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Neuropsychiatric involvement in systemic lupus erythematosus: role of antibodies

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Abbreviations: SLE, systemic lupus erythematosu; NPSLE, neuropsychiatric manifestations of lupus; Anti-dc DNA (double strand), NMDRA, anti N-methyl – D-aspartate receptor

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, with variable clinical expression and severity, with an estimated global prevalence of between 20 – 178 cases per 100,000 people, with multiorgan involvement which is determined by the production of autoantibodies directed against abundant nuclear material and deposition of immune complexes that lead to the activation of the inflammatory response and underlying tissue damage influenced by various variations polygenic cells that confer a predisposition by altering physiological processes such as clearence of immune complexes and autoreactive B lymphocytes to C4 and C1q deficiency.[1]

Many single nucleotide polymorphisms have been identified as elements that predispose to the development of autoimmune diseases, such as STAT4, PTPN22, TNIP1, PRDM1, JAZF1, UHRF1BP1. The alteration in the mechanisms of epigenetic regulation of the expression of these genes through DNA methylation and histone modifications can be affected in the context of environmental factors such as exposure to ultraviolet radiation, drugs such as hydralazine and procainamide, viral infections such as Epstein Barr, and hormonal factors such as hyperestrogenism, the latter conferring greater susceptibility to the female gender as in most autoimmune diseases, in the case of SLE, a 9:1 ratio has been estimated with respect to men, less frequently in prepubertal and postmenopausal ages, however, cases have been described at advanced ages due to the increase in survival.[2]

Given the polygenic nature and clinical heterogeneity for the classification of these patients, criteria have been validated that allow the evaluation of multisystem involvement combined with the serological expression profile, in 2019 the latest classification criteria were developed, supported by the EULAR (European League Against Rheumatism and ACR (American College of Rheumatology) composed of 7 clinical domains and 3 immunological domains. Clinical domains include: Constitutional, Hematological, Mucocutaneous, Sererositis, Musculoskeletal, Renal, and Neuropsychiatric.[3]

The neuropsychiatric manifestations of lupus (NPSLE) have a variable frequency between 6 – 40% at the time of diagnosis and between 17 and 60% during the course of the disease, they can have various clinical expressions and severity from mild to severe10 some of them are focal neurological syndromes (aseptic meningitis, cerebrovascular disease, demyelinating syndromes, headache, movement disorders, myelopathy and seizures), diffuse neurological syndromes (acute confusional state, anxiety disorders, cognitive dysfunction, mood disorders, psychosis), peripheral nervous system involvement: autonomic disorders, Guillain Barré syndrome, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.[4] Within the approach to a patient with SLE and neuropsychiatric manifestations, the first thing that must be ruled out are those non-inflammatory causes of neurological involvement, some such as: the use of certain medications, presence of metabolic disorders and infections.

Pathophysiology

The starting point of the NPSLE is endothelial injury through various mechanisms directly induced by cytokines and/or deposition of immune complexes or through prothrombotic phenomena in predisposed individuals. Antibodies play an important role in the genesis of various phenomena involved, one of the related antibodies is Anti-dcDNA (double strand) that can cross-react with N-Methyl-D-aspartate receptor 2 (NMDAR 2) in neurons. NMDARs have also been implicated in the mediation of neuronal damage due to glutamate excess that ends with cellular apoptosis, the presence of these antibodies is related to dysfunction of the blood-brain barrier (interface that separates brain tissue from circulation) which is the main protective factor for the passage of proteins and antibodies to brain tissue. therefore, the finding of albumin in the CSF (Q albumin) and the presence of antibodies that produce direct injury at the cellular level such as anti Smith (Sm), anti P ribosomal, anti N-methyl – D-aspartate receptor (NMDRA) suggest the disruption of this normally impermeable membrane after inflammatory mechanisms caused by the same antibodies or by the presence of a concomitant infection. There are other pathways capable of transporting inflammatory cells such as the lymphatic pathway, perivascular pathway and the intradural lymphatic network.[5]

Anti-ribosomal P antibodies are a group of highly specific antibodies of SLE, present in 46%, are associated with neuropsychiatric manifestations such as psychosis, seizures, transverse myelitis, by binding of this antibody to the piriform and cingulate cortex that are part of the limbic system linked to mood disorders, from the binding of this antibody to the carboxy-terminal region of three ribosomal proteins (P0, P1, P2) bound to the P epitope found in a transmembrane protein present exclusively in neurons related to ubiquitin ligase function that regulates NMDAR function in the synaptic region in

addition to stimulating the direct release of proinflammatory cytokines such as tumor necrosis factor alpha. Some studies have shown that neurons in both the amygdala and hippocampus are vulnerable to cell death mediated by these anti-NMDAR antibodies, which could lead to the conclusion that both cognitive and behavioral impairment could be secondary to the damage induced by these anti-NMDAR antibodies.[6]

NMDAR are a group of glutamate receptors made up of 2 NR1 and 2 subunits that are expressed in the neurons of the hippocampus where they play an important role in memory and learning, the NMDAR pore allows the entry of calcium into the ligand junction initiating a "downstream" signaling cascade, some studies suggest an association between high titers of antibodies against this receptor and alterations in memory and depression. while in other studies it is not. The NR2A subunit has been found on the surface of neuronal cells of neuropsychiatric lupus patients with different types of epilepsy, Yan yang et al (2017) evaluated the presence of anti NR2A in a cohort of 107 patients with seizures related to neuropsychiatric manifestations of SLE, finding significantly high levels of the antibody and correlation with SLEDAI disease activity. serum anti-DNA dc and complement levels suggesting correlation with NPSLE pathogenesis.[7]

Cross- reaction between anti- NMDA and Anti DNAdc

Anti-NMDRA generate a cross-reaction with circulating anti-dDNAs that bind to NR2A and NR2B subunits, leading to neuronal death due to increased calcium influx and excitotoxicity, despite the fact that these two autoantibodies do not directly correlate with lupus activity at the neuropsychiatric level, even though they are positive. However, not all Anti-DNA are able to react completely with NR2, in patients with SLE a frequency of approximately 30% of Anti-NR2 has been reported, although the positivity of Anti-RN2 in cerebrospinal fluid has been shown to be associated with NPSLE, a significant correlation has not been found between the presence of Anti-NR2 in serum and cognitive dysfunction but it has been found with depression.[6] Given the scarcity of data related to studies in humans on gene expression, exploration in animal models is resorted to, presuming similarity with genotypic and pathophysiological expression in humans.

Conclusion

Neuropsychiatric lupus is a set of manifestations of inflammatory etiology and variable severity, which predispose to progressive damage, resulting in short- and long-term functional limitation related to the type of involvement of either the central or peripheral nervous system. The pathophysiological expression related to neurological involvement, whether focal or diffuse, has been studied in immunized animal models exposed to INF1, highlighting the direct role of autoantibodies on brain tissue when crossing the blood-brain barrier and in addition to the cross-reaction of double-stranded anti-DNA against the N-Methyl-D-aspartate receptor (NMDAR) subunit 2A and 2B. applying these findings to human pathophysiology given the scarcity of data related to direct studies in human brain tissue and according to genetic similarity with animal models (mouse – rabbits – murine).

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None

Conflicts of interest

The author declares that there are no conflicts of interest.

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