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Editorial

# Neuropsychiatric Manifestations in Systemic Lupus Erythematosus: Physiopathogenic and Therapeutic Basis☆

## Manifestaciones neuropsiquiátricas en lupus eritematoso generalizado: bases fisiopatogénicas y terapéuticas

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Systemic lupus erythematosus (SLE) affects at least 0.1% of the global population[1]; its neuropsychiatric expression has been compiled by the ACR into 19 syndrome that range from vascular headache and behavioral alterations to cognitive abnormalities and other severe, disabling manifestations such as transverse myelitis, which have a well defined physiopathogenic basis, leading to a targeted treatment, but represent both a diagnostic as well as therapeutic challenge.[2]

The prevalence of neuropsychiatric lupus (NP-SLE) varies from 37% to 95%,[3] depending upon the definition, heterogeneous designs (prospective or retrospective), the population studied (adult or pediatric), ethnicity, time since onset, severity and follow-up.[4] The most prevalent manifestations include cognitive alterations (55%–80%), headache (24%–72%), mood disorders (14%–57%), stroke (5%–18%), convulsions (6%–51%), polyneuropathy (3%–28%), anxiety (7%–24%) and psychosis (8%). The rest of the syndromes have a prevalence of ≤1%.[2] Cognitive alterations are not related to the time since onset of the disease, activity or treatment, and the most common are a reduced attention, memory (particularly visospatial) and executive dysfunction.[5] It may be variably associated to dementia in 25% and most often improve with treatment.[6] Of the psychiatric alterations, depression, auditory hallucinations and anxiety disorders predominatel.[5] Transverse myelitis (TM) is rare but severe; its onset usually occurs in the first five years of disease. 50% of patients present it at disease onset and it recurs in 21%–55%; A fifth (21%) do not improve or worsen.[7] Convulsions frequently accompany other SLE manifestations, but may occur as an isolated event, most commonly in younger patients and are associated to antiphospholipid antibodies (APL).[8,9]

The diagnosis is clinical and is additionally supported by laboratory and imaging testing, as well as neuropsychiatric evaluations. It represents a therapeutic challenge because none of the syndromes are exclusive to SLE and up to 41% is attributable to other causes; it is specifically necessary to rule out central nervous system infection, uremia, thrombotic thrombocytopenic purpura, reversible encephalopathy, steroid induced psychosis and hypertension.[6] Magnetic resonance (MR) is the test of choice[10]; it detects focal lesions in the subcortical and/or periventricular white matter (15%–60%), hyperintensity in the gray matter (24%–30%), atrophy, ventricular dilation and infarctions, although 30%–40% of NP-SLE has a normal MR.[11] Positron emission tomography and single or unique photon emission computed tomography detect hypoperfused or hypermetabolic areas and have a better sensitivity than MR.[12] In spite of advances, imaging studies do not allow the differentiation of active from inactive disease, and findings are not specific.[2]

In spite of the effort to understand the physiopathology of SLE and of specific therapeutic proposals,[4] because of the varied nature of the physiopathogenic mechanisms underlying NP-SLE, which frequently participate in diffuse (psychosis, depression or cognitive alterations) o focal processes (TM or stroke), we classify them as vasculopathy (generally with small caliber vessel affection), mediated by autoantibodies and inflammatory components.[9]

Vasculitis rarely explains NP-SLE, which is commonly related to vasculopathy, which is characterized by a perivascular mononuclear infiltrate; small subsequent infarctions may be observed due to luminal occlusion with fibrin, platelets and intimal hyperplasia, and consequently an increase in the blood–brain barrier (BBB) and in the extravasation of antibodies.[6]

APL are related to convulsions, stroke, transient ischemic attacks and transverse myelitis; elevated IgG anticardiolipin titers (IgG aCL) lead to a sensitivity of 58% and a specificity of 81% for the diagnosis of ischemic NP-SLE manifestations.[13,14] The accelerated atherosclerosis characteristically associated to SLE increases the risk (5–10 times) of coronary disease and stroke.[6] In the MR, hyperintensities are translated as vasculopathy; they are attributed to demyelination, gliosis and interstitial edema due to ischemia and

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lacunar infarctions; extensive and confluent hyperintensities in the white matter indicate chronic hypoperfusion.[15] Antiphospholipid antibodies occur in 60% of patients with SLE, of which 30% have the antiphospholipid antibody syndrome; they are related to focal dysfunction and cognitive deficit, in particular when lupus anticoagulant is present. There is an association of aCL with psychomotor, learning, verbal memory and execution reduction. LA and aCL inhibit the proliferation of astrocytes and increase the synaptoneurosomal depolarization.[13]

TM is classically considered as an inflammation-mediated syndrome, but its relationship with aCL also indicates a concurrent ischemic contribution, with a very probable thrombosis of the thoracic spinal vessels, and with anticoagulation associated with a better prognosis.[2,16]

Humoral immunity is extensive against neuronal antigens, ribosomes and phospholipids; it has been implicated in the pathogenesis of NP-SLE, with autoantibodies in the CSF and, to a lesser extent, in cerebral tissue (in autopsy).[9]

Antineuronal antibodies are seen in the CSF of NP-SLE cases with diffuse manifestations (65%); there is experimental evidence of direct toxicity; thus, in NZM88 mice, predisposed to lupus nephritis and behavioral alterations, IgG vs cerebral antigens might be found. These antibodies against diamin-1 (a molecule involved in the endocytosis of synaptic vesicles), when injected into healthy models, reproduce the behavioral alterations.[17]

Gangliosides, components of the neuronal membrane, are involved in signal transduction, memory, synaptic transmission and the muscle union; anti-ganglioside IgG antibodies are associated to migraine, dementia and peripheral neuropathy, and IgM to depression.[13] They are common in juvenile NP-SL (83%) and associate to cognitive dysfunction.[18]

There are reports of anti-protein 2 antibodies directed against microtubules, glial fibrillar acidic protein and neurofilaments, important in communication, cell structure and integrity of the BBB.[13] Those directed against alphatubulin occur in 36% of NP-SLE cases, in 4% of SLE and in no controls (multiple sclerosis, epilepsy, healthy); they are associated to psychomotor alterations, obsessive–compulsive neurosis, temporal epilepsy, memory and concentration deficits, depression and migraine.[19]

We know that antibodies against the N methyl D aspartate receptor (NMDAR) occur in 40%–50% of patients with SLE and cross-react with dsDNA. NMDAR is composed of two units NR1, which presents a binding site for glycine (coagonist), and NR2 (with 4 subtypes A–D) A and B, present mainly in the hippocampus (learning and memory) and the amygdala (fear). They function as voltage regulated calcium channels. After electrical stimulation, glutamate and glycine bind to NR2 and NR1 and allow the passage of calcium into the cell.[20] Anti-NMDAR antibodies are not limited to NP-SLE; they may occur without underlying disease or be associated o other diseases such as neoplasia. The experimental administration of anti-NMDAR (R4A) with lipopolysaccharide and epinephrine induce BBB dysfunction. R4A binds to the DWEYS pentapeptide in NR2A and NR2B, permitting an increase in cytosolic calcium, especially mitochondrial, and conditions the depolarization of the membrane potential, a reduction in respiration and an increase in oxygen reactive species, with the consequential increase in permeability and apoptosis.[21] Anti-NMDAR in CSF and the brain correlates with convulsions, delirium, psychosis, headache and stroke.[20]

Anti-endothelium antibodies generate endothelial dysfunction, increase inflammatory markers, adhesion molecules, apoptosis, BBB permeability and the flow of autoantibodies; the activation of endothelial cells is carried out through NF-κB by anti NR2 antibodies.[13,22]

There are other antibodies associated to psychiatric manifestations, such as those against Nedd 5 (27% of NP-SLE) and septin (which belongs to the cytoskeleton GTPase family that intervenes in cytokinesis).[23]

Triosaphosphate isomeraze (TPI) intervene in glucolysis and the production of erythrocyte and neuronal energy; IgM vs TPI favor anemia and neurological abnormalitied[12]; a-TPI IgG with high specificity in NP-SLE (94.5%) favor the activation of complement and low serum levels of C3d, but increased in the CSF, indicating intratechal production.[24]

Ribosomal P antibodies (P0, P1 and P2) are associated LEG-NP (45%–88% psychosis), lupus nephritis, and hepatitis, and determine the alteration of protein synthesis, dysfunction and neuronal apoptosis, impaired memory, cognition, emotion, depression and olfactory dysfunction.[12,25]

Particular attention has been paid to IL-6 in the inflammation associated convulsion and IFN-α has been associated to psychosis; MMP-9, macrophage, T lymphocytes and endothelial cells and smooth muscle cell gelatinase are implicated in the plaque rupture and loss of the BBB, promoting the migration of inflammatory cells. They are associated to cognitive alterations and hyperintense lesions in MR T1 and T2; some periventricular lesions resemble leukoaraiosis, which is translated as a loss of the BBB. There may be thalamic, hippocampal, corpus callosum, cortical atrophy, among others.[1,9,15] In the NZM88 mice model, elevated hypothalamic concentrations of IL-6, IL-10, IL-12, IL-16, IFN-γ and tumor necrosis factor alpha are found, in addition to microglial activation which, along with autoantibodies, increases the proinflammatory cytokines even more.[17,26]

Therefore, its evident that, in the same patient, different physiopathogenic mechanisms converge in NP-SLE, making it necessary to use a combination of drugs for its management, including "symptomatics" (anticonvulsives, antipsychotics, antiplatelet, anticoagulants), high dose steroids (pulse methylprednisolone) and immunomodulators (antimalarials, statins, cyclophosphamide, azathioprine, methotrexate, mycophenolic acid). Plasmapheresis may be useful, in addition to IV immunoglobulin and rituximab, particularly due to the diversity of potentially pathogenic autoantibodies.[27] Long term remission is plausible although symptoms persist in 3%–20%; most require steroids and the recurrence rate is 21%–47%.[6,26–28] Mortality can be high (≥18%).[29]

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