Autoimmune diseases of the nervous system

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Abstract

As a growing number of reports suggests that neurologic diseases have an autoimmune basis, physicians are confronted with new issues in diagnosis and treatment. At the same time, a better understanding of antibody-induced neurologic disorders has been characterized in the last decade by an increasing knowledge of the molecular specificities of autoantibodies. This review summarizes some current concepts in autoimmune diseases of the nervous system.

Key words: auto-antibody, autoimmune disease, myasthenia gravis, inflammatory neuropathy, multiple sclerosis.

Introduction

In recent years, the neurological sciences have witnessed the appearance of numerous studies on the autoimmune bases of various pathologies in this field, which in turn, has brought new prospects in terms of diagnoses and therapeutic approaches. In general, in all these diseases, the pattern of lesion of the nervous system is extremely selective, and antibodies targeted at some of the components of the tissues or organs involved in the process can be detected in the serum or cerebrospinal fluid (CSF) of these patients.

Therefore, autoantibody research currently constitutes a habitual investigation in the neurologist's clinical practice, as autoantibodies have been linked to several pathologies of the central nervous system (CNS), peripheral nervous system and muscle. Vasculitis of the nervous system, which although frequent, constitutes a nerve lesion secondary to the primary involvement of the vascular structures, will not be covered within this topic.

Myasthenia gravis and myasthenic syndromes

Myasthenia gravis (MG) constitutes the paradigm of neurological diseases of autoimmune cause, and is the only one in which the physiopathological mechanisms are relatively well understood. In MG, the autoimmune lesion targets the acetylcholine receptor (AChR) in the postsynaptic membrane of the neuromuscular plate.[1,2] This leads to a decrease in the number of available receptors, whereby the same quantity of acetylcholine (Ach) is not as effective in generating muscle action potentials, resulting in the appearance of the characteristic myasthenic fatigue. If the repeated stimulation continues, there will also be a gradual decrease in the amount of Ach released, which is the mechanism involved in the typical decrease response found in repetitive nerve stimulation carried out in electrophysiological studies.

The neuromuscular alterations in MG are due to the autoimmune response, mediated by the anti-AChR antibodies. These autoantibodies decrease the number of available receptors in the neuromuscular plate, through 3 mechanisms.[1,3]

1) increase in AChR degradation speed (by endocytosis).
2) blockade at the binding site in the Ach receptor;
3) direct lesion of the postsynaptic membrane by the antibody, activating the complement.

The factor responsible for the appearance and maintenance of the autoimmune response has not yet been fully identified. However, the thymus appears to play an important role in this process, as it is altered in around 75% of patients with MG.[1,3] In 65% it presents hyperplasia, with active germinal centers within it, and in 10% we can identify the existence of thymic neoplasia (thymoma).

One of the hypotheses mentioned by some authors1 is that a specific cell group, the intra-thymic myoid cells, with characteristics resembling those of the muscle cells and presenting AChR on their surface, may constitute the source of the autoantigens and trigger the autoimmune reaction in the thymus

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TABLE I

Autoantibodies in diseases of the nervous system

Disease	Antibody
Myasthenia gravis	anti-AChR; AMA
Lambert-Eaton myasthenic syndrome	anti-calcium channels
IgM monoclonal neuropathy	anti-MAG
Motor neuron disease with IgM monoclonal	anti-ganglioside (GM1, GD1B)
Motor neuropathy	anti-GM1
Paraneoplastic sensory neuropathy	anti-Hu
Thrombotic vascular accidents	anti-phospholipids
Paraneoplastic cerebellar degeneration	anti-Yo
Multiple sclerosis	anti-MBP; anti-PLP

gland. Other authors,[2] however, indicate that only in cases associated with thymoma will there be a cross--reaction between the antigens shared by the tumor and by the peripheral structures, while in the others a primary alteration of the immunological reactivity may be the cause (AChR-reactive T lymphocytes were also identified in individuals without MG).

Anti-AChR antibodies can be found in the blood serum of 80-90% of patients with MG[1,4] (in just 50% in the ocular myasthenia forms). The positivity of these antibodies is practically diagnostic of MG, but their absence does not rule out the diagnosis. Their levels cannot be related to the degree of activity of the disease either, but their decrease or disappearance in a patient after therapy is generally correlated with clinical improvement of the situation.

The existence of other antibodies was also demonstrated in these patients, although with less specificity than the anti-AChRs; this is the case of the anti-skeletal muscle antibodies,[2,5-7] strongly related to the occurrence of the former, but apparently not dependent, and whose importance in the pathogenic mechanism is not yet well-known. Anti-sarcoplasmic reticulum antibodies,[2] which can themselves interfere in muscle function, have also been recently described.

Lambert-Eaton Myasthenic Syndrome, meanwhile, is generally associated with neoplasia, in the majority of cases with small lung cell carcinoma.[2] It also constitutes an autoimmune lesion situation, as it affects the calcium channels of the presynaptic membrane of the neuromuscular plate, therefore anti--calcium channel antibodies can commonly be found.[4]

Autoimmune neuropathies

Many of the acquired inflammatory neuropathies are forms of demyelinating neuropathy.[8] Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are examples of a diffused demyelinating process. Their etiopathogenesis appears to be of the autoimmune type, and the antigens responsible for the lesion have not yet been identified.

However, the existence of an antibody targeted at a specific antigenic structure has been described in some types of chronic neuropathy.[8,9] These antigens are frequently glycoconjugates located in the peripheral nerve, and are either glycolipids (especially the various ganglioside - GM1, GD1a, GD1b, GT1b, Gq1b, LM1) or glycoproteins (myelin associated glycoprotein - MAG - and myelin glycoprotein Po). In other situations, the antigen (Hu) presents a cross-reaction with the neoplastic cells of the small lung cell tumor; this antigen is expressed in the neuronal nucleus and cytoplasm, and its habitual function appears to be that of a neurogenesis and neuronal stability regulating protein.

The anti-Hu antibody is related not only to a condition of sensory neuropathy, but also to a process of encephalomyelitis, two paraneoplastic syndromes that are sometimes interlinked.

Therefore, there are already various pathological processes of the nerve related to specific autoantibodies (*Table 1*).

As regards GBS and CIDP, the diversity of pathological alterations is manifested not as a homogeneous entity, but rather, as a diversity of clinical forms ranging from pure demyelinating neuropathy to frank axonal degeneration.[8] The complex nature of the underlying autoimmune process is manifested by a variety of associated mechanisms involving the humoral and cellular immune processes.

Autoantibodies for different ganglioside have been found in the serum of patients with GBS,[10,12] specifically reacting with LM1 antigen, a ganglioside that, in adults, is only expressed in the peripheral nerve, unlike the others that are present either in the peripheral, or in the central structures. However,

the results have not been satisfactory, since the titers referred to are generally low, and are absent in many patients.

The importance of humoral immunity in this pathological process is also highlighted by the therapeutic response, either to plasmapheresis, or to the intravenous administration of immunoglobulin. In relation to the latter, the most likely therapeutic mechanism is that of blocking of demyelinating antibodies, probably by an anti-idiotypic effect.[8]

As regards to cell immunity, the increased levels of interleukin-2 in patients with GBS and in some cases of CIDP suggests accentuated proliferation of T lymphocytes in these pathologies. In animal studies, a major antigen was identified for T lymphocytes in the myelin of the peripheral nervous system, the P2 protein.[8] In Lewis rats, the passive transfer of this protein gives rise to a recurrent chronic inflammatory neuropathy. Whether or not this constitutes an important mechanism in patients with GBS or CIDP has not yet been demonstrated.

In relation to CIDP, in those related to IgM monoclonal gammopathy, about 50% of the cases present an anti-MAG autoantibody. Several authors do indeed mention that this situation presents unique clinical, pathological and immunological characteristics.[8,9,13]

It is a primary demyelinating neuropathy in which, unlike the situations linked to an IgA or IgG paraproteinaemia, immunoglobulin is identified in the myelin in the nerve biopsy (this phenomenon is even more frequent in patients that test positive for anti-MAG antibodies). The marked decrease identified in the thickness of the myelin lamellae is also almost pathognomonic for this situation.

From a clinical point of view, some factors differentiate this situation from the other paraproteinaemias:[8]
1) greater frequency of sensory alterations and ataxia;
2) greater frequency of alterations in nerve conduction;
3) greater frequency in dispersion of muscle action potential.

From an immunological point of view, it was also identified that monoclonal IgM binds, in this situation, either with MAG or the Po antigen, or with two other glycosphingolipid compounds present in the peripheral nerve.[9]

The CIDP linked to IgM paraproteinaemia with anti-MAG antibodies therefore appears to be an immunologically mediated process, and the lesion sequence can be initiated by the binding of the antibodies to the MAG and Po antigens.[4] An experimental model by passive transfer of antibodies has already proven possible in laboratory animals.

Multiple sclerosis

Demyelinating diseases occupy an important place in the area of neurological sciences, either due to their frequency, or to their habitual tendency to affect young people. Today these pathologies still give rise to various problems in relation to the neurobiological, immunological, virological and genetic aspects involved. Their evolution may be chronic (multiple sclerosis - MS) or acute (acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis); all these pathologies present selective inflammatory lesion of the CNS, generally without peripheral involvement.[14]

With regard to MS, nowadays this disease is the main non-traumatic cause of neurological dysfunction in young adults in the USA, from an epidemiological perspective. In terms of its etiopathogenesis, there is evidence to suggest that it has an autoimmune etiology, probably triggered by a viral infection in a genetically susceptible individual.

There have been studies on this genetic susceptibility in humans and there is a marked association between MS and some HLA haplotypes, specifically with DR15, DQ6 and Dw2.[15,16]

The investigation on the autoimmunity of MS has focused, in recent years, on the importance of T lymphocytes in its pathogenesis. This concept is derived from the evidence that T lymphocytes which are reactive against some myelin antigens, specifically myelin basic protein (MBP) and myelin proteolipid protein (PLP) are mediators of the inflammatory process in experimental allergic encephalomyelitis (EAE), a laboratory-produced model of demyelinating diseases. This hypothesis is supported by the possibility of passive transfer of sensitized lymphocytes that trigger the disease in the receptor animal, provided it is genetically susceptible.[14,17]

The evidence that the T lymphocytes play an important role in the pathogenesis of MS is, therefore, indirect, and based on clinical and experimental observations. Thus, the frequency of the appearance of MBP-reactive T lymphocytes appears to be increased in the peripheral blood of these patients, and these cells present a high frequency of mutations, which is

suggestive of in vivo chronic stimulation. Other data also reveal that lymphocytes sensitized to MBP and PLP are found in patients with MS in significantly higher concentrations in the CSF, compared with their frequency in the peripheral blood.[14] The lesional process in MS has been inferred through data obtained in the EAE study. It is a phased process that involves the following stages:[17]

• Passage through the haematoencephalic barrier by the activated T cells, a step not dependent on antigenic stimulation;

• Recognition of the T cells of the antigen to which they are sensitized, expressed in various cells of the CNS, particularly the perivascular microglia;

• After local re-stimulation, the T cells produce various cytokines and inflammatory mediators, including interferon-gamma (IFN-γ) and the tumor necrosis factor-alpha (TNF-α). These mediators induce the expression of antigens of the major complex of histocompatibility by a higher number of cells, thereby functioning as an amplifier of the inflammatory reaction;

• Finally, the myelin lesion occurs through the combination of various factors, such as the cytokines, autoantibodies, complement activation and cytotoxic T cells.

It has also been demonstrated that there are several other autoantigens that play an important role in this process, besides MBP and PLP, such as MAG, myelin oligodendrocyte glycoprotein (MOG) and an astrocyte-derived protein, S-100B.[15,17]

Less is known about the importance of autoimmune humoral mechanisms MS, although it is acknowledged that one of the main characteristics of this pathology is intrathecal IgG synthesis. Anti--MBP autoantibodies, and less frequently and in lower titers, anti-PLP antibodies, have been identified in the CSF of these patients.[15,18] A recently-published study enables us to foresee a hypothesis that these autoantibodies could, in fact, be different forms of MS, since they have not been identified together in the same patient.[18]

The importance of this investigation obviously reflects the therapeutic strategies that may be followed in the future, with these patients. Thus, interferon--beta (IFN-β) can be considered a prototype of a biological immunomodulator, with its action apparently consisting of: [19]

• Activation of the suppressor cells;

• Decrease in peripheral activation of T lymphocytes;

• Ddecrease in the production of IFN-ψ, TNF-a and other cytokines.

Other strategies, however, are being analyzed, focusing mainly on controlling the production of inflammatory mediators by the activated T cells. ■

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