Editorial

The Pathogenesis of Neuropsychiatric Manifestations in Systemic Lupus Erythematosus: A Disease in Search of Autoantibodies, or Autoantibodies in Search of a Disease?

Current concepts suggest several mechanisms contribute to the immunopathogenesis of neuropsychiatric manifestations in SLE (NP-SLE), including antiphospholipid (aPL) antibody-mediated ischemia, microthrombosis and noninflammatory vasculopathy[1,2], local production of cytokines leading to neuronal cytotoxicity[3-5], and direct interaction of autoantibodies (aAb) with autoantigens (aAg) on neuronal cell membranes, leading to interference with neurotransmission, loss of neuronal plasticity, and neuronal cell death[6]. In this brief review, we discuss NP-SLE nomenclature and provide an opinion on how strongly current evidence does indeed support the concept of aAb-mediated neural cell injury in NP-SLE, with emphasis on the central nervous system (CNS).

HISTORICAL BACKGROUND

Over 35 years ago, Johnson and Richardson, in their seminal description of neuropathological findings in SLE, noted at autopsy a high prevalence of brain microinfarcts and concluded that "SLE of the nervous system is, in most cases, a vascular disease involving very small vessels"[7]. However, they also noted that this vascular involvement was strikingly associated histopathologically with the "lack of any true arteritis," raising the question of what might cause these lesions. Ten years later, Mary Betty Stevens and colleagues reported on the remarkable diversity of NP-SLE manifestations, encompassing psychosis, seizures, strokes, cranial nerve abnormalities, chorea, meningitis, myelitis, and peripheral neuropathies[8]. Since then, many groups have expanded these observations. In the past 5 years alone, hundreds of reports have been published on NP-SLE, demonstrating not only the widespread scientific interest for these manifestations and their complexity, but also the elusive nature of their pathogenic causes (for reviews[1,9]).

Virtually all parts of the central, peripheral, and autonomous nervous systems can be involved in SLE[1]. The prevalence of CNS disease varies widely, from 15% to 75%. Such involvements are a major cause of reduction in quality of life, increased cumulative organ damage, and increased mortality. Some types of NP-SLE are uncommon (e.g., chorea), whereas others are common but often subtle (e.g., cognitive disorders). In many cases, the differential diagnosis is broad, including infection, side effects of medication, and metabolic abnormalities (e.g., uremia), making it a challenge for clinicians to diagnose and treat NP-SLE. These issues are compounded by the lack of universal diagnostic standards for NP-SLE disease. Also, application of sophisticated brain imaging and cognitive testing frequently reveals subclinical deficits whose clinical significance is unclear[10].

NEW NP-SLE NOMENCLATURE AS A TOOL FOR IMPROVED STUDIES

A timely initiative was the publication in 1999, under the auspices of the American College of Rheumatology (ACR), of a standard nomenclature and set of case definitions for NP-SLE, providing a uniform methodology for defining clinical subsets of NP-SLE[11]. Although designed primarily to facilitate and enhance clinical research, particularly multicenter studies, and not as a substitute for a clinical diagnosis, these concise diagnostic criteria and the broad differential diagnosis of the 19 NP-SLE syndromes are required reading for clinicians providing care to SLE patients. The complete case definitions are available on the

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Internet at: www.rheumatology.org/publications/ar/1999/aprilappendix.asp?aud=mem.

In this issue of *The Journal,* Hanly and colleagues use the ACR nomenclature and case definitions to determine the prevalence and attribution of NP disease in an unselected cohort of 111 Canadian patients with SLE from a single center[12]. During a mean disease duration of 10 years, 74 NP events occurred in 41 (37%) patients. These events were attributed to SLE itself, to non-SLE causes, or to both in 47%, 41%, and 12% of cases, respectively. Most events attributed to non-SLE causes consisted of migraine, tension headache, and mood disorders. Thus the criteria as they currently stand predictably picked up several non-SLE NP manifestations. In fact, the nomenclature has been criticized for some lack of specificity and inclusion of findings without objective abnormalities, such as headache, and revised criteria have been proposed[13,14].

Nevertheless, several conclusions stem from the study by Hanly, *et al* and the few other reports based on ACR nomenclature[12,15]. First, discriminating accurately between NP manifestations truly attributable to SLE versus non-SLE causes is of paramount importance to achieve nosologically homogenous patient subsets, a prerequisite for studies focused on pathogenesis[12,14,15]. The ACR nomenclature and case definitions, although not perfect, are an important step in that process. Second, multicenter studies collectively using the ACR nomenclature will be needed to achieve a sufficiently large sample size for etiological study of the rarer NP-SLE manifestations. Third, the great diversity of NP-SLE manifestations noted by Stevens[8] and highlighted by the ACR nomenclature again raises the fundamental question of the pathogenesis of nervous system involvement in SLE. Moreover, although SLE is the prototypical systemic autoimmune disease associated with multiple aAb, the ACR nomenclature and diagnostic criteria for NP-SLE conspicuously exclude any aAb diagnostic test in the serum or cerebrospinal fluid (CSF)[11].

BY WHAT MECHANISMS ARE AUTOANTIBODIES TO INTRACELLULAR AUTOANTIGENS PATHOGENIC IN SLE?

To understand the immune mechanisms that may lead to CNS dysfunction, it is useful to review briefly the major pathogenic mechanisms of aAb to intracellular autoantigens in other organ systems. SLE is characterized by the presence of multiple aAb, several of which contribute to the pathogenesis of specific manifestations and are used as diagnostic criteria. Hence, elevated serum levels of aAb to nuclear autoantigens (ANA) are present in almost all SLE patients, and high levels of ANA such as anti-dsDNA, anti-Sm, or anti-nuclear lamin B1 are rarely seen in any other disease[16–18]. Moreover, extensive studies over the past decades have yielded major insights on the mechanisms whereby certain ANA may contribute to SLE pathogenesis, as summarized in Table 1[18-24].

Interestingly, although the presence of antineuronal aAb has been known in SLE for over 2 decades[25] and several aAb potentially associated with NP-SLE have now been identified, optimal study of their pathogenicity has lagged behind those of ANA because of the great complexity of the nervous systems and the limited availability of nervous tissues[26]. Therefore it is logical to apply to aAb associated with NP-SLE the mechanistic framework learned from the study of ANA (Table 1) in order to formulate some *a priori* guidelines for evaluation of pathogenicity: (1) SLE aAb directed to intracellular aAg may exert pathogenic effects by binding to extracellularly expressed cognate aAg or to cross-reactive epitopes. Therefore, strict neural tissue specificity may not be expected from all pathogenic aAb in NP-SLE. (2) As seen for nephritogenic anti-dsDNA (Table 1), a given aAb specificity is not necessarily restricted to a single pathogenic mechanism. (3) From the highly diverse NP-SLE manifestations, which correspond to involvement of distinct neural tissues, it can be predicted that no single aAb would account for all forms of injury, i.e., distinct aAb with different CNS targets would be expected. (4) Although the hallmark of the blood-brain barrier is its impermeability, therefore blocking access of serum autoantibodies to the CNS, its disruption by SLE disease processes and other permeating events could allow inflow of activated B cells, T cells, monocytes/macrophages, and potentially pathogenic serum autoantibodies into the CNS. Furthermore, activated lymphocytes can also cross the intact blood-brain barrier[26a]. Also, *in situ* autoantibody synthesis from B cells within the CNS may also ocur *de novo*[1]. (5) In contrast with anti-dsDNA aAb, immune-complex–mediated inflammation is not the central mechanism for CNS lupus[27]. With few exceptions, autopsy studies usually demonstrate no evidence of vasculitis and little inflammation in sites of injury[7]. Therefore other pathogenic mechanisms, such as outlined in Table 1, are likely involved. (6) The identification of neural tissue-specific aAb cannot be construed as necessarily indicative of pathogenicity, since certain SLE-specific aAb actually exert a protective function. For example, aAb to nuclear lamin B1 are associated with thromboprotection in SLE patients by cancelling out high thrombotic risk (including strokes) associated with the presence of lupus anticoagulant aAb[16,28]. (7) Finally, the criteria for aAb pathogenicity defined by Naparstek and Plotz should be applied in the evaluation of aAb associated with NP-SLE[29].

PITFALLS IN THE INTERPRETATION OF AUTOANTIBODY ASSOCIATIONS IN NP-SLE

Table 2 lists most autoantibodies reported in NP-SLE and associated clinical manifestations[25,30-41] (for detailed reviews[26,42]). First, in general, the scientific interpretation of data in Table 2 is rendered difficult by retrospective

Table 1. Major pathogenic mechanisms involving human autoantibodies to intracellular autoantigens in SLE.

Pathogenic Mechanisms	Autoantibodies	Representative Clinical Outcomes	References
Circulating immune complexes, complement cascade activation, and inflammation	Anti-dsDNA, anti-nucleosomes	Glomerulonephritis	18, 19, 20
In situ immune complex formation, complement cascade activation, and inflammation	Anti-dsDNA, anti-nucleosomes	Glomerulonephritis	18, 19, 20
Intracellular penetration leading to cell dysfunction and apoptosis	Anti-dsDNA	Renal tubular injury	18, 19, 21
Reactivity with autoantigens present at apoptotic cell surface leading to ADCC or opsonization	Anti-Ro, anti-La	Complete heart block in neonatal lupus, subacute cutaneous LE	22, 23, 24
Crossreactivity with extracellular epitopes, e.g., heparan sulfate	Anti-dsDNA	Glomerulonephritis	18, 19, 20

ADCC: Antibody dependent cellular cytotoxicity.

Table 2. Human autoantibodies associated with neuropsychiatric SLE.

Antigenic Specificities	Major Autoantigens	Associated Clinical Manifestations	References
Neural tissue-specific autoantibodies			
Anti-neurofilament (NF) antibodies	NF triplet proteins (205 kDa, 160 kDa, 70 kDa)	Diffuse CNS clinical presentation	30
Anti-glial fibrillary acidic protein (GFAP)	GFAP	Organic/major type neuropsychiatric manifestations	31
Anti-neuronal antibodies	Brain and other neural proteins of unknown definitive identity	Diffuse CNS disease	25, 32, 42
Anti-microtubule-associated protein 2 (MAP-2)	MAP-2	Various NP-SLE manifestations	33
Non-neural tissue-specific autoantibodies			
Anti-dsDNA antibodies cross-reactive with neuronal receptors in the CNS	NR2 subtype of glutamate receptors	Progressive cognitive decline (single patient)	34
Antiphospholipid antibodies	Cardiolipin, $ß_2$-GPI, other autoantigens	Focal neurologic deficits (strokes, seizures, transverse myelopathy), deterioration in cognitive function	2, 15, 35, 36
Antilymphocyte antibodies cross-reactive with brain antigens	Brain and lymphocyte cell-surface proteins of unknown identity	Encephalopathies, seizures, visuospatial deficits	6, 37
Antiribosomal P protein antibodies	60S ribosomal subunit phosphoproteins P0, P1, P2	Controversial assocation with psychosis and severe depression	38, 39
Antiganglioside	Ganglioside GM1	Controversial assocation with NP-SLE, stronger assocation with peripheral neuropathy (IgG)	40, 41

CNS: central nervous system; $ß_2$GPI: $ß_2$-glycoprotein I.

design, small sample size of patient groups with specific NP-SLE manifestations, and the fact that most studies were reported before the ACR nomenclature and case definitions. Second, adequate disease controls with acute, subacute, and chronic neurological diseases in a sufficiently large sample size are missing in several reports, causing uncertainty as to the diagnostic specificity of several aAb for NP-SLE. Third, the lack of standardized methods for the detection of aAb associated with NP-SLE is blatant. Taken together, these weaknesses may explain in part the controversial associations between NP-SLE and certain aAb, such as anti-ribosomal P (Table 2)[38,39]. The need for an international standardization of anti-ribosomal P immunoassays was recently emphasized[43]. Fourth, because neuroblastoma cells (used in

many reports) are derived from peripheral nervous system malignant cells, they are not an optimal cell line for the detection of aAb to CNS aAg[26]. Fifth, some of the reported aAb are anticytoskeletal aAb, e.g., aAb to neurofilament proteins, glial fibrillary acid protein, and microtubule associated protein-2 (Table 2). These immune responses may be secondary to brain injury[44] and/or represent quantitative amplification of natural aAb secondary to SLE polyclonal B cell activation[45-47]. Hence their claimed pathogenic role appears premature, if not unwarranted. Sixth, the lack of concurrent CSF aAb assay in studies of serum aAb limits their significance. Finally, when criteria for immunopathogenicity are used[29], very few reports actually demonstrate a definitive link between the presence of aAb and NP-SLE manifestations.

A PROVOCATIVE PATHOGENIC STUDY

An exciting potential development in the immunopathogenesis of NP-SLE was the demonstration by Diamond and colleagues that a subset of anti-dsDNA from SLE patients cross-reacts with NR2 glutamate receptors in the CNS[34]. Glutamate is the principal excitatory amino acid (EAA) neurotransmitter in the brain. Glutamate membrane receptors operate prominently in many normal neurologic functions, including cognition, mood, movement, and sensation. EEA are essential for normal neuronal function, yet they are potentially neurotoxic molecules since overstimulation of EEA receptors may lead to excitotoxic neuronal cell dysfunction and death[9]. Using murine antibodies as well as anti-dsDNA aAb obtained from the serum of a small number of SLE patients, Diamond, et al showed not only that anti-dsDNA aAb cross-reacted with NR2 glutamate receptors, but also that these aAb mediated apoptotic death of neurons in vivo and in vitro[34]. Moreover, CSF from a single SLE patient with progressive cognitive decline contained these aAb and mediated neuronal death via an apoptotic pathway. These data suggested that SLE serum aAb may gain access to the CSF and mediate some of the non-vasculitic CNS abnormalities originally observed by Johnson and Richardson[7]. Thus far this is the only report fulfilling 4 of the 6 stringent pathogenicity criteria outlined for aAb[29].

Although provocative, the report remains preliminary from a diagnostic standpoint because of the small number of serum and CSF samples studied[27]. Recent data in mice support the pathogenic role of these autoantibodies; however, no other data thus far support this clinical-serologic association in humans[48]. Moreover, as reported at the recent 7th International Congress on SLE, anti-NR2 aAb did not identify cognitive dysfunction in a general SLE population[49].

CONCLUSION

Although aAb have long been suspected of playing a role in the pathogenesis of NP-SLE, we conclude that as yet none of the reported aAb has been established as pathogenic beyond any doubt[26]. Thus, despite extensive research, NP-SLE is still a disease complex much in search of pathogenic aAb, whereas most aAb thus far described in NP-SLE are still in search of a disease.

There is clearly a major need for a multicenter international study using the ACR criteria and nomenclature for NP-SLE, and performing state of the art assays for autoantibodies to NR2 glutamate receptors and to ribosomal P protein. To our knowledge, at least one such study is under way. An international, multicenter, prospective, inception cohort study of NP-SLE has been initiated, utilizing the Systemic Lupus International Collaborating Clinics, a network of 27 international academic medical centers with a particular interest in SLE (Hanly JG, personal communication). This study, sponsored by the Canadian Institutes of Health Research, will help clarify whether specific aAb are of value for the diagnosis of NP-SLE manifestations, and may provide insights on the puzzling patient selectivity and fluctuation over time of NP-SLE manifestations.

As shown by the work of Diamond and colleagues[34], the key to establishing an immunopathogenic role for aAb in NP-SLE is to determine the effects of specific aAb on brain function. An SLE brain bank is being developed at Cornell University, New York, and information can be obtained from Bruce Volpe, MD (bvolpe@burke.org). Several potential research avenues have been suggested by Moore[26]. Much research thus far has focused only on single aAb. However, given the multiple aAb present in SLE, mechanistic research models should focus more on the added pathogenicity resulting from the interplay between several antibodies, cytokines, and immunocompetent cells[22,50].

Finally, understanding of the exceptional complexity of the nervous systems and of NP-SLE dictates multidisciplinary research approaches bringing together clinical and basic scientists from the disciplines of rheumatology, immunology, and neuroscience. Such approaches offer the greatest hope for developing novel therapies for NP-SLE with fewer adverse effects[51].

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