Deciphering the association of anti P ribosomal antibodies and neuropsychiatric affection in systemic lupus erythematosus

Descifrando la asociación de los anticuerpos antiproteína P ribosomal y el cuadro neuropsiquiátrico del lupus eritematoso sistémico

Jozélio Freire de Carvalho,* Vilma S. Trindade Viana, and Eloísa Bonfá

The central nervous system involvement with a wide spectrum of neurological and/or psychiatric events is a common finding in systemic lupus erythematosus (SLE), and is seen in 25% to 70% of patients. Among the neuropsychiatric manifestations (NP) severe depression, psychosis, mood changes, headache, anxiety and cognitive dysfunction are included.

Evidence has strengthened the role of various antibodies in the pathogenesis of psychiatric complications of SLE, including antibodies to ribosomal P protein (anti-rib P). These antibodies were described in the serum of patients with SLE by Elkon et al, and exhibit reactivity to a complex of three phosphoproteins, molecular constituents of the large ribosomal subunit-called P0 (38kD), P1 (19kD) and P2 (17KD). The growing interest in anti-rib P comes from the demonstration of its high specificity for SLE, which attaches great importance to them and their inclusion in the antibody menu that aids in the diagnosis of this condition, which includes antibodies to native DNA (dsDNA) and Smith antigen.2-4

The incidence of rib-P antibody in SLE is highly variable, depending on the ethnicity of patients tested, the temporality of the sample in relation to disease activity and the specificity and sensitivity of the methodology used in the detection of these antibodies. Regarding ethnic factors, it is known that the incidence of antibody-rib P is lower in Caucasians (13%) and black patients (20%) with SLE and higher in Asians (Chinese: 38%).5-7 This ethnic variability has been attributed to the association with certain alleles of the class II major histocompatibility complex (MHC-II), as shown by a higher positivity of anti-rib P in patients with HLA-DQB1 * 0602.8

Its incidence also exhibits a relationship with the overall activity of lupus in the fact that, while in the general population of patients with idiopathic lupus it ranges from 10% to 15%, this value increases to 40% when faced with disease flares.8 Another significant finding is that it is found positive more often in juvenile SLE (40%) than in adults.8

The relationship between P-rib antibody positivity and NP activity in SLE has been well demonstrated in several studies.9-11 Bonfá et al first reported that the presence of anti P-rib antibodies showed an association to NP SLE.12 In this study, from 20 patients with severe lupus psychosis that required hospitalization, 18 had P rib antibodies. Moreover, the temporal relationship of these antibodies with the manifestation of psychosis was evidenced by longitudinal monitoring of 2 patients that showed a significant increase in serum antibody levels, preceding the onset of the psychiatric manifestations and their reduction with clinical improvement. In contrast, anti-dsDNA antibody titers were not increased during the psychosis flare.12 Subsequently, Schneenbaum et al13 confirmed the association between anti-rib P and psychosis in a study of 269 patients with SLE. In addition, the authors reviewed the titers of these antibodies and found them were lower in CSF than in serum, suggesting a possible link between the anti-rib P and neurons. Another study showed an increase of these antibodies in the cerebrospinal fluid compared with serum in patients with NP manifestations associated to lupus.14 The in vitro demonstration of the relationship between anti P-Rib antibodies purified from the surface of neuroblastoma cells supports the hypothesis that these antibodies may have a role in the pathogenesis of NP lupus.15 The association of anti-rib P antibody with the NP manifestations was also evidenced in children with SLE, since the detection of high levels of these antibodies allowed the distinction of psychosis associated with lupus from primary psychosis.16 In the same study, anti-rib P antibody detection was useful in monitoring disease activity, since 40% of children with psychosis associated
with SLE had elevated antibody levels during the acute phase of the psychotic outbreak and then levels declined during remission.

Despite such strong evidence from the 1980s and 1990s, the temporal relationship of the rib-P-antibody with the NP manifestations in SLE has not been a universal finding. Possible causes for this discrepancy include using different antigen preparations of the ribosomal P proteins and different methodologies in the detection of anti-riP, non-uniform criteria for establishing positivity and the time relationship between the collection of the sample and the clinical event. Besides this, consider the difficulty of establishing rigorous definitions and classifications of the wide clinical spectrum of manifestations of the psychiatric presentation of SLE. In fact, in the largest meta-analysis, which included 1537 patients with SLE, the absence of rib-P antibody test accuracy for the diagnosis of NP lupus was possibly related to the use of non-uniform criteria for defining this complication because the frequency of NP manifestations was extremely variable in the different centers participating in the study.

On the other hand, a recent inception cohort study of 420 patients with SLE provided data that confirms the specific association of the anti-riP-antibody and lupus psychosis. Despite this discrepancy observed in humans, experimental models have strengthened the relationship of antibody-riP with NP disorders. The first induced behavioral disorders associated to the expression of interleukin-12, tumor necrosis factor alpha (TNF alpha) and iNOS (inducible nitric oxide synthase) in cultures of macrophages and increased production of interleukin-10, justifying thus increasing in the Th2 response (Th helper subtype 2) which is the most commonly observed immune response model in SLE.

In addition, the ability of anti-riP to penetrate cells and compromise protein synthesis, inducing cellular dysfunction has been described. Several types of cells express proteins similar to ribosomal P protein (T cells, monocytes, endothelial cells) with potential pathological consequences. The production of cytokines may also be influenced by anti-riP. In this sense, the work of Sun et al. showed that these antibodies inhibit the expression of interleukin-12, tumor necrosis factor alpha (TNF alpha) and iNOS (inducible nitric oxide synthase) in cultures of macrophages and increase production of interleukin-10, justifying thus increasing in the Th2 response (Th helper subtype 2) which is the most commonly observed immune response model in SLE.

References


