



Editorial

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

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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).¹ 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 * 0602.⁶

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.⁹

The relationship between P-rib antibody positivity and NP activity in SLE has been well demonstrated in several studies.^{10,11} Bonfa 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, Schreenbaum 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

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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.^{10,11,17–19} Possible causes for this discrepancy include using different antigen preparations of the ribosomal P proteins and different methodologies in the detection of anti-rib P, 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.²⁰ On the other hand, a recent inception cohort study of 420 patients with SLE provided data that confirms the specific association of the anti-rib P antibody and lupus psychosis.²¹

Despite this discrepancy observed in humans, experimental models have strengthened the relationship of antibody-rib P with NP disorders. The first induced behavioral disorders associated to outstanding electroencephalographic changes after intraventricular cerebral injection (IVC) of anti-rib P in mice.²² More recently, autoimmune depression was induced in mice by injecting these antibodies IVC while simultaneously inducing motor or cognitive deficits in the animals.²³ The evidence of the relationship between antibodies and the neurons in the olfactory and limbic areas suggests the involvement of these in the pathogenesis of depression. In fact, treatment with antidepressant drugs (fluoxetine), and exposure to citrus smells improves depressive symptoms in these animals.²⁴

The pathophysiological mechanisms that may be involved in this association have not been completely clarified. However, the demonstration of P protein expression on the membrane of some cell types suggests that the accessibility of the molecule to bind to the antibodies may have pathological consequences. It is possible that P protein on the surface of cells may act as a receptor that can be modulated by specific antibody.²³ Several types of cells express proteins similar to ribosomal P protein (T cells,^{25–28} monocytes, endothelial cells^{29–31}) with potential pathological consequences. The production of cytokines may also be influenced by anti-rib P. 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 (T helper subtype 2) which is the most commonly observed immune response model in SLE.²⁸

In addition, the ability of anti P-rib to penetrate cells and compromise protein synthesis, inducing cellular dysfunction has been described.^{32,33}

But the biggest breakthrough in understanding the possible mechanism leading to neuronal dysfunction comes from the study of Matus et al, which shows the relationship of antibody-rib P with a new membrane protein on the surface of the neuron. This protein is present in neurons from brain areas involved with memory, knowledge and emotions, but not in astrocytes. The addition of anti-rib P to cultured brain cells induced increased calcium entry into neurons, resulting in death by apoptosis.³⁴ These results show an elegant possible mechanism for psychosis induced by anti-rib P.

In the past two decades there has been a breakthrough in understanding the possible pathogenic role of anti-rib P and its possible association with the NP manifestations in lupus. Despite this evidence, not all patients with anti-rib P have psychosis or are antibodies necessarily present in all patients with psychosis associated with lupus. Moreover, the finding of antibodies in

patients with SLE and psychiatric disturbances is a great help for the longitudinal follow up of these patients and may even precede new NP outbreaks.

In an attempt to obtain less divergent evidence, and a better understanding of the elements involved in the NP manifestations of SLE, it is advisable to follow a work plan that includes a diagnosis based on strict, established criteria and related to a more uniform classification of the various NP manifestations, including the detection of a select group of autoantibodies in serum and/or CSF, the use of standardized methodologies, neuroimaging assessment and implementation of appropriate neuropsychometric tests.

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