Central nervous system (CNS) involvement occurs in 21-85% of patients with systemic lupus erythematosus. This large variability is due to the heterogeneity of manifestations, diagnostic criteria, selected population and study design [1-3]. Neuropsychiatric SLE (NPSLE) includes neurological syndromes of central, peripheral, and autonomic nervous system. In NPSLE, attribution of neuropsychiatric events to SLE warrants a thorough investigation and exclusion of alternative causes such as infections, hypertension, metabolic abnormalities or drug toxicity.

In 1999 the American College of Rheumatology proposed a standard nomenclature for NPSLE, with definitions of 19 neuropsychiatric syndromes including seizures, stroke, headache, polyneuropathy, mononeuropathy, depression, and psychosis [4]. In 2010 the European League Against Rheumatism (EULAR) made an effort to homogenize the management of patients with NPSLE by developing a set of recommendations which addressed diagnostic and therapeutic issues by using a combination of evidence-based approach and expert consensus [5]. Despite that, NPSLE remains a diagnostic and therapeutic challenge since diagnostic workup and treatment decisions are still performed on a patient-by-patient basis.

The pathogenesis of NPSLE is still unknown. Several autoantibodies (Abs) have been suggested to play a pathogenetic role, such as anti-P ribosomal proteins antibodies and anti- N-methil-D-aspartate (NMDA) antibodies [6-8]. Phosphorylated ribosomal (P ribosomal) proteins are three ubiquitous, highly conserved acidic phosphoproteins (P0, P1, P2) of different molecular weights (38 kDa, 17 kDa, and 15 kDa) forming
the stalk of the 60S ribosomal subunit, where they play a role in protein synthesis. The ribosomal protein P0 immunolocalizes on the membrane surface of neuronal, hepatic, and endothelial cells, in an immunological accessible way. Abs to the P ribosomal proteins are considered a highly specific marker of SLE and appear to correlate with disease activity, liver, kidney as well as with CNS involvement, including psychosis and peripheral nervous system complications [8].

The NMDA receptors that contain the NR2A and NR2B subunits (NR2A/B) are expressed in neurons throughout the brain, but are at highest density within cells of the hippocampus, amygdala and hypothalamus. Anti-NMDA-NR2A/B antibodies were detected in a significant proportion of patients with SLE, ranging from 14 to 35 % [7]. It has been hypothesized that high levels of anti-NMDA-NR2A/B antibodies cross the damaged blood-brain barrier, kill neurons by activating NMDA receptors and inducing ‘excitotoxicity’ through enhanced mitochondrial permeability transition, damage the brain, cause decrease of membrane NMDA receptors expressed in hippocampal neurons, and, eventually, induce behavioral cognitive impairments in animal models [7, 8].

Unfortunately, studies on humans showed controversial results in the case of anti-NMDA-NR2A/B antibodies; thus, further basic and clinical studies are highly required, not only to better elucidate the role of Abs antibodies, but also to better understand the pathogenesis of NPSLE and its clinical manifestations.

References


