NR2 antibodies in neuropsychiatric systemic lupus erythematosus

This editorial refers to ‘Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus’, by Takahisa Gono et al., doi:10.1093/rheumatology/ker015, on page 1578.

In the past few decades, patients with SLE have experienced increased longevity in part due to earlier diagnosis and treatment. However, late sequelae have gained increased attention in special cardiovascular disease and cognitive impairment [1].

The prevalence of neuropsychiatric (NP) manifestations ranges between 17 and 75%, reflecting different methods of patient selection and assessment, varying expertise of the assessors and lack of a consensus for diagnosing active and chronic NP symptoms [2]. Clinical symptoms arise from CNS and peripheral nervous system dysfunction and vary from overt neurological and psychiatric disorders to more subtle signs and symptoms such as headache, mood disorders and impairment of cognitive function [2]. In ~40% of cases secondary insults, such as infections, metabolic derangement or side effects of drugs may be identified as possible aetiological factors [3]. However, in 60% of the patients NP manifestations are considered primary and pathogenesis of these focal or diffuse manifestations are now being elucidated [1, 2].

One growing interest is the identification of a subset of anti-DNA antibodies that cross-react with a consensus pentapeptide present in the NR2A and NR2B subunits of the N-methyl-D-aspartate receptor (NMDAR) [1]. NMDARs are receptors for the neurotransmitter glutamate, the major excitatory neurotransmitter in the brain, which is critically important for many brain functions [1]. Excessive exposure to glutamate results in increased calcium influx that causes mitochondrial stress and activates caspase cascades, leading to neuronal death [1, 4]. Neuronal death leads to reduced tissue volume, visualized on MRI as atrophy [5, 6]. Systematic MRI studies have shown that atrophy, although frequently found in SLE patients, is not uniformly present [6]. The fact that NMDARs are differentially expressed regionally in the brain may be one explanation [1]. Receptors containing NR2A and NR2B are most dense on neurons in the CA1 region of the hippocampus, and in the amygdala: hence, the strong interest in the association of these antibodies with cognitive impairment and hippocampal volume [1, 5–7].

In the first part of the study by Gono et al. [8], in this issue, the authors compare two different types of peptide, ISVSYDDWDYSLE and DWEYSWLSN, as autoantigens to detect anti-NR2A autoantibodies. The median anti-NR2A antibody optic density (OD) value was significantly higher and the range more broad in the ELISA system using the peptide ISVSYDDWDYSLE compared with DWEYSWLSN, although the OD values from the two peptides correlated significantly with each other. The difference between the two peptides is a sequence near Asp 283 and the authors speculate that this sequence may be important because Zn binds to Asp 283 and modulates intercellular Ca\(^{2+}\) signalling in cells expressing NR2A. Since most previous studies have used DWEYSWLSN peptide, this difference may explain some discrepancies regarding clinical significance of NR2 antibodies in SLE in previously published studies.

In the second part of their study, Gono et al. [8] analysed the association between anti-NR2A antibody and various clinical manifestations. They observed a higher prevalence of positive NR2A antibodies in patients with both focal and diffuse NP manifestations, in addition to active SLE patients. Many studies have attempted to correlate the presence of NR2A antibodies in serum and cerebrospinal fluid (CSF) with aspects of NP SLE. Although CSF titres were more closely associated with NP manifestations, results of serum titres are still controversial. Different peptides, frequencies of NP manifestations and ethnic background may explain these different results. Further studies comparing the two peptides in large cohorts are necessary to confirm these findings. Despite all controversies, the search for biomarkers, especially serum biomarkers for NP SLE is welcome for allowing earlier diagnosis and intervention.

The importance of this study relies on the comparison of two different types of peptide, explaining, at least in part, previous controversial results. In addition, identifying molecules that bind to these sequences may help in establishing a therapeutic approach to SLE patients with NP manifestations. The strength of the current study is the number of patients with well-established NP manifestations. Most of the patients had standard cognitive testing performed. The weakness is the absence of structural and functional MRI findings that could further help in identifying the pathogenic mechanism of NR2 antibodies. However, several questions have still to be answered such as how and when anti-NMDAR antibodies access the brain and how the clearance of these antibodies occurs [1]. The great efforts of different researchers will probably soon answer some of these questions.

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