Autoantibodies associated with neuropshychiatric systemic lupus erhytematosus

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by damage to multiple organs caused by systemic autoimmunity. One of the characteristic features in SLE is the presence of numerous autoantibodies. Although certain autoantibodies such as anti-double strands DNA antibodies are known to be pathological, the correlation between many autoantibodies and tissue damage in patients with SLE remains unclear. Although the prognosis for survival in patients with SLE has improved dramatically in recent decades, its neuropsychiatric complications remain a major cause of morbidity. The neuropsychiatric manifestations can be attributed to SLE itself and are referred to as neuropsychiatric SLE (NPSLE). Multiple factors are involved in the pathogenesis of NPSLE including the genetic background, vasoculopathy, autoantibodies, and inflammatory mediators associated with SLE. However, neuropsychiatric manifestations can also be caused by other factors not associated with SLE, including steroid psychosis, infectious diseases, and metabolic factors. Therefore, NPLSE can be diagnosed in patients with SLE only if other causes have been excluded; difficulty in diagnosing NPSLE often occurs in many cases.

Various potential biomarkers for the diagnosis of NPSLE have been reported. However, useful and practical diagnostic biomarkers with high specificity for NPSLE have not been established to date. This review summarized the current data on autoantibodies recognized in NPSLE, and described their diagnostic value and pathogenic roles.

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a distinct pathology. The pathogenesis of SLE is multifactorial, and can involve vasculopathy and immune abnormalities including upregulation of various inflammatory mediators and pathogenic autoantibodies associated with SLE. Although the overall prognosis for survival in patients with SLE has improved dramatically in recent decades,[1–3] the involvement of the central nervous system (CNS) in SLE remains a major complication and contributes significant to the patients' morbidity and mortality.

Neuropsychiatric manifestations (NP) occur in 6–12% of SLE cases during the first year of disease onset. NPSLE is observed throughout the course of SLE from 19% to 38%, depending on the diagnostic criteria and patient selection.[4] Considering that the classification of NPSLE has not defined individual neuropsychiatric manifestations for the diagnosis, the American College of Rheumatology (ACR) Ad Hoc Committee published a consensus document defining the diagnostic and exclusion criteria for 12 CNS and seven peripheral nervous system syndromes in SLE (Table 1).[5] The European League Against Rheumatism (EULAR) developed these criteria further and summarized 10 specific manifestations observed in patients with NPSLE (Table 2).[6] Although the ACR definition has improved the description and classification of NPSLE in clinical studies, its usefulness in clinical practice remains limited, because many of these symptoms may occur not only as primary manifestations of NPSLE but also as a consequence of secondary causes not related to NPSLE, including infections, side effects of drugs, and metabolic disturbances.[7] Moreover, neuropsychiatric manifestations such as neuromyelitis optica and posterior reversible encephalopathy, which are often associated with SLE, are not included in the ACR definition.[8,9]

Table 1. Neuropsychiatric syndrome in systemic lupus erythematosus (SLE) defined by the American College of Rheumatology (ACR)

Central nervous system	Peripheral nervous system
●Aseptic meningitis ●Cerebrovascular disease ●Demyelinating syndrome ●Headache ●Movement disorder ●Myelopathy ●Seizure disorders ●Acute confusional state ●Anxiety disorder ●Cognitive dysfunction ●Mood disorder ●Psychosis	●Acute inflammatory demyelinating polyradiculoneuropathy (Guillan-Barre syndrome) ●Autonomic neuropathy ●Mononeuropathy ●Myasthenia gravis ●Cranial neuropathy ●Plexopathy ●Polyneuropathy

Adapted from ''The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," by ACR AD HOC COMMITTEE ON NEUROPSYCHIATRIC LUPUS NOMENCLATURE. 1999, Arthritis Rheum, 42(4):599-608.

Table 2. Specific neuropsychiatric systemic lupus erythematosus (NPSLE) manifestations defined by the European League Against Rheumatism (EULAR)

Specific NPSLE disorders
● Cerebrovascular disease
● Headache
● Movement disorder
● Myelopathy
● Seizure disorders
● Acute confusional state
● Cognitive dysfunction
● Major depression and psychosis
● Cranial neuropathy
● Peripheral nervous system disorders

Adapted from ''EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs," by Bertsias GK, Ioannidis JP, Aringer M, Bollen E, et al. 2010, Ann Rheum Dis. 2010,69(12),2074-2082.

Currently, there are no specific biomarkers or radiographic tests that can distinguish between NPSLE and secondary symptoms. Although autoantibodies, inflammatory mediators, and neuroimaging tests such as magnetic resonance imaging (MRI) have been clinically used in the diagnosis of NPSLE, findings from these examinations are not specific to NPSLE. However, several autoantibodies have been reported as possible biomarkers for NPSLE, including the anti-ribosomal P, anti-N-methyl-D-aspartate receptors (NMDAR), and anti-phospholipid antibodies.[10–14]

2. Pathogenesis of autoantibodies in NPSLE

The pathogenesis of NPSLE is multifactorial and mainly includes vasculopathy, inflammatory mediators, and pathogenic autoantibodies. Although their precise mechanisms in causing NPSLE are still not clear, the binding of certain autoantibodies to neuronal or vascular autoantigens has been postulated as a potential mechanism.

In vasculopathy, anti-phospholipid antibodies (APL) frequently identified in SLE have been recognized as a risk factor for NPSLE because APL contributes to the development of thrombosis in CNS blood vessels, consequently resulting in NPSLE manifestations. Although a direct mechanism of APL in thrombosis is not fully understood, APL may possibly promote the pro-coagulant activity of vascular endothelial cells through binding to phospholipid antigens.

The production of pathological autoantibodies and increased inflammatory mediators are mediated by systemic autoimmunity in SLE. In conditions with the immune dysregulations, a disruption of the

blood brain barrier (BBB) has been considered to play a crucial role in the onset of NPSLE. The BBB protects the brain parenchyma from toxic molecules and harmful cells. Moreover, the BBB functions as an interface between blood vessels and brain tissues in order for macromolecules such as antibodies do not excessively infiltrate into the brain parenchyma. Therefore, a BBB disruption is possibly considered as an initial step towards NPSLE associated with pathogenic autoantibodies. Various factors including inflammatory cytokines, complement activation, infections, and toxic reagents have been shown to influence the integrity of the BBB, thus altering its function.[15,16] A disrupted BBB becomes more accessible to autoantibodies. The autoantibodies may directly interact with the neuronal antigens on cell surface, and then, the interaction cause damage to the brain parenchyma as antibody-dependent cellular cytotoxicity (ADCC) are possibly caused by the autoantibodies. Otherwise, the interaction may interfere with the cellular function if the autoantibodies have agonistic or antagonistic effects.

In contrast to the cell surface antigens, the pathological role of autoantibodies in intracellular autoantigens is not clear because immunoglobulins cannot infiltrate the intracellular space across the cell membrane. However, some intracellular molecules have shown their ability to migrate from the cytoplasm to the cell surface when the cells undergo activation or apoptosis. Therefore, cytoplasm-to-cell membrane translocation of certain neuronal autoantigens in aberrant conditions such as SLE may occur; in such cases, the autoantibodies may be pathological.

3. Autoantibodies recognized in NPSLE

3.1 Anti-phospholipid antibodies

The anti-phospholipid syndrome (APS) is an autoimmune disease featuring a pro-thrombotic disorder related to the presence of anti-phospholipid antibodies (aPL). APS is diagnosed when the patients have at least one clinical criterion (thrombosis or recurrent pregnancy loss) with coexistence of aPL. APS occurs either in the absence of any other related diseases (primary APS) or with other autoimmune diseases, including mainly SLE (secondary APS). The aPL consist of a heterogeneous group of autoantibodies, which interact with both phospholipids (PL) and PL-binding proteins, namely β2-glycoprotein-1 (β2GP1). In addition to β2GP1, various other PL-binding proteins were reported including prothrombin, protein C, protein S, and annexins.[17] The PL recognized by aPL are mainly cardiolipin (CL) and phosphatidylserine (PS). Phosphatidyletha-nolamines (PE) are also reported as PL interacting with sPL. Moreover, lupus anticoagulants (LAC), which have a paradoxical effect on coagulation between *in*

vitro and *in vivo* studies, are immunoglobulins that bind to PL. Although LAC are associated with recurrent thrombosis *in vivo,* they prolong the PL-dependent clotting time (known as lupus anticoagulant activity) *in vitro*.

LAC, anti-CL antibodies (aCL), and anti-β2GP1 antibodies are involved in the diagnostic criteria of APS.[18] Although the direct mechanisms of APL for thrombosis have not been fully elucidated, APL, especially anti-β2GP1 antibodies, have been shown to exert pro-thrombotic activities such as the up-regulation of tissue factors, expression of adhesion molecules, and increase of pro-inflammatory cytokines to monocytes and endothelial cells.[17] A total of 30–40% of patients with SLE are positive for APL.[19] A strong correlation between aPL and NPSLE was reported in several studies.[20–22] A recent meta-analysis have also reported that aPL are significantly associated with specific manifestations of NPSLE, in particular cerebrovascular diseases.[23]

3.2 Anti-ribosomal P protein antibodies

Ribosomes are complex macro-molecular structures incorporating both protein and ribonucleic acid (RNA) elements. Anti-ribosomal P protein antibodies mainly react with P0 (38 kDa), P1 (19 kDa), and P2 (17 kDa) proteins located on the ribosomal subunit 60S.[24] The autoimmune response to ribosomal components is often observed in systemic autoimmune diseases, in particular SLE. Interestingly, numerous studies have demonstrated an association between serum anti-ribosomal P protein antibodies and NPSLE, especially in the psychosis manifestations.[25,26] Serum anti-ribosomal P protein antibodies were stated to be present in one-third of NPSLE cases. Although the sensitivity and specificity of the serum anti-ribosomal P protein antibodies for the diagnosis of NPSLE have been estimated at 26% and 80%, respectively, they are not effective in discerning the specific NPSLE manifestations.[27] However, a recent systemic review analysis indicated that anti-ribosomal P protein antibodies are significantly associated with specific manifestations of NPSLE, psychosis.[23] In addition to the serum anti-ribosomal P protein antibodies, increased levels of cerebrospinal fluid (CSF) anti-ribosomal P protein antibodies have also been reported in patients with NPLSE with diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE) compared with patients with NPLSE with neurological syndromes or peripheral neuropathy (focal NPSLE).[28]

Interestingly, anti-ribosomal P antibodies appear to be pathological for NPSLE as they have been reported to penetrate living cells by binding the cell-surface 38-kDa protein (P0). Moreover, they can cause cellular dysfunction and tissue damage by inhibiting protein synthesis, consequently inducing apoptosis

or proinflammatory cytokine production.[29] In addition, other studies have also indicated the neuropathogenic potential of anti-ribosomal P protein antibodies.[30,31] Therefore, the anti-ribosomal P protein antibodies may possibly be pathogenic autoantibodies in NPSLE through their direct interaction with neural antigens.

3.3 Anti-NMDAR antibodies

The NMDAR are expressed on neuronal cells and play an important role in neurological functions such as memory. Functional NMDAR consist of two sets of subunits, NR2 (NR2A, 2B, and 2C) or NR3 (NR3A and 3B). Anti-NMDAR antibodies are a subset of pathogenic murine anti-double stranded DNA antibodies that cross-react with a consensus peptide sequence of the extracellular domain of mouse and human NMDAR subunits NR2A and NR2B.[32] Lepteva et al.[33] have reported that the serum anti-NMDAR antibodies (anti-NR2) were associated with depressive mood in NPSLE manifestations. In addition to serum anti-NMDAR antibodies, CSF anti-NR2 antibodies have also been reported to be upregulated in patients with NPSLE with acute confusion state (ACS) compared with patients with diffuse NPSLE without ACS, which consists of anxiety disorder, cognitive dysfunction, mood disorder, and psychosis.[34]

The potential pathogenic role of anti-NMDAR antibodies has also been demonstrated. Interestingly, the administration of anti-NR2 antibodies induced BBB breakdown and led to neuronal cells apoptosis, consequently resulting in impaired memory and learning in mice.[32,35] These data suggested that the anti-NR2 antibodies directly participate in the pathogenesis causing specific manifestations of NPSLE.

3.4 Other autoantibodies

Other autoantibodies have been linked to NPSLE, but further supportive studies are still required. CSF anti-U1 RNP antibodies have been reported to represent a clinically important biomarker for NPSLE.[36] Moreover, an association between serum anti-endothelial cells antibodies (AECA) and NP manifestations in SLE have also been reported.[37] Moreover, we have recently identified two autoantibodies related to NPSLE, namely anti-chromatin assembly factor 1 (CAF-1) antibody[13] in serum and anti-microtubule associated protein 2 (MAP-2) in CSF[14]

CAF-1 was originally identified by complementation as a factor participating in the chromatin assembly during DNA replication in human cell extracts.[38] We have identified the serum anti-CAF-1 antibodies as novel antibodies specifically recognized in SLE (Table 3).[13] Moreover, compared with other organs, we reported significantly more CNS involvement in patients with SLE positive for anti-CAF-1 antibodies than in those negative for the antibodies (Table 4).[13]

Table 3. Prevalence of anti-chromatin assembly factor 1 (CAF-1) antibody in connective tissue diseases

	NHC	SLE	PM/DM	SSc	SjS	MCTD	RA
Number of patients		116	100	100	100	100	100
100							
Number of anti-CAF-1 antibody	0	33	3	2	3	6	4
Statistical analysis (P value *vs* SLE)	< 0.0001		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Immunoreactivity against recombinant CAF-1 antigen was measured by ELISA using sera with normal healthy controls (NHC) and patients with connective tissue diseases. Cut off point was designed as mean value of NHC + 3 standard deviations and a value above the cutoff point was considered as anti-CAF-1 positive sera. Statistical analysis was performed by qui square test against systemic lupus erythematosus (SLE), and a p value less than 0.05 was considered statistically significant.

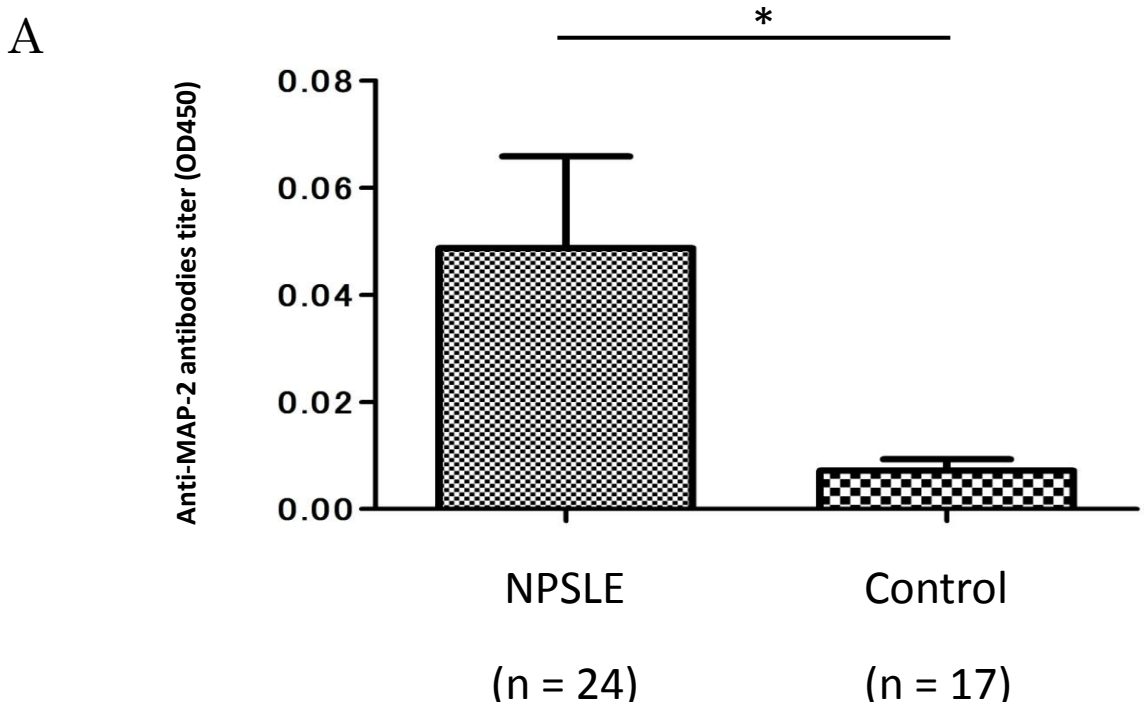
Adopted from ''Antibody against chromatin assembly factor-1 is a novel autoantibody specifically recognized in systemic lupus erythematosus," by Doe K, Nozawa K, Hiruma K, Yamada Y, Matsuki Y, et al. 2014, Lupus, 23(10):1031-1041.

Table 4. Comparison of clinical profile in SLE patients with or without anti-CAF-1 antibody

	Anti-CAF-1 antibody(+)	Anti-CAF-1 antibody(-)	Statistical analysis
Number of patients	33	67	
Gender			
Female	27	61	
Male	6	6	P=0.1819
Age(mean age)	24.9±10.2	30.2±14.0	P=0.0662
Rash(%)	21(63.6%)	40(59.7%)	P=0.7044
Nephritis(%)	23(69.7%)	35(52.2%)	P=0.0963
Lymphopenia(%)	29(87.9%)	60(85.7%)	P=0.8014
Hemolytic anemia(%)	3(9.1%)	6(9.00%)	P=0.9822
Thrombocytopenia(%)	11(33.3%)	29(43.3%)	P=0.3396
Arthritis(%)	20(60.6%)	47(70.1%)	P=0.3399
Serositis(%)	5(15.2%)	8(11.9%)	P=0.6534
CNS involvement(%)	6(18.2%)	3(4.5%)	P=0.0243*

Adopted from ''Antibody against chromatin assembly factor-1 is a novel autoantibody specifically recognized in systemic lupus erythematosus," by Doe K, Nozawa K, Hiruma K, Yamada Y, Matsuki Y, et al. 2014, Lupus, 23(10):1031-1041.

In addition to the anti-CAF-1 antibodies, we also reported a high specificity for CSF anti-MAP-2 antibodies for NPSLE, thus suggesting them as a useful biomarker for NPSLE diagnosis.[14] MAP-2 is part of an abundant group of cytoskeletal components predominantly expressed in neurons. Originally, anti-MAP-2 antibodies have been found in sera of patients with SLE, especially those with neuropsychiatric manifestations.[39] The authors reported that 17% of patients with SLE were anti-MAP-2 positive compared with only 4% of the controls. More specifically, 76.5% (13/17) of the patients with NPSLE were anti-MAP-2.[39] Based on that previous study, we investigated the CSF anti-MAP-2 antibodies to determine whether anti-MAP-2 antibodies can be used to diagnose NPSLE. We found significantly higher anti-MAP-2 antibody titers in the CSF of patients with NPSLE than in controls without NPSLE (Figure 1A, B). Furthermore, none of the patients who are positive for anti-MAP-2 antibodies were included in the control patient group.[14] The pathological roles of anti-MAP-2 antibodies in NPSLE are not clear because MAP-2 is an intracellular antigen and antibodies against MAP-2 are not able to bind directly to MAP-2 under physiological conditions. However, MAP-2 may be expressed on the surface of neuronal cells in pathological conditions, and thus functions as pathological antibodies in NPSLE. We are now undergoing further studies to investigate whether both autoantibodies are useful biomarkers for the diagnosis of NPSLE.



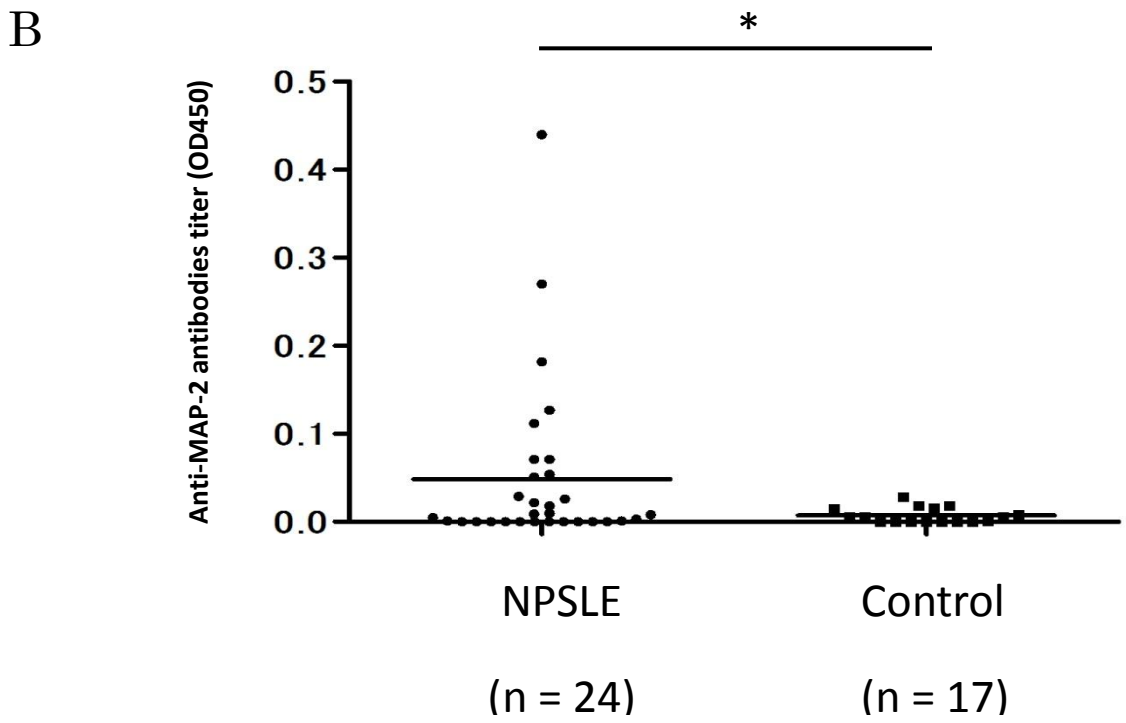


Figure 1: Anti-microtubule associated protein (MAP)-2 antibodies in the cerebrospinal fluid (CSF) of patients with neuropsychiatric systemic lupus erythematosus (NPSLE).

Immunoreactivity against MAP-2 protein was evaluated in the non-diluted CSF of patients with NPSLE (n = 24) and non-NPSLE controls (n = 17) by ELISA. (A) The anti-MAP-2 antibodies titers, wherein the bars indicate the standard deviation (SD). (B) A scatter plot of the anti-MAP-2 antibodies titers. The cutoff value for a positive reaction (dotted line) was designated as the mean optical density (OD) of the non-NPSLE controls + 3 SDs. In all cases, statistical analyses are considered significant at $p < 0.05$ (*).

Anti-microtubule associated protein (MAP)-2 antibodies in the cerebrospinal fluid (CSF) of patients with neuropsychiatric systemic lupus erythematosus (NPSLE) from ''Antibodies to microtubule-associated protein-2 in the cerebrospinal fluid are a useful diagnostic biomarker for neuropsychiatric systemic lupus erythematosus,'' by Y Yamada et al, 2016, Mod Rheumatol, 26(4), 562-568.

4. Conclusion

NP highly influences the morbidity and mortality attributed to SLE. The etiology of NPSLE has not been fully elucidated and multiple factors are involved in its pathogenesis. Furthermore, NPSLE is often not diagnosed when secondary factors not related to SLE are present. Therefore, if highly specific NPLSE biomarkers exist, the measurement of the autoantibodies becomes

a useful tool for the diagnosis of NPSLE. Among the biomarkers, autoantibodies have been postulated as one of possible candidate molecules. Although the precise mechanism of the autoantibodies-induced pathogenesis is not fully understood, certain autoantibodies may play direct pathological roles in NPSLE and can be used as diagnostic biomarkers. Advancement of future studies on the autoantibodies associated with NPSLE will have great advantages for the clinical management of patients with NPSLE.

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