and help to maintain the homeostasis of the CNS (6).

Antibodies often attack brain target receptors, causing encephalitis. Specific disease-causing antibodies can also be found in the cerebrospinal fluid (CSF) and serum of patients with neuroimmune disorders (7). Magnetic resonance imaging (MRI) examination can help in the diagnosis, and positron emission tomography (PET) imaging is also very effective (8,9).

Neuroinflammation that occurs in brain tissue is different from inflammation of peripheral tissues, as it involves cells with different characteristics. The inflammation can become chronic, damaging neurons and surrounding tissue. Neuroinflammation that occurs not in response to microorganisms has been referred to as sterile inflammation (10). The molecular elements that mediate this sterile inflammation are ATP and calcium cation (Ca^{2+}) flows; while glutamate, nitric oxide (NO), and ATP itself, mediate the crosstalk between glial cells and neuronal glia (11). Among neuroimmune diseases, there are rare neurological disorders that are very complex pathologies which are often genetically derived (12,13). For these diseases, the diagnosis is often difficult to identify, as is the clinical-care management procedure.

Among the neuroimmune diseases that affect the CNS, MS is a leading disorder (14). MS is one of the most common diseases affecting the brain and spinal cord and is an inflammatory demyelinating disease. Myelin constitutes the sheath that covers part of the neuronal body which allows for the rapid transmission of nerve impulses by acting as an insulator, and the loss of myelin results in plaques or lesions and prevents nerves from transmitting electrical impulses in the brain. Nerve conduction velocity is severely affected in MS patients, with the speed of transmission likely dropping to less than 5 m/s in peripheral demyelinated axons over time (15). This pathological mechanism is not yet fully understood by the scientific community and for this reason many researchers around the world are engaged in studying MS diagnosis and therapy. To date, the major hypothesized causes of this autoimmune disease include hereditary and self-factors (16), family history (17), dietary factors (18), excessive lipid peroxidation (19), viral infections (20), and damage to the encephalic barrier (21).

Ataxia is a disease of the CNS characterized by a lack of muscular coordination, with difficulty performing voluntary movements such as walking and grasping objects. Ataxia can be caused by dysfunction of the spinal and/or peripheral nerves, resulting in the lack of coordination between the trunk, arms, and head, and the disease may also present with eye movement dysfunction, incontinence, and difficulty swallowing (22). The first symptoms can be seen starting from childhood or up to around 40 years of age. Viral infections, brain and/or spinal lesions, toxic substances, radiation, or alcohol abuse can also cause ataxia (23). This disease is a rare genetic pathology of the CNS, which also involves immune system dysfunction (24). Ataxia is progressive and disabling, and there is no effective therapy available at the moment.

MG is an acquired autoimmune disease that affects the brain and is characterized by pathological muscle weakness. The disorder predominantly affects female subjects and there is an estimated global prevalence rate of 54 to 350 cases per million persons (25). In 15% of cases, infants may develop transient neonatal MG when the myasthenic mother transmits the antibodies to the fetus during pregnancy (26). MG is an autoimmune disease caused by the dysregulation of the immune and nervous systems. Today it is considered rarer than other neurological diseases and the diagnosis must be made early to achieve improvements with pharmacological treatment.

Obviously, the diagnosis of neuroinflammatory diseases can be different based on the type of pathology. However, there may be diagnostic points that different neurological disorders have in common. For example, it has been noted that in non-degenerative neuropsychiatric disorders, biomarkers and high concentrations of certain phosphorylated amino acids in CSF can be specific, such as that which occurs in Alzheimer's disease (AD) with tau protein (27).

Biomarkers are used for patients with different pathologies and are useful for distinguishing not only the different neurodysfunction, but also for highlighting different variants of the same disease. However, the use of specific biomarkers often leads to results that can be confused with secondary neurological disorders, so to avoid these drawbacks, biomarkers

should be combined with clinical laboratory tests, careful symptomatology, and radiological tests. Blood biomarkers, coming from a simple blood test, can be elevated for various neurological diseases and are therefore very informative, allowing one disease to be distinguished from another.

CONCLUSIONS

In most cases, neuroimmune diseases are disabling and have a great impact on the socio-economic sphere. This heterogeneous group of immune system pathologies also includes autoimmune disorders where the host immune system attacks self-antigens. In neuroimmune diseases, therapy often involves the use of steroidal and non-steroidal anti-inflammatories. If autoantibodies target autoantigens, where B cells produce highly specific autoantibodies against neurons, immunotherapeutic elements may be diverse and involve the use of steroids, immunoglobulins, plasmapheresis, and alkylating agents. However, the use of these therapeutic treatments causes unwanted side effects and therefore, they must be administered with caution. Recently, the use of monoclonal antibodies against B cells is gaining ground and could be a method that complements traditional therapies which are unsatisfactory at the moment.

Conflict of interest

The author declares that they have no conflict of interest.

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NEUROTRANSMITTERS AND BRAIN DEGENERATION

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ABSTRACT

Neurodegeneration is characterized by the death of neurons which leads to progressive damage with the loss of cognitive abilities. Neurotransmitters are divided into neuropeptides, amino acids, purines, amines, and many other molecules, and mediate information in the central nervous system (CNS). Additionally, these neurotransmitters mediate many brain disorders, including Alzheimer's Disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), amongst others. Monoamine neurotransmitters include the catecholamines, dopamine, norepinephrine, and epinephrine, which are vital to the CNS where they indirectly or directly influence most physiological brain functions. Dopamine modulates glutamate-induced excitation in the basal ganglion and cortex, while serotonin, or 5-hydroxytryptamine (5-HT), regulates several higher brain functions such as cognitive control and learning. In addition, acetylcholine (ACh) regulates blood pressure, muscle and cardiac contractions, and intestinal peristalsis, amongst other functions. The regulation of neuropeptides could represent a promising target for the therapy of neurodegenerative diseases.

INTRODUCTION

Neurodegeneration is the progressive damage of the central nervous system (CNS) caused by the decline and death of neurons. The damage gradually worsens with increasing nerve cell death, leading to the loss of cognitive abilities and memory impairment.

The CNS controls muscle and organ functions of the body through the synaptic transmission of signals from the brain to the peripheral nervous system (PNS). Neurotransmitters are neurochemicals that play a vital role in transmitting information in the nervous system, sending signals from pre- to post-synaptic neurons. They are chemicals stored in the axon terminal in synaptic vesicles released across the synapse cleft to be bound to post-synaptic receptors and are vital for the communication of sensory, motor, and integrative neuronal messages and for the functioning of the brain. These small molecules include amino acids, purines, amines, and neuropeptides, among other types. More than a hundred neurotransmitters have been identified; however, more research is continuing to unveil others (1). These neurotransmitters have excitatory, inhibitory, or modulatory effects and are involved in cognition and behaviour.

Aberrant levels of neurotransmitters affect the proper functioning of the brain and cause mental illness and physical and neurodegenerative diseases (2, 3). Neurotransmitters have been implicated in different neurodegenerative diseases, including Alzheimer's disease (AD) (4, 5), Parkinson's disease (PD) (6, 7), Huntington's disease (HD) (8), multiple sclerosis (MS) (9), and amyotrophic lateral sclerosis (ALS) (10) and continue to be studied for their effects on the health of the brain.

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The neurotransmitters can be categorized chemically into three groups: amino acids, amines, and peptides. The main neurotransmitters in the brain include the dopaminergic, cholinergic, glutamatergic, and GABAergic systems, all of which have been shown to be implicated in the complex process of neurodegeneration (11).

This short review aims to serve as an update on the involvement of these as well as other neurotransmitters in major neurodegenerative diseases.

Amino acid neurotransmitters

The amino acid neurotransmitters are an important class common in the CNS, playing a role in fundamental processes of brain functioning, and are implicated in the pathogenesis of different neurodegenerative diseases. The amino acids include neurotransmitters such as glutamate, glycine, and γ-aminobutyric acid (GABA), which play roles in essential brain processes. These neurotransmitters are small molecules with a simple structure; there is an anionic carboxylate group at one end, with a cationic ammonium group at the other.

Raised levels of glutamate, which is produced from glutamine and is the precursor of GABA, can cause the activation of N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to an excess of calcium ions in the post-synaptic neuron that can cause hyperexcitability, excitotoxicity and cytotoxicity (12-14). Animal studies have shown that in the hippocampus, excitotoxicity induced by glutamate has been associated with dendritic branching and limited neuronal regeneration, with subsequent impairment in spatial learning (15). Furthermore, this excitotoxicity may potentially be involved in MS (16), ALS (17), and PD (18). Evidence has also shown that there is an excitotoxic component at work in the pathology of AD (19). Glutamate receptors, which are complex and numerous in the CNS, include twenty different types that are categorized as ionotropic or metabotropic, and then further subdivided into groups. Metabotropic group II glutamate receptors (mGluR2 and 3) have been shown to play a role in AD, while group III receptors (mGluR4, 6, 7 and 8) may be implicated in PD (20). It has been reported that disrupted glutamate homeostasis may be involved in neurodegenerative diseases including ALS, MS, AD, PD, and HD (21,22).

Astrocytes are vital for regulating glutamate homeostasis, as they control extracellular levels of glutamate through uptake and release mechanisms (23). Reduced glutamate uptake by astrocytes has been detected in HD patients (24) and astrocyte reactivity is implicated in other neurodegenerative diseases as well, such as AD, PD, and ASL (25).

The amino acid neurotransmitter GABA is formed through glutamate decarboxylase and has inhibitory effects in the adult brain, where it is the main inhibitory neurotransmitter within CNS, PNS, and enteric nervous systems. Low levels of GABA lead to neuronal hyperexcitability and, therefore, an equilibrium is important for brain functioning. Disruption of GABA homeostasis is associated with different neurological and neurodegenerative disorders including AD, PD, HD, and possibly MS, where lower levels of sensorimotor GABA concentration have been seen correspondence with the worsening of motor function (26-28).

Monoamine neurotransmitters

The monoamine neurotransmitters are a class of neurotransmitters involved in diverse physiological and mental functions containing one amino group which is connected to an aromatic ring by a two-carbon chain. This group of neurotransmitters includes catecholamines, which contain the chemical structure catechol, with the amino acid tyrosine as the precursor. The category of catecholamines includes dopamine, norepinephrine, and epinephrine.

Dopamine (4-(2-aminoethyl)-1,2-benzenediol) is a vital neurotransmitter in the CNS that indirectly or directly affects most physiological functions in the brain (29).

The important enzyme monoamine oxidase (MAO) is involved in the catabolism of monamine neurotransmitters and xenobiotic amines and has been established to play an important role in the neurodegenerative disorders of PD and AD (30,31). In PD, MAO is involved with the degeneration and death of dopaminergic neurons in the substantia nigra (32) and the administration of dopa therapy can be proactive for increasing levels of dopamine and reducing the production of ROS and oxidative stress (33). In AD, the elevation of type B monoamine oxidase (MAO-B) has been linked to dysregulated equilibrium that includes impaired mitochondrial function, and increased oxidative stress, with excitotoxicity and apoptosis that leads to the death of neurons (30, 34).

Dopamine dysfunction also affects HD; striatal levels of the neurotransmitter are initially increased, causing increased hyperkinetic movements, with a decrease seen in the later stages of the disease that results in hypokinesia (35). Moreover, dopamine modulates glutamate-induced excitation in the basal ganglion and cortex so that dopamine dysregulation may contribute to excitotoxic cascades (35).

The neurotransmitter serotonin (5-hydroxytryptamine) also regulates many physiological functions, including regulating different higher brain functions such as cognitive control, learning, and affect (36, 37). Serotonin also directly

affects other neurotransmitters, inhibiting the release of dopamine and modulating GABA and glutamate transmission (38).

Serotonin is implicated in the pathogenesis of AD, with serotonergic denervation and alteration having been suggested to play a role, and improved serotonergic functioning has been seen with modified and improved symptoms concerning memory and cognition in AD patients (39). In fact, modulation of the serotonergic system could represent a promising target for AD therapy (40).

Additionally, serotonin may play a role in PD, which was believed to be predominantly affected by the dopaminergic system. Serotonergic dysfunction has been shown in PD animal studies (41), as well as imaging studies (42), and may affect the nonmotor symptoms of the disease, such as fatigue (43), depression (44), visual hallucinations (45), and changes in weight (46).

Epinephrine and norepinephrine act as hormones as well as neurotransmitters in the autonomic nervous system. Elevated concentrations of these neurotransmitters are thought to be involved in AD (47), with most evidence showing changes in the noradrenergic system, and loss of noradrenergic innervation contributes to the pathogenesis and progression of the disease (48-50). At the start of the disease, this affects the noradrenergic neurons of the locus coeruleus, together with the formation of tau protein, and at later stages, there is a loss of noradrenergic neurons and affects neuronal anatomy, neurotransmitter systems, and the noradrenergic receptors (51, 52).

In the CNS, histamine acts as a neurotransmitter where it is released by histaminergic neurons in the hypothalamus. It is involved in a variety of physiological functions, including arousal, cognition, circadian rhythms, and neuroendocrine regulation (53). Analysis of postmortem brains from AD patients have shown increased histamine levels (54), and other studies have indicated an association of the disease with histaminergic dysfunction (53, 55, 56).

Acetylcholine

Acetylcholine (ACh), the first neurotransmitter that was discovered, plays a role in numerous physiological processes in the PNS and the CNS. In the PNS, ACh regulates blood pressure, muscle and cardiac contractions, and intestinal peristalsis, amongst other functions. In the CNS, it is involved in the control of voluntary movements and sleep, as well as cognitive processes such as learning, attention, and memory. The chemical structure of ACh is reflected in its name; it consists of an ester of acetic acid and choline.

Cholinergic alterations can result in neurodegenerative diseases such as AD, PD, and HD, with effects concerning the cognitive, behavioral, and motor disabilities of these pathologies (57). Memory impairments are related to the degeneration of central cholinergic neurons, and neuroinflammation, a trademark of neurodegenerative diseases, may result, as cholinergic signaling has anti-inflammatory effects and modulates inflammation (58).

Pathological disruptions have been seen in the cholinergic system of AD patients and it is believed that disruption of this system indirectly leads to the impairment of cognitive function (5 Francis). Additionally, the hallmark characteristics of AD, amyloid-β plaques and neurofibrillary tangles of hyperphosphorylated tau, have direct and indirect cytotoxic effects on neurotransmission, impairing synaptic integrity and altering the release of neurotransmitters (59).

CONCLUSIONS

In the last century, hundreds of neurotransmitters have been discovered, with intense investigation continuing for the identification and elucidation of their roles in the body. Altered homeostasis of neurotransmitters and dysfunctional neurotransmission leads to severe pathology, and thus far, research has shown that neurotransmitters play key roles in neurodegenerative disorders such as AD, PD, HD, and ALS.

Further research is necessary to better understand the complex mechanisms of neurotransmitters in neurodegenerative disease and their actions on brain health, with the goal of improving the treatment and early monitoring of these disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

IMMUNOLOGICAL RESPONSE IN MULTIPLE SCLEROSIS

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that results in demyelination. The disease affects millions of individuals worldwide (1), afflicting more women than men (2). MS is characterized by T lymphocytes attacking and destroying myelin, a process that leads to neurological disease. Patients affected by MS present neurological and physical disabilities with motor impairment and difficulty with movement coordination.

Neurodegenerative diseases, including MS, are characterized by inflammation in the CNS, due to the activation of immune cells. In recent scientific literature, many studies have dealt with MS and notable progress has been made in both diagnosis and therapy (3-5). Today, several drugs are available for this chronic progressive disease, although all the currently available therapies are still unsatisfactory. The diagnosis should be made as early as possible, even though it is often difficult in patients who do not present typical symptoms.

MS is an autoimmune disease that creates inflammatory damage, affecting nerve cells in the brain and causing physical and mental disorders. Widespread brain damage occurs with inflammation, demyelization, and damage to neurons both in the CNS and at the medullary level, affecting both the white matter and deep gray matter (6). White matter lesions, which are visible with magnetic resonance imaging, are now treated with better results, however there is still no specific therapy. The disease can affect young individuals, including those under 35 years of age, and occurs with a ratio between females and males of approximately 3 to 1, respectively. Interestingly, over the last century, the incidence of MS in women has risen while there has been no increase in that of men (7). The main symptoms that occur in MS are loss of sensation, weakness, depression, cognitive impairment, diplopia, and others (Table I).

Table I. *Some of the symptoms that occur in multiple sclerosis.*

• weakness	• unstable mood	• incontinence
• fatigue	• ataxia	• dysphagia
• cognitive impairment	• pain	• diarrhea
• depression	• loss of sensation	• muscle spasms
• anxiety	• paraesthesia	• problems with speech or swallowing
• diplopia		

The diagnosis of MS is mainly based on the symptoms and behaviour of the patient. Clinical tests include MRI scans, which can highlight demyelization plaques that appear in the brain and spinal cord. Diagnostic help is also given

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by the examination of the cerebrospinal fluid through a lumbar puncture, which highlights leucocytosis with an increase in antibodies (presence of elevated IgG) that testify to the excessive immune response.

Therapy in this disease is somewhat deficient because there are no specific drugs for treating MS, although treatment with corticosteroids has been seen to delay the worsening of the pathological state and prevent secondary effects (immunosuppression). The individual suffering from MS should undergo both physical and psychological rehabilitation. The disease has been roughly classified into four clinical aspects: a) relapsing and remitting, b) secondary progressive, c) primary progressive, and d) progressive relapsing. These four categories often present overlapping clinical signs that do not precisely define the state and complexity of the disease.

MS is multifactorial and is most likely a combination of immune dysfunction, genetic tendency, and environmental factors. Regarding genetic risks, patients show risk alleles in the genes for the major histocompatibility complex, but also dysfunctions of the receptors of some cytokines such as T cell growth factor (TCGF) (also called IL-2) and IL-7 (8). In addition, it was recently seen that MS is also associated with low levels of vitamin D, some viruses such as the Epstein Barr virus, and cigarette smoking.

The immunological response in multiple sclerosis

Autoimmune diseases affect approximately 5% of the population in industrialized countries (9). These are very complex and poorly understood diseases that involve the immune system and in particular, T cells or B cells. In these cases, the immune system intervenes without any infection or other apparent pathology, causing damage throughout the body. In MS, the immune system attacks the self-components, in particular, myelin which is the protective sheath surrounding nerve fibers.

At the immune level, the disease originates in the thymus, which is unable to eliminate immunoreactive cells that react against the patient's own body. The immune cells involved in this process are T and B lymphocytes, as well as macrophages, which intervene with CD68 in demyelinated areas.

Adaptive immunity is involved in MS, and CD4+ T cells represent a genetic risk factor. Th1-type cells also take part in this pathological disease by mediating inflammation. Th1 cells generate the interferon gamma-producing cytokines TGF-β1, IL-23, IL-6, and IL-21, which differentiate Th17 cells that in turn produce IL-17. The pathogenic effect of these cells is limited by Treg cells, which produce the anti-inflammatory cytokine IL-10, and the dysregulation of these leads to a pathological effect of T cells. CD8+ cells contribute to the MS disease state and are found in high numbers in the white and gray matter of patients, causing damage to the CNS. CD8+ lymphocytes produce pro-inflammatory cytokines such as IL-17.

In MS, innate immunity participates in CNS damage with several cells, including mast cells (MCs) which are present in large numbers in plaques. MCs contribute to the inflammatory state by secreting cytokines and chemokines, as well as histamine, tryptase, and chymase, that promote neuronal degeneration. Innate immune cells such as macrophages are also involved in neurodegeneration and inflammation. The disease is characterized by immune cell-derived inflammation that damages myelin and this causes plaques to become chronic.

The underlying causes of MS are still unknown. It is certain that the disease is characterized by the loss of myelin due to an abnormal immune response. This characterizes it as an immune disease in which self-cells attack myelin as if it were recognized as non-self. Various hypotheses concerning the onset of MS have been studied in recent years. The factors that are most taken into consideration are: climate, genetic predisposition, infectious agents, and ethnicity. MS occurs more often in higher-latitude countries (where vitamin D is lacking), in individuals whose lifestyle includes habits such as the use of alcohol and cigarette smoking, and in subjects of Caucasian origin (10). However, infectious agents such as bacteria and viruses, and genetic predisposition can also be predisposing elements for developing MS. The hereditary factor in MS is also very important and involves the HLA region of chromosome 6, a phenomenon that occurs in many autoimmune diseases. However, all these hypotheses still need to be evaluated and confirmed by scientific research.

CONCLUSIONS

MS is a disabling disease that affects the brain and spinal cord, causing pathological effects throughout the body with degeneration of the CNS. The pathogenesis of the disease involves different immune cells with B lymphocytes and effector CD4 T-cells playing important roles. Additionally, CD8 T cells may also play a distinguishing role in the disease. In fact, these lymphocytes represent the main therapeutic target for MS. T and B cells activated by autoantigens expand and contribute to the inflammatory state, affecting the neuroaxonal degeneration of the CNS. In addition, some cytokines such as IFN-γ and IL-17 appear to be more involved in the pathogenesis of the disease, where they are found in abundant quantities both in the CNS and in the cerebrospinal fluid.

New therapies have helped improve longevity in MS and hindered disease progression, but research needs to continue to provide better diagnostic and therapeutic options for treating patients.

Conflict of interest

The author declares that they have no conflict of interest.

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