



# Autoantibodies associated with neuropsychiatric systemic lupus erythematosus: the quest for symptom-specific biomarkers

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## Autoantibodies associated with neuropsychiatric systemic lupus erythematosus : the quest for symptom-specific biomarkers

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### Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs, including the central nervous system. Neuropsychiatric SLE (NPSLE) is a severe and potentially fatal condition. Several factors including autoantibodies have been implicated in the pathogenesis of NPSLE. However, definitive biomarkers of NPSLE are yet to be identified owing to the complexity of this disease. This is a major barrier to accurate and timely diagnosis of NPSLE. Studies have identified several autoantibodies associated with NPSLE ; some of these autoantibodies are well investigated and regarded as symptom-specific. In this review, we discuss recent advances in our understanding of the manifestations and pathogenesis of NPSLE. In addition, we describe representative symptom-specific autoantibodies that are considered to be closely associated with the pathogenesis of NPSLE.

**Key words :** autoantibody, biomarker, neuropsychiatric systemic lupus erythematosus, pathogenesis, symptom-specific

### 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs, including the central nervous system (CNS)<sup>1)</sup>. SLE is characterized by the loss of immune tolerance to nuclear antigens due to development of autoantibodies and immune complex formation ; the resultant complement activation results in cell destruction and tissue injury<sup>1,2)</sup>. Patients with SLE show considerable variability with respect to symptoms. In particular, neuropsychiatric (NP) SLE is a severe and potentially fatal condition that is characterized by CNS manifestations<sup>1,2)</sup>. In 1999, the American College of Rheumatology Research Committee developed standard nomenclature and case definitions for 19 manifestations of NPSLE (Table 1)<sup>3)</sup>. NP manifestations usually occur in the early

stage of SLE and 39%–50% of patients exhibit SLE symptoms. The reported prevalence of NPSLE varies widely from 4%–91% ; this may be attributable to variability in clinical presentations, different selection criteria, and heterogeneity among study populations<sup>4–6)</sup>. In a recent 3-year prospective study of 370 SLE patients with no history of CNS involvement (excluding non-specific minor CNS complaints and peripheral nervous system symptoms), the prevalence of major CNS events was 4.3% with an estimated incidence of 7.8 events/100 person-years<sup>7)</sup>. In spite of recent advances, the diagnosis of NPSLE is typically challenging, due in part to the absence of specific and reliable laboratory or imaging biomarkers<sup>2,8)</sup>. The diagnosis of NPSLE requires exclusion of other causes such as infection, concurrent disease, metabolic abnormalities, or drug adverse events<sup>1,2,5,6,8)</sup>. Therefore, investigation of dis-

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Table 1. Neuropsychiatric syndromes according to the criteria proposed by the American College of Rheumatology (Reference 3)

Central NPSLE	Peripheral NPSLE
Aseptic meningitis <sup>1</sup>	Guillain-Barre syndrome
Cerebrovascular disease <sup>1</sup>	Autonomic neuropathy
Demyelinating syndrome <sup>1</sup>	Mononeuropathy
Headache <sup>1</sup>	Myasthenia gravis
Movement disorder <sup>1</sup>	Cranial neuropathy
Myelopathy <sup>1</sup>	Plexopathy
Seizure disorders <sup>1</sup>	Polyneuropathy
Acute confusional state <sup>2</sup>	
Anxiety disorder <sup>2</sup>	
Cognitive dysfunction <sup>2</sup>	
Mood disorder <sup>2</sup>	
Psychosis <sup>2</sup>	

1. Focal NPSLE, 2. Diffuse NPSLE

NPSLE : neuropsychiatric systemic lupus erythematosus

ease-specific or symptom-specific autoantibodies observed in NPSLE is a key imperative to facilitate timely and accurate diagnosis. Here, we review recent NPSLE studies that focused on the pathogenesis of NPSLE and the autoantibodies associated with NPSLE manifestations, especially symptom-specific autoantibodies.

## 2. Pathogenesis of NPSLE

The pathogenesis of NPSLE is highly complex, with detailed mechanisms yet to be elucidated<sup>1,2,6</sup>. The pathogenic pathways suggested thus far include blood-brain barrier (BBB) dysfunction, vascular occlusion, neuroendocrine-immune imbalance, and tissue and neuronal damage caused by autoantibodies and proinflammatory cytokines [interleukin (IL)-1, IL-6, IL-8, IL-10, IL-17, type 1 interferons, tumor necrosis factor, colony-stimulating and macrophage-stimulating factors]<sup>1,2,6,8,9</sup>. Predisposing genetic factors, neuroendocrine factors, and environmental factors are also thought to be important. Figure 1 illustrates the currently proposed pathogenetic mechanisms of NPSLE<sup>1,2,6</sup>.

### 2.1 Predisposing factors

Predisposing genetic factors are believed to play an important role in SLE pathogenesis<sup>2,6</sup>. In NPSLE patients, mutations in *TREX1*, which encodes three-prime repair exonuclease 1 (DNase III), were shown to be associated with neurological involvement. Polymorphisms in *TREX1* were

found to be associated with neurological involvement in European patients with SLE<sup>10</sup>. Loss-of-function mutations in *TREX1* augment the production of type 1 interferons in mice and lead to early-onset cerebral NPSLE<sup>11,12</sup>. In addition, HLA-DRB1\*04 and rs10181656(G) alleles were shown to be associated with ischemic cardiovascular disease (CVD) in Caucasian patients with SLE<sup>13,14</sup>. More recently, Rullo *et al.* reviewed recent advances in our understanding of the genetic basis of SLE, including genetic variants in recently identified SLE-associated loci, the immunological pathways affected by these gene products, and the disease manifestations linked to these loci<sup>15</sup>. In addition, environmental factors and neuroendocrine factors play an important role in the development of SLE. In previous studies, silica exposure, smoking, oral contraceptives, postmenopausal hormone therapy, and endometriosis were found to be risk factors for SLE<sup>16</sup>. Indeed, sex steroid hormones (17 $\beta$ -estradiol, testosterone, prolactin, progesterone, dehydroepiandrosterone) reportedly impact the immune response and the severity of disease in SLE; this also explains the sex disparity in SLE. Other environmental factors, such as ultraviolet radiation, vitamin D, infection (e.g., Epstein-Barr virus), vaccination, heavy metals, solvents, and pesticides are considered as risk factors for SLE<sup>6,16</sup>.

### 2.2 Mechanisms of NPSLE

Recent reports have identified two major mechanisms for the development of NPSLE, i.e., vascular mechanisms and neuroinflammatory mechanisms (Figure 1)<sup>1,2,6</sup>. Among the vascular mechanisms, vasculopathy is implicated in CNS damage in patients with NPSLE; autopsy studies have shown pathological findings of multi-focal microinfarcts, small-vessel noninflammatory vasculopathy and occlusion, embolism, cortical atrophy, and microhemorrhages<sup>1,17,18</sup>. Anti-phospholipid antibodies (aPL) and deposition of immune complexes are likely to be associated with these conditions<sup>1,18-20</sup>. Injury to large and small blood vessels mediated by aPL initiates vascular damage, finally resulting in focal, and in part, diffuse neuropsychiatric events (seizures, cognitive dysfunction, etc.). The second mechanism involves autoimmune inflammation mediated by autoantibodies, resulting in increased permeability of the BBB, intrathecal formation of immune complexes, and production of inflammatory mediators (IFN- $\alpha$ , IL-6, IL-8, IP-10, MCP-1, etc.)<sup>20,21</sup>. Direct CNS tissue injury caused by excitatory amino acid toxicity, oxidative stress, plasminogen activator in-

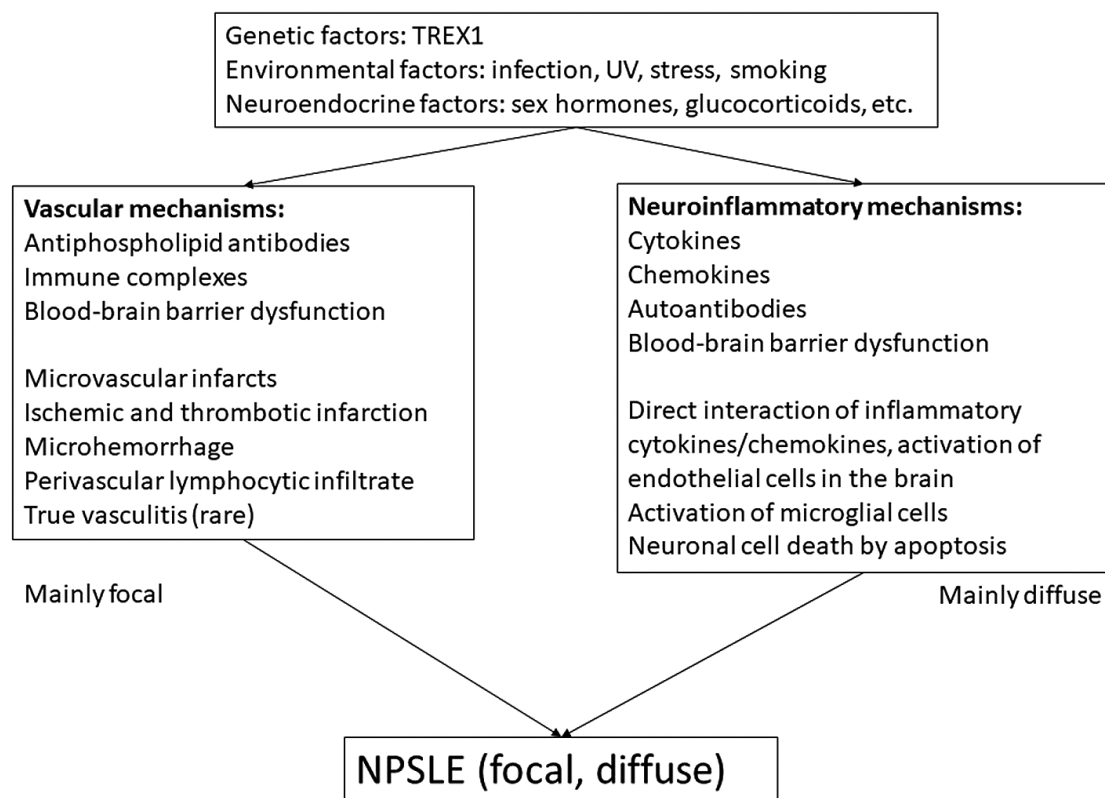


Fig. 1. Pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus (NPSLE)  
Abbreviations : UV, ultraviolet

hibitor 1 (PAI-1), and matrix metalloproteinase 9 (MMP9) activity have also been suggested<sup>20,22,23</sup>. These processes can cause CNS damage by activation of microglial cells and induction of neuronal cell death by apoptosis<sup>1,6</sup>, leading to mainly diffuse NPSLE symptoms, such as acute confusional state and psychosis<sup>1,20</sup>. As previously described, BBB dysfunction plays an important role in the pathogenesis of NPSLE. Normally, the brain is immunologically privileged and is sheltered from foreign substances in the circulation. The BBB limits the entry of soluble molecules and cells into brain parenchyma and regulates both uptake into and efflux out of the brain<sup>1,20,24</sup>. Although the precise mechanism of BBB dysfunction is still unclear, permeability of the BBB can be affected by both SLE factors (immune complex deposition, cytokine/chemokines) and non-SLE factors (smoking or hypertension) that induce endothelial dysfunction in brain vasculature<sup>1,8,20,25</sup>. In this regard, autoantibodies reacting with neuronal cells or those that have been reported as specific for each NPSLE symptom (from the circulation or intrathecal production) might be associated with BBB dysfunction. Here, we review the representative autoantibodies that are potentially associated with the pathogenesis of NPSLE.

### 3. Autoantibodies potentially associated with specific NPSLE symptoms

Table 2 shows the representative autoantibodies that have been recently described as potentially associated with NPSLE pathogenesis. More than 100 autoantibodies have been described in patients with SLE or NPSLE<sup>26</sup>; however, none of these have been definitively implicated in the complex process of NPSLE pathogenesis. Therefore, extensive research is ongoing to establish distinct pathogenic roles for each autoantibody.

#### 3.1 Anti-phospholipid antibodies (aPL)

The aPL antibody family targets proteins associated with anionic phospholipids in the plasma membrane that regulate the blood clotting cascade; subsequent activation of procoagulants promotes thrombosis and cerebral infarction<sup>27</sup>. Anti-cardiolipin (aCL), anti- $\beta$ 2GP1 antibodies, and lupus anticoagulant (LAC) are the most widely investigated autoantibodies targeting phospholipids. These have been recognized as major risk factors for NPSLE and are believed to contribute to the development of thrombosis and other NPSLE symptoms, such as seizures, stroke, chorea, movement disorder.

Table 2. Representative autoantibodies associated with NPSLE

Target of autoantibodies (autoantibodies)	Serum/CSF	Prevalence in SLE patients	Associated NPSLE symptoms
Phospholipid : $\beta$ 2-glycoprotein 1 and cardiolipin (aCL-Ab)	Serum, CSF	Up to 45%	Focal NPSLE (CVD, seizures, chorea) Diffuse NPSLE (cognitive dysfunction, psychosis, depression, headache)
Ribosomal P protein (anti-ribosomal P Ab)	Serum, CSF	6%-46%	Elevated titers in active SLE Diffuse NPSLE (psychosis, depression)
NMDA receptor subtype 2 (anti-NMDA/NR2 Ab)	Serum, CSF	30%-40%	Diffuse NPSLE (depression cognitive dysfunction)
MAP-2 (anti-MAP-2 Ab)	Serum, CSF	17%, 33.3% (CSF)	Focal NPSLE (seizures, chorea, sensory neuropathy) Diffuse NPSLE (psychosis, headache)
U1 ribonucleoprotein (Anti-U1RNP Ab)	Serum, CSF	18% (CSF)	NPSLE in general
Structural endothelial proteins (AECA)	Serum	17-75%	Psychosis, depression
TPI (anti-TPI Ab)	Serum, CSF	30%-40%	Focal NPSLE (aseptic meningitis) Less frequent in acute confusional state
GAPDH (anti-GAPDH Ab)	Serum	47%	Increased intracranial pressure, cognitive dysfunction

AECA : anti-endothelial cell antibody ; aCL : anti-cardiolipin ; CVD : cerebrovascular disease ; CSF : cerebrospinal fluid ; GAPDH : glyceraldehyde-3-phosphate dehydrogenase ; MAP-2 : microtubule-associated protein 2 ; NMDA/NR2 : N-methyl-D-aspartate receptor 2 ; NPSLE : neuropsychiatric systemic lupus erythematosus ; U1-RNP : U1 ribonucleoprotein ; TPI : triosephosphate isomerase

ders, cognitive dysfunction, and myelopathy<sup>28-32</sup>. *In vitro* studies have demonstrated direct binding of aPL with CNS cells ; in addition, intrathecal passive transfer of IgG isolated from aPL-positive patients was shown to induce cognitive dysfunction in mice<sup>33</sup>. At least, exacerbation of procoagulant state by aPL is believed to be associated with focal NPSLE causing intravascular thrombosis and cerebral ischemia<sup>20</sup>.

### 3.2 Anti-ribosomal P protein antibodies (anti-ribo P)

Anti-ribo P are specific autoantibodies occurring in up to 46% of patients ; target epitopes are located in the C-terminal end of three highly conserved phosphorylated proteins, P0, P1, and P2, which are present in the 60S subunit of ribosomes<sup>6,34</sup>. Many retrospective studies have suggested an association between elevated serum or CSF levels of anti-ribo P and NPSLE manifestations ; however, the results have been contested<sup>35-37</sup>. Recent longitudinal studies and prospective studies have shown their association with lupus psychosis<sup>38-41</sup>. In a study by Hanly *et al.*, anti-ribo P was found to be a predictor of psychosis<sup>42</sup>. In a mouse model, anti-ribo P recognized neurons in the hippocampus, cingulate, and primary olfactory piriform cortex, and induced long-term depressive-like behavior when introduced into cerebral ventricles<sup>43</sup>. Matus *et al.* reported that anti-ribo P from psychiatric lupus induced a rapid and sustained in-

crease in calcium reflux and apoptosis in rat neurons expressing cell-surface P-antigen protein P331. The death of these neurons in specific brain regions (such as hippocampus) was found to affect the memory and emotional behavior of rats<sup>44</sup>. Direct evidence of a pathogenic role for these antibodies in humans is still lacking ; nevertheless, experimental data and prospective studies support the role of anti-ribo P in the causation of diffuse NPSLE.

### 3.3 Anti-N-methyl-D-aspartate receptor antibodies (anti-NMDA)

Anti-NMDA antibodies occur in 30%-40% of patients with SLE ; these have been demonstrated as a subset of double-stranded DNA (dsDNA) antibodies that cross-react with NMDA receptors, specifically with the NMDA receptor subunit 2 (NR2)<sup>45</sup>. NMDA receptors are widely distributed in the brain and localized within glutamatergic synapses ; a particularly high density is observed in the amygdala and hippocampus, which modulate cognitive function, emotional processes, and memory<sup>46,47</sup>. Activation of NMDA receptors is critical in learning and memory ; however, prolonged stimulation can cause apoptotic death of neuronal cells. The potential pathogenic role of anti-NMDA detected in CSF has been demonstrated in both *in vitro* and *in vivo* studies<sup>48,49</sup>. Interestingly, no neuronal damage was observed if the BBB remained intact ; however, several pathological changes were detected when the



BBB was disrupted<sup>46-48</sup>). Correlation between CSF anti-NMDA and diffuse NPSLE manifestations has also been reported<sup>50</sup>. Furthermore, it has been suggested that anti-NR2/dsDNA antibodies may also help distinguish SLE patients with central diffuse NPSLE manifestations from patients with peripheral manifestations; the pathogenic factors and mechanisms underlying these manifestations are probably different<sup>51</sup>. Then, how do these autoantibodies gain access to the brain in SLE? Yoshio *et al.* have reported that anti-NR2/dsDNA antibodies from SLE patients activate endothelial cells and induce expression of surface molecules [intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1)] as well as the production of IL-6 and IL-8<sup>52</sup>. Hirohata *et al.* also reported that the severity of BBB damage plays a critical role in the development of diffuse NPSLE (acute confusional state) through the accelerated entry of larger amounts of anti-NR2 antibodies into the CNS<sup>53</sup>. These results indicate that activation of BBB endothelial cells by anti-NMDA may cause inflammation, disrupt the BBB, and promote entry of autoantibodies into the CSF in patients with SLE.

### 3.4 Anti-microtubule-associated protein 2 antibodies (anti-MAP-2)

MAP-2 is one of the abundant groups of cytoskeletal components predominantly expressed in neurons<sup>54</sup>. MAP-2 regulates the nucleation and stabilization of microtubules, organelle transport protein kinases that are involved in signal transduction<sup>55</sup>. In a study by Yamada *et al.*, 33.3% of NPSLE patients tested positive for anti-MAP-2 in the CSF<sup>54</sup>. Williams also reported that 17% of SLE patients had anti-MAP-2 in contrast to 4% of neurologic injury/disease control patients<sup>56</sup>. Patients who tested positive for anti-MAP-2 exhibited neuropsychiatric symptoms (psychosis, seizures, neuropathy, and cerebritis). Moreover, both anti-ribo P titers and IL-6 levels in CSF were significantly higher in NPSLE patients having anti-MAP-2, indicating some association between them<sup>54</sup>.

### 3.5 Anti-U1 ribonucleoprotein antibodies (anti-U1RNP)

Anti-U1RNP reacts with proteins that are associated with U1 RNA and form U1 small nuclear ribonucleoprotein (snRNP); these are detectable in 25%-47% of SLE patients<sup>57</sup>. The snRNP are RNA-protein complexes that are abundant in the nucleus; these are involved in the nuclear processing of pre-mRNA along with other proteins compris-

ing the spliceosome<sup>58</sup>. In a study by Sato *et al.*, anti-U1RNP in CSF, but not that in serum, was associated with NPSLE and mixed connective tissue disease<sup>59</sup>. Recent studies have shown that anti-RNP as well as anti-Sm antibodies were less likely to be produced within the CNS; this was assessed by calculating anti-RNP and anti-Sm indices in the CSF (indices of each reflect the intrathecal production of these antibodies)<sup>60</sup>. Nevertheless, the detailed role of anti-U1RNP should be further investigated.

### 3.6 Anti-endothelial cell antibodies (AECA)

AECAs target a heterogeneous group of antigens including structural endothelial proteins (ranging from 10 to 200 kDa) as well as adhesion molecules to endothelial cells; these are found in a variety of diseases that are characterized by vessel wall damage<sup>61</sup>. The reported prevalence of AECA in SLE patients ranges from 17% to 75%. Conti *et al.* found an association of serum AECA with psychosis and depression in NPSLE<sup>62</sup>. AECA can activate endothelial cells by inducing the expression of adhesion molecules (ICAM-1 and VCAM-1) and stimulating the production of cytokines (IL-1, IL-8) and chemokines [such as monocyte-chemotactic protein 1 (MCP-1)]. AECA can also enhance the production of tissue factor and von Willebrand factor, promoting thrombosis. However, low specificity due to the lack of a standardized detection method and possible presence of natural AECAs (seen in a small percentage of healthy individuals and showing low affinity for their target antigens) limit the use of AECAs as diagnostic and prognostic markers<sup>61,62</sup>.

### 3.7 Anti-triosephosphate isomerase antibodies (anti-TPI)

Triosephosphate isomerase (TPI) is an important glycolytic enzyme that catalyzes the interconversion of dihydroxyacetone phosphate and D-glyceraldehyde-3-phosphate<sup>63</sup>. TPI is mediated solely by glycolysis in red blood cells and in brain cells, and its deficiency is associated with hemolytic anemia and neurological disorders. TPI is involved in the stability of neuronal microtubules<sup>63-66</sup>. Watanabe *et al.* have suggested some association with the pathogenesis of NPSLE<sup>64-66</sup>. Furthermore, in our previous study, anti-TPI-TPI immune complex was detected in the CSF of anti-TPI-positive NPSLE patients<sup>65</sup>. In a lupus model mouse, anti-TPI was detected in MRL/lpr mice; in addition, anti-TPI was shown to bind to brain tissue in the meninges, choroid plexus, hippocampus, and periventricular le-

sions using anti-TPI-producing hybridoma inoculation into the brain hemisphere<sup>66</sup>). Recently, we reported a higher frequency of aseptic meningitis in anti-TPI-positive NPSLE patients; in addition, serum anti-TPI index showed a positive correlation with serum IgG levels<sup>8</sup>). These results indicate that anti-TPI may be associated with NPSLE, mainly focal NPSLE (aseptic meningitis); the underlying mechanism may involve disruption of the BBB via formation of immune complexes in the CNS. Indeed, the underlying mechanism of aseptic meningitis in SLE patients is still unclear. A possible mechanism can be considered along with meningeal inflammation similar to that proposed for multiple sclerosis<sup>67</sup>): immune cells first pass through the meninges via the bloodstream to the choroid plexus, as a part of immune surveillance. The interaction of autoimmune myelin-specific T cells with myelin-loaded antigen-presenting cells can induce T cell reactivation and production of inflammatory cytokines/chemokines in the meninges. The additional inflammatory cells compromise local BBB integrity, which finally triggers immune cell infiltration into the CNS<sup>8,67</sup>). In any case, further investigation is needed to clarify the pathogenic role of anti-TPI in NPSLE.

### 3.8 Anti-glyceraldehyde-3-phosphate dehydrogenase antibodies (anti-GAPDH)

GAPDH is a glycolytic enzyme; however, more recent evidence indicates that mammalian GAPDH performs a number of other functions<sup>68</sup>). Its activity contributes to membrane fusion, microtubule bundling, phosphotransferase activity, nuclear RNA export, DNA replication and repair, and further, to neuronal cell death<sup>68,69</sup>). Takasaki *et al.* first reported that anti-GAPDH is one of the elements of proliferating cell nuclear antigens, specifically those reactive with serum from SLE patients<sup>69</sup>). Furthermore, Delunardo *et al.* demonstrated the reaction of anti-GAPDH with neuronal cells and its association with cognitive dysfunction in patients with SLE<sup>70</sup>). Recently, Sun *et al.* also reported a positive correlation of serum anti-GAPDH with SLEDAI-2K, ESR, IgG, and IgM; in addition, anti-GAPDH showed an association with increased intracranial pressure, indicating its potential role in the induction of brain tissue damage<sup>71</sup>). Although the direct effect of anti-GAPDH is yet to be elucidated, it may serve as a useful biomarker for cerebrovascular damage in NPSLE patients.

## 4. Conclusion

Neuropsychiatric sequelae are among the main causes of morbidity and mortality in patients with SLE, but they are the least well-understood aspect of the disease. Appropriate evaluation and accurate classification of NP manifestations is an important focus of NPSLE treatment and research. However, its complex pathogenesis and polymorphic phenotype hampers the identification of pertinent, robust biomarkers. Further investigation of biomarkers (such as disease-specific or symptom-specific auto-antibodies and cytokine/chemokine expression profiles) is required to increase our knowledge and improve the management of NPSLE.

## Conflict of interest

The authors declare there is no conflict of interest.

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