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Chapter 5

AUTOANTIBODIES AS PROGNOSTIC OR DIAGNOSTIC MARKERS OF PSYCHIATRIC MANIFESTATIONS IN SLE

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ABSTRACT

In the course of Systemic Lupus Erythematosus (SLE), a variety of psychiatric disturbances are reported, including mood disorders (depressive symptoms), psychosis and anxiety. The reported prevalence of psychiatric disorders in SLE varies widely, ranging from 17% to 75%, but the diagnosis of these syndromes is difficult and depends on the exclusion of complications due to an iatrogenic effect of drugs, to metabolic abnormalities or to infections. Moreover, the diagnosis requires a careful psychiatric evaluation to exclude merely reactive psychological disturbances.

It has been suggested that several autoantibody specificities play a role in the pathogenesis of neuropsychiatric SLE. Potential pathogenic relevance has been attributed to, among others, antineuronal, antiphospholipid, antiganglioside, anti-DNA, anti-ribosomal P protein and anti-endothelial cell antibodies. However, particularly regarding psychiatric syndromes, conflicting results have been reported on the association between serum autoantibodies and symptoms.

The diagnostic and/or prognostic role of autoantibodies associated to psychiatric disorders in SLE is discussed.

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INTRODUCTION

Neuropsychiatric involvement in patients with Systemic Lupus Erythematosus (SLE), first mentioned by Kaposi more than 100 years ago, still remains one of the main challenge facing rheumatologists and other physicians [1]. The American College of Rheumatology recently proposed a classification of 19 different neurological and psychiatric syndromes of SLE [2, 3]. These case definitions encompass neurological syndromes, involving the central and peripheral nervous system as well as psychiatric disorders, cognitive deficits and acute confusional states (Table). However, major problems are still related to low specificity of some of these syndromes such as headache, cognitive impairment or mood disorders [4].The diagnosis of neuropsychiatric SLE (NPSLE) is complex not only because of the considerable prevalence variation (14-80%) but also because of the wide spectrum of neuropsychiatric manifestations. Different neuropsychiatric manifestations result from a variety of mechanisms including antibodies, vasculitis, thrombosis, hemorrhages and cytokine-mediated damages.

Table 1. American College of Rheumatology Classification of Neuropsychiatric Manifestations in SLE

Neurological manifestations
Myasthenia gravis
Acute inflammatory demyelinating polyradiculoneuropathy (Guillan-Barrè syndrome)
Demyelinating syndrome
Myelopathy
Headache
Neuropathy, cranial
Aseptic meningitis
Mononeuropathy (single/mutiplex)
Plexopathy
Autonomic disorder
Polyneuropathy
Cerebrovascular disease
Movement disorder (chorea)
Seizure and seizure disorders
Psychiatric manifestations
Acute confusional state
Cognitive dysfunction
Anxiety disorder
Mood disorder
Psychosis

Of note, despite the dramatic clinical manifestations, too often changes at the morphological neuroimaging techniques are minimal and non specific. The diagnosis of NPSLE remains largely one of exclusion and is approached in individual patients by thorough clinical evaluation, supported when necessary by autoantibody profiles, diagnostic imaging, electrophysiologic studies and objective assessment of cognitive performance [5]. Autoantibodies associated to NPSLE may have a diagnostic and/or prognostic role. This chapter describes and discusses the role of the autoantibodies reported to be associate to NPSLE.

Autoantibodies in NPSLE

Anti-Neuronal Antibodies

Anti-neuronal antibodies are a group of antibodies that react to neuronal components. Several studies, using different techniques to detect antibodies, demonstrated that anti-neuronal antibodies are detected predominantly in sera of patients with neuropsychiatric SLE than in patients without neuropsychiatric manifestations [6-13]. Competition assays showed that the binding of anti-neuronal antibodies was blocked by mycobacterial glycolipids, suggesting a link between mycobacterial infection and neuropsychiatric SLE [9]. Hanson and coworkers showed that a 50-kDa protein may be an important target for these autoantibodies, preponderantly found in NPSLE patients and that the antigen may play a role in the pathogenesis of some neurological manifestations in SLE [8]. To validate the hypothesis that some neuropsychiatric manifestations of SLE are mediated by the direct effect of antibody binding to neuronal membranes, one study of Bluestein and coworkers showed that anti-neuronal antibodies were significantly more concentrated in cerebrospinal fluid (CSF) of patients with SLE and central nervous system diseases than in CSF of SLE patients without neurological involvement [13].

Brain Reactive Antibodies

Brain reactive antibodies (BRA) are a subgroup of anti-neuronal antibodies that bind to integral membrane proteins of the brain. BRA correlates with psychosis and/or seizures in SLE patients [14].

Anti-Microtubule-Associated Protein 2 Antibodies

Microtubule-associated proteins (MAPs) interact with the microtubules of the cellular cytoskeleton. Other specific immunological markers of neuropsychiatric SLE are the autoantibodies to microtubule-associated protein 2. This cellular protein is restricted to neurons and is important in the control of cytoskeletal integrity and other neuronal functions [15].

Anti-Neurofilament Antibodies

Antibodies to cytoskeletal neurofilament protein antigens (ANFA) had an increased incidence in patients with neuropsychiatric SLE compared with SLE patients without neuropsychiatric symptoms. ANFA were found to be directed against the 205 and 160 kDa proteins of the neurofilament triplet [16].

Anti-Ganglioside Antibodies

Ganglioside is a compound composed of a glycosphingolipid with one or more sialic acids linked on a hydrophilic sugar chain that contains antigenic determinants. It is a component of the cell plasma membrane which modulates cell signal transduction events. The gangliosides most commonly recognized by neuropathy-associated autoantibodies are GM1, asialo-GM1, GD1a, GD1b, GM2 and GQ1b. Persistent high titer of anti-ganglioside (AGA) IgM is associated with several diseases, particularly neuropathies. The role of AGA IgM is to eliminate the immunosuppressive gangliosides shed from tissues during ageing, degeneration of neural and extraneural tissues and tumor growth and necrosis. In addition, *in vitro* observations with human and murine monoclonal antibodies suggest that they are capable of complement dependent cytotoxicity and apoptosis. AGA IgM can cause leakage of the blood brain barrier (BBB) in a concentration-dependent and complement-independent manner, bind to neuronal gangliosides to create a neuromuscular block and serve as a marker of axonal damage in neuropathies such as multiple sclerosis [17]. Several studies demonstrated the association between AGA and neuropsychiatric SLE and one study demonstrated that AGA may have predictive value [18], but these autoantibodies are not specific of NPSLE and are present also in sera of patients with different neuropathies. In a study, Pereira and coworkers showed a significant correlation between IgG AGA in the CSF and IgM AGA in the serum of NPSLE patients. Some NPSLE patients had AGA in the CSF but not in the sera, suggesting that intrathecal antibody production can result in the development of this manifestations [19]. Galeazzi and coworkers, in a study of a large cohort of European patients with SLE, showed an association between AGA IgG and migraine, dementia and peripheral neuropathy and an association between AGA IgM and depression [20]. In another study, Chen and coworkers demonstrated the presence of AGA in the CSF of children with NPSLE, and showed a clear association between AGA and brain computerized tomography scan. This study suggested that the detection of AGA in the CSF have a predictive value for the onset of a neuropsychiatric flare [21].

Anti-Triosephosphate Isomerase Antibodies

Sera from patients with NPSLE were screened for antibodies to mouse choroid plexus cell line ECPC-4 by Western blotting. A 29-kDa protein band detected in NPSLE sera was identified as triosephosphate isomerase (TPI). TPI plays an important role in glycolysis and is essential for efficient energy production. Using western blotting technique, Watanabe and coworkers demonstrated IgG specific to TPI in sera and CSF of patients with NPSLE. The serum anti-TPI IgG index was higher in the NPSLE than in other autoimmune diseases, demonstrating a high specificity for the diagnosis of NPSLE [22]. In CSF anti-TPI IgG form immunocomplexes and contribute to the pathogenesis of NPSLE by activating the complement system [23].

Anti-Glial Fibrillary Acidic Protein Antibodies

Glial fibrillary acidic protein (GFAP) is expressed in the central nervous system in astrocyte cells. It is involved in cell structure and movement, in cell communication and in the functioning of the BBB. A high positive predictive value of anti-GFAP antibodies for NPSLE has been described [24]. Recently, Trysberg and coworkers showed increased levels of GFAP in the cerebrospinal fluid of patients with NPSLE. Moreover, successful therapy with cyclophosphamide in NPSLE patients resulted in significantly decreased CSF levels of GFAP [25]. On the contrary, Conti and coworkers found no correlation between anti-GFAP antibodies and psychiatric morbidity [26].

Serum Lymphocytotoxic Antibodies

An important place in the immune network is reserved for specific interactions between regulatory antibodies and their ligands on T and B lymphocytes. Lymphocytotoxic antibodies (LCA) are detected in a great majority of patients with SLE. Several studies show or claim a relationship between the presence of LCA and neurological manifestations in SLE patients; the results, however, remain questionable due to the difference in detection methods as well as in definition of central nervous system (CNS) involvement [27]. Analysing frequency of HLA class II antigens (DR and DQ) and LCA in patients with NPSLE, Silva and Donadi showed that HLA-DR4 may have a protective role for the development of NPSLE whereas HLA-DR9, in addition to HLA-DR3 and to LCA, may predispose to neuropsychiatric abnormalities [28]. Analysis of LCA serially in SLE patients revealed fluctuations in LCA associated with NPSLE relapses or remissions [29].

Anti-CD4 Antibodies

Several lines of evidence indicate that the CD4 glycoprotein may be recognized by autoantibodies. Lenert and coworkers evaluated the presence of serum anti-CD4 antibodies in patients with SLE. The antibody reactivity has been analyzed both on native CD4 (by immunofluorescence) and on recombinant CD4 (by ELISA and Western blot). The results of this study showed that the anti-CD4 reactivity occurred in SLE patients with active disease and, as measured by the SLEDAI, was associated with particular clinical manifestations, including neuropsychiatric disease [30].

Anti-SSA/Ro Antibodies

The SSA/Ro antigens are nuclear and cytoplasmic polypeptides which serve as autoantigens in SLE and Sjögren's syndrome. They contain two major isoforms of 60 and 52 kDa. Initially, these antibodies were thought to be an epiphenomenon of autoimmune diseases. Recent studies have shown that they are associated with specific clinical manifestations and disease subsets [31]. To identify factors predictive of NPSLE, a large cohort of SLE patients was followed over 11 years. The presence of anti-SSA/Ro antibodies was demonstrated to be one independent predictor of significant neuropsychiatric damage [32]. Anti-SSA/Ro antibodies were detected also in CSF of patients with NPSLE [33]. In a clinical observation regarding suicide attempts in NPSLE patients, all harbored elevated titers of anti-SSA/Ro antibodies [34]. On the other hand, Shimojima and coworkers investigating the predictive value of distinct clinical factors in patients with NPSLE, demonstrated that

anti-SSA/Ro antibodies were not significant for NPSLE and they did not predict the development of NPSLE [35]. In accordance with the previous study, Conti and coworkers did not find any significant correlation between the presence of anti-SSA/Ro autoantibodies and psychiatric involvement [26].

Anti-Sm Antibodies

Anti-Sm antibodies are directed against 7 proteins (B/B', D1, D2, D3, E, F, G) that constitute the common core of U1, U2, U4 and U5 small nuclear ribonucleoprotein (snRNP) particles [36]. Winfield and coworkers, in a serologic study on patients with NPSLE, found a higher incidence of anti-Sm antibodies in the patients with CNS dysfunction compared with a large group of patients without neuropsychiatric disease, suggesting an association of anti-Sm with CNS disease in SLE [37]. On the contrary, results of another study found no association between anti-Sm antibodies and neuropsychiatric features [38].

Anti-DNA Antibodies Cross-Reactive with NMDA Receptor

Many clinical manifestations of SLE are mediated by anti-DNA antibodies that in particular correlate with disease activity and cause kidney damage [39]. The anti-DNA antibodies may react directly with DNA or cross-react with non-DNA tissue antigens. In a study to determine the distinct antigens that anti-DNA antibodies recognize, a phage display library was screened with a monoclonal antibody specific to double stranded DNA and a pentapeptide consensus sequence (DWEYS) was revealed [40]. This consensus sequence is contained in *N*-methyl-D-aspartate (NMDA) receptors NR2A and NR2B (residues 283-287). NR2A and 2B are polypeptide chains that associate with the NR1 polypeptide to form NMDA receptors. NR2 receptors bind the neurotransmitter glutamate and play a role in learning and memory [41]. DeGiorgio and coworkers demonstrated that a subset of anti-DNA antibodies cross-react with NMDA receptors and, through an excitotoxic mechanism, can induce neuronal apoptosis both *in vitro* than inoculated directly in mouse brain [42]. These anti-DNA antibodies are present in CSF of patients with SLE who experienced cognitive decline, but it is not yet known whether they are produced *in situ* in the brain or cross the BBB.

BALB/c mice are a strain of mice which not present spontaneous brain pathology, permitting the analysis of antibody-mediated brain pathology and cognitive dysfunction. To study whether the anti-dsDNA/NR2 antibodies could cause brain damage when present in systemic circulation, BALB/c mice were immunized with the peptide to develop cross-reactive anti-DNA and anti-NR2 antibodies [43]. The administration of LPS to mice breaking the integrity of BBB, allowed to antibodies to pass from circulation to the brain. In fact, neuropathology requires a breach in the integrity of BBB and bacterial infection leads to a loss of the BBB function. The anti-NR2 antibodies showed a preferential binding in the hippocampus and consequent loss of hippocampal neurons. The loss of neurons in hippocampus leaded to an impairment in memory function. Mice receiving LPS and intravenously human antibodies specific to DNA and NMDA receptors extracted from sera of patients with SLE, elicited cognitive impairment [44]. To determine whether anti-NR2

antibodies exist in the brain of patients with SLE, IgG was eluted from patients' brain. The eluted IgG showed binding to DNA and NR and induced neuronal apoptosis when injected into mouse brain.

The breakdown of BBB may occur not only as infection, but also as cerebral vasculitis, stress, nicotine exposure, etc. The rise of epinephrine induced by stress is known to increase cerebral blood flow and to break the integrity of BBB, preferentially in the amygdale. In the mouse model immunized with the pentapeptide, the administration of epinephrine leaded to apoptosis of neurons of the lateral amygdale, resulting in behavioral disorders [45]. So the same antibody specificity can cause either a cognitive or an emotional disorder depending on the agent used to break the BBB. The presence of anti-DNA, anti-NR2 antibodies are found in 25-50% of patients with SLE [46]. Several studies yielded conflicting data about the correlation between the neuropsychological function and serum anti-NR2 antibody levels, but brain dysfunctions seem clearly correlate to the presence of antibody to the pentapeptide in CSF and symptom severity correlate with antibody titer [47]. An emerging quantitative magnetic resonance imaging technique offers the promise of a quantitative physiological measure of cellular integrity. A recent study using this technique showed that a small group of patients with SLE and anti-NR2 antibodies presented alteration in amygdale compared with patients without anti-NR2 antibodies [48].

Non-competitive inhibitors of NMDA receptors, such as MK801 and memantine, are promising therapeutic tools to protect mice from neuronal injury caused by the direct injection of anti-NR2 antibodies into the mouse brain. The use of the D-isoform of the consensus peptide could also lead to neuronal sparing binding to anti-NR2 antibodies and so preventing their binding to NR2 [45].

Anti-Ribosomal P Antibodies

Anti-ribosomal P antibodies recognize 3 specific ribosomal proteins P0, P1 and P2 [49]. One of the major points of interest of anti-ribosomal P antibodies derives from their high specificity for NPSLE [50,51]. Elevated titers of anti-ribosomal P antibodies are mainly detected in SLE patients immediately before and during active disease [52] and may be associated with particular clinical manifestations, including lupus nephritis, hepatitis [53-55] and neuropsychiatric involvement [5, 56-60].

In particular, the clinical association between elevated titers of anti-ribosomal P antibodies and psychosis was originally described by Bonfa and coworkers in patients with psychosis secondary to SLE [61]. Several studies showed a strong association between elevated titers of serum anti-P antibodies and NPSLE, predominantly psychosis and severe depression [54, 61-73]. One study of West and coworkers, examining a cohort of SLE patients with and without psychiatric manifestations over a period of 10 years, demonstrate the relationship between psychosis and depression and anti-ribosomal P antibodies [68]. On the contrary, some reports failed to find any relationship between anti-ribosomal P antibodies and NPSLE [26, 54, 74-78]. In particular, in a recent study the association between the presence of anti-ribosomal P antibodies and either lupus psychosis or depression, among a large cohort of patients with SLE, was not observed [79]. There are conflicting reports on the importance of anti-ribosomal P antibodies in the CSF. In a recent study, elevated titers of anti-ribosomal P antibodies were measured in the CSF and in the serum samples of a large

cohort of patients with SLE. Patients were divided into 4 groups: patients with neurologic syndromes of the CNS; patients with diffuse psychiatric/neuropsychological syndromes; patients with complex presentations (neurologic syndromes of the CNS and diffuse psychiatric/neuropsychological syndromes); patients without NPSLE based on ACR diagnostic criteria [2]. In patients with NPSLE the frequency of CSF anti-ribosomal P antibodies was significantly higher than in patients without NPSLE. These results suggest that the presence of IgG anti-ribosomal P antibodies in CSF of SLE patients may be involved in the appearance of NPSLE, expecially in complex presentations [62].

Anti-ribosomal P antibodies bind and penetrate cells in culture. The cellular receptor appears to be a membrane form of the P0 38 kDa phosphoprotein, which mediates the binding and penetration of anti-ribosomal P antibodies. Following penetration, anti-ribosomal P antibodies were found to localize in the cytoplasm and in the nucleus [80]. Anti-ribosomal P antibodies are potent inhibitors of protein synthesis and *via* this pathway mediate cellular dysfunction. The ability of anti-ribosomal P antibodies to bind and penetrate into living cells was shown to induce the production of pro-inflammatory cytokines and to increase apoptosis of penetrated cells. This raises the possibility that these antibodies are of importance in the pathogenesis of NPSLE [52].

Anti-Endothelial Cells Antibodies

Anti-endothelial cells antibodies (AECA) are a heterogeneous group of autoantibodies directed against antigens in the membrane of endothelial cells. Originally described in 1971, a number of targets have now been identified for these autoantibodies [81]. They have been detected in several autoimmune diseases and have been associated with nephritis and vasculitis in SLE patients [82]. Recent data suggest their implication in endothelial dysfunction and a pathogenic role of AECA in SLE [82, 83]. AECA are capable of causing up-regulation of pro-inflammatory markers and apoptosis in endothelial cells [84]. Song and coworkers showed a clinical association of AECA with disease activity and neuropsychiatric manifestations in SLE [85]. Meroni and coworkers found AECA positivity in a high percentage of SLE patients with involvement of the CNS [86]. In a recent study Conti and coworkers, investigating the possible correlation of psychiatric manifestations in SLE and the reactivity of autoantibodies to different autoantigens (endothelial cells, cardiolipin, beta2 glycoproteinI (beta2-GPI), SSA/Ro, La, glial fibrillary acidic protein, ribosomal P protein, dsDNA and nucleosomes), demonstrated a significant association between AECA and psychiatric involvement in SLE patients [26, 87]. In this study, patients were categorized as either with or without psychiatric disorders on the basis of the clinical psychiatric examination. Patients were considered with psychiatric manifestations only when presented a severe psychopathology such as psychosis and mood disorders (recurrent major depressive disorders, dysthymic disorder, and depressive disorder not otherwise specified). Anxiety and mild depression were not included since these disorders are frequently detected in SLE patients and are predominantly psychoreactive [3, 88].

Identifying endothelial autoantigens involved in the autoimmune processes during neuropsychiatric SLE could help to explain the pathogenetic mechanisms involved in the initiation and progression of psychiatric symptoms.

Anti-Nedd5 Antibodies

With the aim of seeking and characterizing molecules that behave as autoantigens in NPSLE, Margutti and coworkers provided evidence that the C-terminal region of Nedd5 (Nedd5 C-ter) is a novel autoantigen with a role in neuropsychiatric manifestations [89]. In fact, the percentage of patients with anti-Nedd5 C-ter serum IgG was higher in group of patients with neuropsychiatric manifestations than in patients without these disorders. Nedd5 is a mammalian septin known to associate with actin-based structures, such as the contractile ring and stress fibers [90, 91]. The septins are a family of cytoskeletal GTPases that play an essential role in cytokinesis, in yeast and mammalian cells [92]. Interestingly, Nedd5 is predominantly expressed in the nervous system and may contribute to the formation of neurofibrillary tangles as integral constituent of paired helical filaments in Alzheimer's disease [93, 94]. Margutti and coworkers demonstrated that Nedd5 presented an intracellular redistribution on the cell surface during apoptosis, which may be in part responsible for its immunogenicity. Indeed, apoptosis may play an important role in by-passing tolerance to intracellular autoantigens. The specific modification of autoantigens and their redistribution into blebs at the surface of apoptotic cells may contribute to the induction of autoimmune responses [95, 96]. Moreover, apoptotic defects and impaired removal of apoptotic cells could contribute to an overload of autoantigens in the circulation or in target tissues that could become available to initiate an autoimmune response [97]. In susceptible individuals, this can lead to autoantibody-mediated tissue damage. Interestingly, the C-terminal region of Nedd-5 displays a coiled-coil domain. Several autoimmune autoantigens are characterized by the presence of such domain [98]. Coiled-coil proteins may be exposed to the immune system as surface structures in aberrant disease states associated with unregulated cell death and could become autoimmune targets [98]. The unanswered question is whether anti-Nedd5 C-ter antibodies can cause direct damage, thus contributing to the pathogenesis of psychiatric manifestations, or whether they are an epiphenomenon of these disorders.

Anti-Phospholipid Antibodies

Anti-phospholipid (aPL) autoantibodies are directed against anionic phospholipids or protein-phospholipid complexes. The negatively charged phospholipid targets include phosphatidyl inositol, phosphatidyl glycerol, phosphatidyl serine, phosphatidyl acid, and cardiolipin. Neutrally charged autoantigen targets include phosphatidyl ethanolamine, phosphatidyl choline, platelet activating factor and sphyngomyelin. By far, aPL antibodies, in particular anti-cardiolipin (aCL) antibodies and lupus anti-coagulant (LAC), have been the most widely investigated antibodies in NPSLE. The association of aPL antibodies in NPSLE has been reviewed [99]. This class of antibodies are reported to associate with focal neurological disease such as stroke, transient ischaemic attacks and transverse myelitis [99]. In a study on a large cohort of SLE patients, elevated titers of aPL antibodies were an independent risk factor for the development of cerebrovascular disease, seizures, and headache [100].

Anti-Cardiolipin Antibodies

A strong correlation between aCL antibodies and the overall frequency of neuropsychiatric manifestations was reported in many studies [101-103], but refuted in others [104,105]. In pediatric SLE, elevated titers of aCL antibodies are also frequently encountered, and aCL IgG are often associated with CNS involvement [103]. The frequency of aCL antibodies (IgG isotype) was significant for patients with cognitive dysfunction, chorea and cranial neuropathy [32]. In an open pilot study of children with NPSLE manifested as encephalopathy with or without grand mal seizures, focal seizures with depression or hallucinations, optic neuritis with transverse myelitis and psychosis with audiovisual hallucinations, a high percentage of these patients had elevated aCL IgG [106]. Paired measurements of aCL antibodies, in the serum and CSF, were performed using the ELISA method in SLE patients and in controls with other diseases. High titers of CSF aCL IgG were detected in NPSLE patients with lupus headache, acute psychosis, cognitive impairment, high cortical dysfunction and altered consciousness. Intrathecal synthesis occurred in these NPSLE patients, rather than the diffusion of aCL IgG from serum to CNS compartments [107]. In another study, aCL antibodies were studied in the serum and CSF of patients with SLE admitted for the assessment of NP disease. Patients with active neuropsychiatric complaints had positive aCL antibodies in the CSF, some of these patients presented simultaneous presence of antibodies in their sera and in their CSF. The assessment of the Q-albumin index revealed abnormal values in a subset of patients with active neuropsychiatric changes who exhibited positive CSF aCL antibodies, suggesting that impairment of the BBB function may lead to a leakage of intrathecal aPL antibodies from the systemic circulation. Additionally, a few patients revealed normal Q-albumin values with a high IgG-CSF index, suggesting increased intrathecal synthesis of antibodies. The study of aCL antibodies in CSF was useful in detecting active NPSLE [108]. In another small study, aCL antibodies were not detected in any CSF samples [109].

Experimental models show direct evidence for the pathogenicity of aCL antibodies and cognitive dysfunction. In one study, BALB/c mice were immunized with a pathogenic monoclonal aCL antibody and developed clinical and neurological manifestations [110]. In another mouse model, polyclonal aCL antibodies purified from pooled serum samples of patients with SLE had inhibitory effects on cultured normal rat brain astrocytes (RBA-1 cells). These results suggest that aCL Abs have an inhibitory effect on brain cells and elicit thrombus formation in brain vessels, both of which play a role in NPSLE [111].

Lupus Anti-Coagulant

One study evaluated the relationship between LAC and cognitive dysfunction in SLE patients. LAC-positive patients were 2 to 3 times more likely than LAC-negative patients to be designated as cognitively impaired. This study suggests that LAC positivity is associated with subclinical nervous system compromise and a pattern of deficits compatible with subcortical involvement, perhaps related to microthrombotic events or vasculopathy [112]. In a large study, utilizing MEDLINE from 1966 to 1989 to evaluate the validity of LAC in SLE patients, LAC was significantly associated with neuropsychiatric manifestations[113]. The findings of an association between LAC with seizures, cerebrovascular accidents and cognitive dysfunction were also corroborated in another study [32]. The association between

neuropsychiatric manifestations and LAC was reported in many other studies [100, 101], but refuted in others [105].

Chapman and coworkers in a study on the LAC mechanism, showed that these antibodies may be involved in the pathogenesis of NPSLE by nonischemic mechanisms, including the inhibition of astrocyte proliferation and the nonspecific permeabilization and depolarization of synaptoneurosomes [114].

Anti-Phosphatidyl Ethanolamine Antibodies

In one study, Kamorchkine and coworkers investigating the presence of anti-phosphatidyl ethanolamine (aPE) antibodies in a population of SLE patients, showed that neurological involvement was present in most of the patients with aPE antibodies [115].

Other Autoantibodies

The antigenic targets of other autoantibodies demonstrated associated to NPSLE are the microfilament protein L-fimbrin, the nuclear protein DA1, the galactocerebrosides and the serine proteinase 3 [24, 116-118]. Further studies are necessary to assign to these autoantibodies a role as immunological markers of NPSLE.

Conclusion

Several published data reported the association between neuropsychiatric manifestations in SLE and the presence of autoantibodies, although in some cases contrasting data are reported. The high variability among different studies is probably related to differences in the populations of patients studied and the laboratory tests used to detect serum antibodies. Some autoantibodies had specificity to brain constituents such as neurotransmitter receptors, raising the possibility that autoimmune mechanisms could interrupt or modulate the neurotransmission or could signal neuronal death through an excitotoxic mechanism (Figure 1). Other autoantibodies could react against self molecules that cross-react with brain components, with the above described pathological effect. Other autoantibodies reacted against endothelium. These antibodies could react with BBB, breaking down the barrier integrity by induction of apoptosis and expression of adhesion molecules (Figure 2). In conclusion, further studies are necessary to better characterize the specific antigens or epitopes recognized by autoantibodies associated with NPSLE and to evaluate their potential use in the diagnosis of NPSLE. The characterization of the target molecules might help defining the precise role that specific autoantibodies may play in the autoimmune mechanisms, underlying psychiatric manifestations, and might let us investigate new and more effective therapeutical strategies.

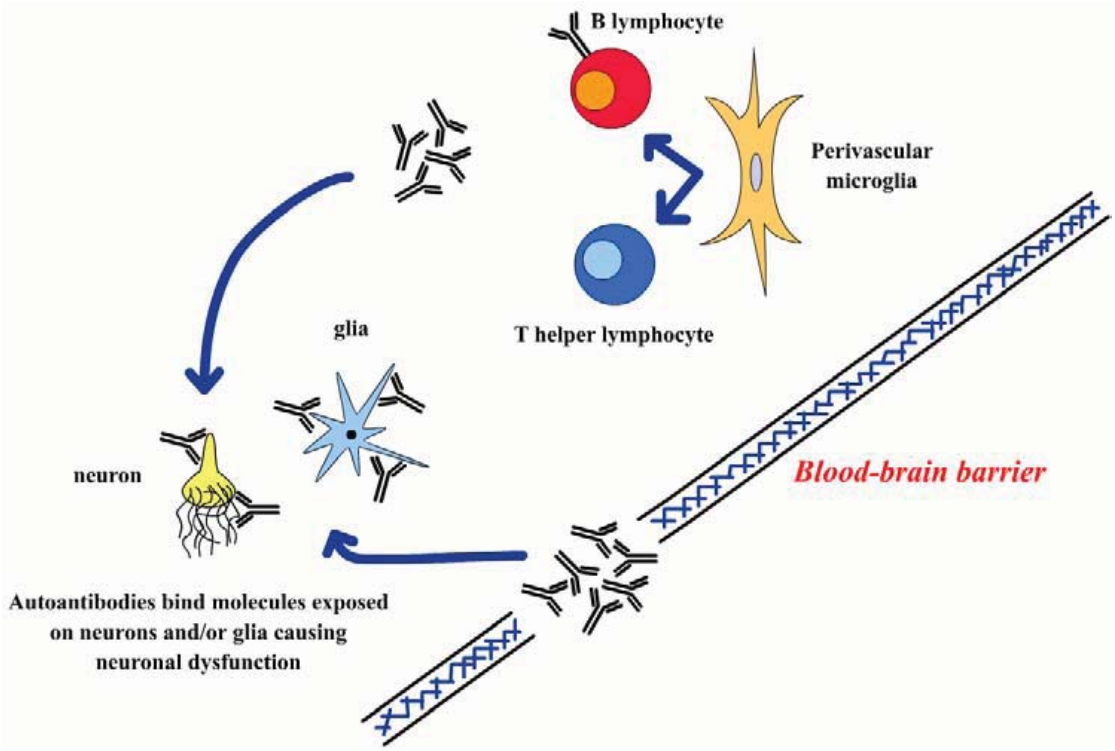

Figure 1. Access of antibodies to the central nervous system may occur through a disrupted blood-brain barrier or through *de novo* synthesis in nervous system. Autoantibodies, binding molecules exposed on the surfaces of neurons, lead to a neuro-toxic effect.

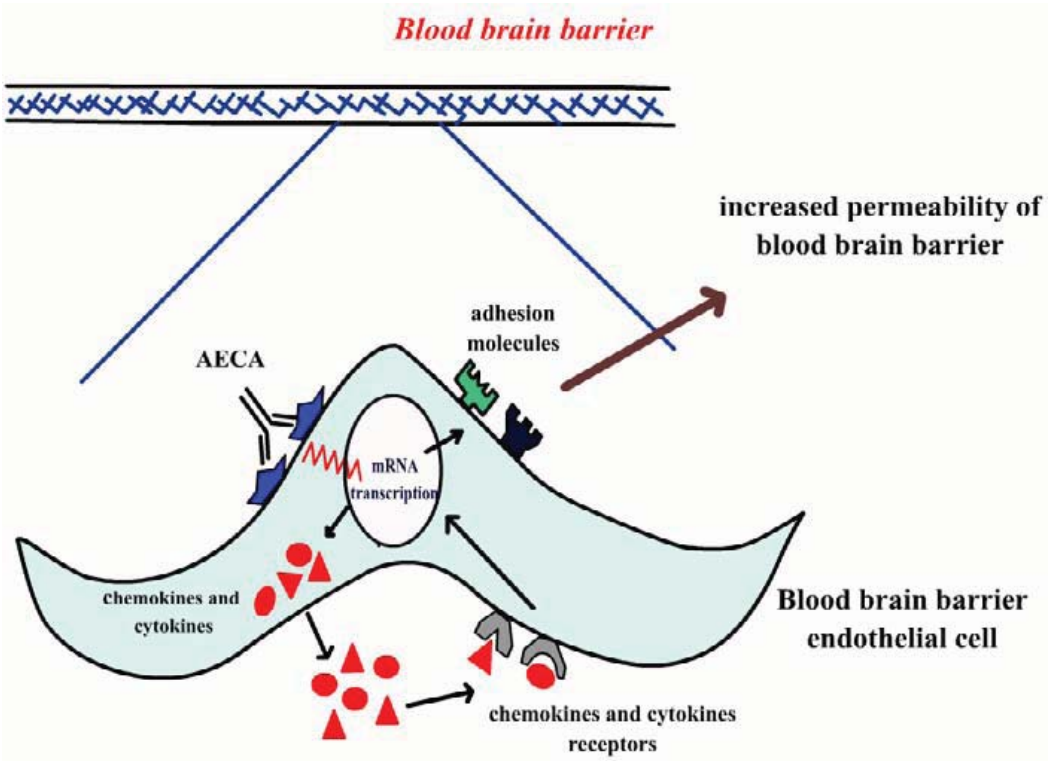

Figure 2. Effects of anti-endothelial cell antibodies. Anti-endothelial cell antibodies may activate the endothelium inducing the synthesis of pro-inflammatory cytokines and chemokines and expression of adhesion molecules, lead to the permeability of the blood-brain barrier.

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