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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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