

Review Article

Current concepts of neuropsychiatric systemic lupus erythematosus (NP-SLE)

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Introduction

Nervous system involvement in systemic lupus erythematosus (SLE) may present with diverse neurological or psychiatric symptomatology and may involve both central and peripheral dysfunction. Presentations may include stroke syndrome, seizures, psychoses, dementia, organic brain syndromes, chorea, coma as well as transverse myelopathy, peripheral neuropathy, myositis and a variety of syndromes affecting the optic nerves. Estimations of the prevalence of neuropsychiatric (NP) SLE vary from 14% to 75% reflecting variable diagnostic methodologies and criteria.^{1–9}

In addition to these major clinical syndromes, patients with SLE may often be subject to 'soft' neurological and/or psychiatric problems, for example, parasthesias, migraine-type headaches, anxiety states, mood swings, and cognitive problems such as difficulty in concentration, memory and word finding.

A few of the above symptomatology may antedate the appearance of definitive, diagnosable SLE by months, or even years. An example of this is epilepsy, an isolated phenomenon which has been noted in childhood or early teens, only to be followed many years later by SLE.¹⁰ Chorea is another example of such a manifestation.¹¹ It has recently become clear that many of the focal manifestations of NP-SLE such as transient ischaemic attacks (TIAs) or strokes may occur on the basis of vascular occlusions associated with anti-phospholipid antibodies (aPL).^{12–15} Epilepsy itself, as the sole manifestation of such vascular occlusions has also been associated with aPL.^{16,17} However, organic brain syndromes¹⁸ and multi-infarct dementias^{19,20} are examples of diffuse, non-focal conditions also associated with this group of

antibodies, so an attempted distinction into focal and diffuse is not as clear as originally conceived with regard to the clinical presentations associated with the aPL coagulopathy.

Neurological (or psychiatric) problems in lupus patients and their therapy confront the neurologist and rheumatologist with major therapeutic dilemmas. Should the patient receive 'pulse' steroids or cytotoxics and should these be combined with anticoagulant therapy if the aPL are present? Anticoagulation alone may be sufficient in patients presenting with clearly focal vascular events. Should psychotropics be administered to lupus patients with predominantly psychiatric presentations? It is in the latter group of patients, particularly those who are on high-dose steroid therapy and who may present with a psychotic state, that most diagnostic and therapeutic dilemmas occur. Does the patient suffer from a primary psychiatric disorder, for example, manic depressive psychosis/schizophrenia, or is the condition solely lupus induced, and to what extent are the steroids contributing to the psychotic state? Some of these difficulties and some current concepts relating to NP-SLE will be addressed in this review article.

Pathology

The first study of pathology in patients with lupus presenting with neurological symptoms and signs was that by Kaposi in 1872.²⁰ He reported on patients with headache, delirium and coma and noted a variety of abnormalities, including cerebral atrophy and thickened, inflamed meninges. Subsequently, however, neurological abnormalities were most often attributed to cerebral vasculitis, particularly if patients demonstrated vasculitis of other organs, for example, the skin.²¹ No neuropathological correlations, however, were obtained. The first series correlating neurological dysfunc-

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tion and neuropathological findings was published by Johnson and Richardson in 1968.²² They reported that true vasculitis in the brains of lupus patients was in fact rare, but that perivascular inflammation was more common. They also noted the frequent occurrence of microinfarcts and microhaemorrhages but were impressed that some patients with clinical evidence of neurological dysfunction appeared to have normal brains on postmortem evaluations. This rarity of cerebral vasculitis was confirmed at autopsy by Devinski and Petito in 1988²³ who noted cardiac sources of emboli in the majority of their patients studied with stroke. Others have also reported this association, particularly with anti-phospholipid antibodies and stroke in patients with SLE.²⁴⁻²⁶

There is clearly no single clinical picture of NP-SLE,²⁷ nor is there a single pathological feature of brain involvement in patients with the disease.

Pathogenesis

(a) Anti-brain antibodies

The puzzle, then, as to the pathogenesis in NP-SLE, is the existence of those patients with definite brain dysfunction, who appear to have normal brains by both gross and microscopic evaluation at autopsy.^{23,28} Since autoantibodies are not seen with standard stains, it seems possible that an antibody-mediated process could produce dysfunction in the absence of a demonstration of pathology when standard autopsy tests are used. It has previously been noted that antibody deposition may be seen in the choroid plexus.²⁹ Because of the suggestion that lymphocytes and brain might share antigens which may both serve as targets for an autoimmune response, many studies have focused on the identity of these 'shared' antigens.²⁸⁻³⁴ In spontaneous SLE syndromes in mice, there is a high prevalence of antibodies directed against basic brain extracts, homogenates or tissue and in some mice these antibodies may be associated with the presence of learning and cognitive defects.³⁵⁻⁴⁰ It is therefore possible, that some, though not all, features of NP-SLE in humans might be mediated by these brain-reactive autoantibodies. Some of the antigens evoked as being implicated in the pathogenesis of NP-SLE are listed in Table I.

Lymphocyte/brain antigens include those related to microbial antigens,⁴¹ thymic-brain antigens,⁴² and T-cell antigens such as CD4, a specific receptor for the human immunodeficiency virus (HIV),^{43,44} which may mediate both AIDS dementia and NP-SLE.⁴⁵⁻⁴⁷ Antibodies to the suppressor T-lymphocyte molecule CD8, which have been found on myelin-producing oligodendrocytes,⁴⁸ may explain involvement of T-suppressor cells or

lymphocytotoxic antibodies in multiple sclerosis as well as NP-SLE.^{30,31,49-51} It has therefore been hypothesized that some cases of NP-SLE might involve T-cell brain cross-reactive autoimmune responses, resulting in neuronal or glial cell loss, demyelination and/or inflammation in the brain.

Other candidate antigens include myelin-associated glycoprotein, an asialo-GM1 glycoprotein present on natural killer cells, as well as in central myelin.^{41,52,53} Antibodies against asialo-GM1 have been related temporally to exacerbations of NP-SLE.⁵⁴ Similar antibodies against mycobacterial glycosphingolipids may be associated with NP-SLE.⁵³⁻⁵⁵ A recent study⁵⁶ demonstrated antibodies to Semliki Forest virus (SFV) and to galactocerebrosides (GALC) in SLE patients as well as in patients with the 'primary' anti-phospholipid syndrome; the authors hypothesized that the antibody reactivity to SFV, particularly in the SLE anticardiolipin-positive patients appeared to be more specific than the reaction of antibodies to native GALC, and might represent reactivity to an undetermined glycopospholipid present in the envelope of some viruses such as SFV.⁵⁶

Recently, several potential lymphocyte/brain antigens have been studied by immunoprecipitation techniques.^{32,57-61} Many SLE patients have significant elevations of autoantibodies which bind to neuroblastoma cells,^{61,62} which are lymphocytotoxic *in vitro*.^{32,33,51,59} The nature of the surface antigens against which IgG class antibodies are directed in sera and in cerebrospinal fluid of SLE patients has also been explored.^{62,63} These include a 97 kD protein uniquely present on the surface of neuroblastoma cell lines^{60,61} and several determinants on the surface of peripheral blood lymphocytes or on CD4-positive lymphocytic cell lines.^{32,60,64}

The most recent autoantibody candidates invoked in the causation of NP-SLE are the antibodies directed to anti-ribosomal P, mostly seen in association with psychosis and depression.⁶⁵⁻⁶⁷ One patient with recurrent psychotic episodes studied recently was, however, negative for these antibodies in a prospective study.⁶⁷ However, a second more recent case study tended to confirm the original observations.⁶⁸

Table I Antibodies implicated in pathogenesis of CNS lupus

1.	CD4, CD8
2.	Glycosphingolipids (mycobacterial)
3.	Neuroblastoma cells
4.	Thymic - brain antigens
5.	Ribosomes (anti-ribosomal-P)
6.	Phospholipids
7.	Neurones
8.	Galactocerebrosides

(b) Cytokines

Some of the systemic manifestations of SLE, including uremia or hypoxemia, could adversely affect brain function in patients with lupus.⁶⁹ One of the important groups of circulating factors which could produce brain dysfunction with resultant normal brain pathology are the cytokines, which are produced both by infectious agents as well as during inflammatory processes. Excess concentrations of cytokines can damage the brain and produce neurovascular lesions similar to those described in lupus. Clinically, IL-2-mediated neurological toxicity has certainly resulted from cytokine administration in cancer trials.⁷⁰ Increased levels of IL-6 have been found in the cerebrospinal fluid of patients of NP-SLE and cerebritis due to infection.⁷¹⁻⁷⁴ The presence of cytokine-containing cell populations in the hypothalamus⁷⁵ as well as involvement of neuropeptides in immune regulation and in the synthesis of neuroendocrine-active molecules by lymphoid cells has been documented.⁷⁶

Since abnormalities of both cytokine and antibody production occur with lupus, future studies of the mechanisms of brain dysfunction should include both a study of cytokines as well as antibodies in the sera and cerebrospinal fluid of lupus patients.

Cognitive impairment

A number of factors have been postulated as being involved in the production of cognitive impairment in SLE. These include: (1) the use of corticosteroids; (2) the non-specific effects of disease activity; and (3) psychological distress. Some of these will be briefly reviewed.

1. Steroids

Since high doses of corticosteroids have been reported as being associated with psychosis⁷⁷ it is certainly plausible that corticosteroid therapy could, to some extent, contribute to cognitive impairment found in SLE patients. However, most investigators have found no significant association between cognitive impairment and either steroid therapy at the time of test⁷⁸⁻⁸² or steroid dosage.^{78,83} In fact it seems possible that steroid therapy may actually improve memory or other cognitive functions in SLE. Each of ten patients participating in single patient ($N = 1$) corticosteroid trials showed better performances after the first three week exposure to drug than to placebo,⁸⁴ and Ginsburg *et al.*⁸¹ reported an association between steroid use and improved performance on complex attention tasks in their older SLE patients. Taken together,

these findings strongly suggest that the higher prevalence of cognitive impairment in lupus patients cannot be attributed to corticosteroid treatment. A similar conclusion has in fact been reached with respect to the possible effect of corticosteroids on the memory impairment documented in patients with multiple sclerosis.⁸⁵

2. Chronic disease

Similarly, the contribution of chronic disease and/or constitutional symptoms to cognitive impairment has been evaluated. There was no significant association between cognitive impairment and scores on either the LACC (Lupus Activity Criteria Count),^{78,79} an index of lupus activity which tallies the number of active organ systems,⁸⁶ the SLEDAI⁸³ and SLAM⁸¹ scales, or other newer indices of disease activity.⁸⁷ It is worthwhile noting that a lack of association between the degree of physical disability and significant cognitive function, particularly memory impairment, has also been reported in studies on patients with multiple sclerosis.^{88,89} There have also been very few significant associations found between individual organ system involvement in SLE and cognitive impairment; in particular, patients with renal involvement, which may be associated with CNS complications, were not more likely to show significant cognitive impairment than those with skin and joint involvement.⁹⁰ It is thus unlikely that the high prevalence of significant cognitive impairment in SLE patients is simply a reflection of systemic illness.

3. Psychological distress

Lastly, although SLE patients experience and report considerable psychological distress, irrespective of whether their NP symptoms are active or inactive,^{91,92} there is no significant association between the presence of emotional distress and cognitive impairment.⁷⁸ This is consistent with a recent report of symptoms of anxiety and depression in ambulatory SLE patients independent of cognitive defects.⁹³ It would therefore appear that significant emotional distress is unlikely by itself to result in significant cognitive impairment in SLE, and, conversely, that emotional distress is not a necessary response to cognitive dysfunction. The two, however, may certainly co-occur.⁷⁸

There is considerable diversity in the kinds of cognitive impairment shown by SLE patients, although memory problems are very common.⁹⁴ Cognitive impairment has been found in up to one-half of SLE patients using quantitative criteria alone, reaching two-thirds if qualitative criteria (that is, test taking behaviours) are also considered.⁷⁸ Detailed neuropsychological studies of

SLE patients have the potential to both contribute substantially to evaluation of the more subtle signs and symptoms of this form of impairment and possibly to redefine the criteria for diagnosing CNS involvement. They also provide invaluable information to the clinician to aid in patient counselling and management.

Diagnosis

A significant difficulty in establishing diagnostic criteria for NP-SLE is the absence of an acceptable gold standard. Electrophysiological, radiological and CSF analyses have been used with limited success.⁹⁵ Magnetic resonance imaging (MRI) has been able to identify focal lesions undetected by CT scanning in patients with recent strokes or seizures.^{96,97} Patterns of MRI abnormalities have been found in association with the presence of anti-cardiolipin or anti-neurofilament antibodies.⁹⁸ However, the value of MRI in documenting structural abnormalities related to minor CNS symptomatology or objectively documented cognitive dysfunction in SLE is unknown. Brain imaging based on metabolic function may prove to be even more sensitive than MRI in documenting central nervous involvement in SLE, for example, positron emission tomography (PET) is an even more sensitive method than MRI testing. Using this new methodology, abnormalities have been identified even when no structural lesions are evident on MRI.⁹⁹⁻¹⁰¹ Studies of cerebral oxygen (O^{15}) consumption or regional blood flow (Xe^{133}) have revealed abnormalities which are suggestive of sub-clinical CNS involvement and changes have been seen with relapse and remission of CNS symptomatology.¹⁰²⁻¹⁰⁴ However, there have been no systematic, long-term studies of the functional (behavioural) correlates of changes in cerebral metabolism. Recently, a concordance between PET abnormalities and cognitive function has been reported in selected SLE patients.¹⁰⁵ The potential utility of neuropsychological studies for delineating behavioural problems associated with CNS dysfunction as indicated by PET or other forms of brain imaging/scanning is therefore great.

A recent prospective study of the neuropsychiatric manifestations of SLE attempted to differentiate between primary involvement by the lupus process and secondary causes.¹⁰⁶ Included in the primary group were psychoses, seizures, multiple cerebral infarction, papillitis, neuropathy and myelopathy. The commonest causes in the secondary group were infections, the administration of steroids, or encephalopathy associated with hypertension. These secondary patients manifested confusional states, seizures, headaches as well as

psychosis (steroids). Infections included chronic bacterial (tuberculosis), fungal (aspergillus, cryptococcus, micormycosis, nocardia, or candida), acute bacterial (staphylococcus), klebsiella or viral (hepatitis, cytomegalovirus). These are most likely to result in major behavioural changes (suicide attempts, disorientation, major depression, confusion, hallucinations, states of altered alertness). These same manifestations were also noted in the series recently documented by Futrell *et al.*²⁷ who noted that these manifestations were often accompanied by contributing factors such as infections and/or azotaemia. The presence of systemic infection seem to occur most frequently in patients with decreased states of alertness. Steroids were only really implicated as a factor and were considered as a cause of psychosis in two patients in the previous study.¹⁰⁶ Psychosis developed within 7 days after the commencement of prednisone (60 mg and 30 mg, respectively) in both patients. Both had active disease during the episodes of psychotic behaviour. The prednisone was reduced to 5 mg daily and oral azathioprine and cyclophosphamide were given as steroid-sparing agents. The patients recovered without any neurological deficits.

There may on occasion be difficulties resulting from the differentiation of a primary lupus psychosis from steroid-induced states. Steroid psychosis in SLE patients is rare and appears in less than 5% of SLE patients.¹⁰⁷ Several studies of steroid-induced psychiatric syndromes have shown that the predominant psychiatric manifestations appear to be changes in mood or affect (depression or mania), while frank psychosis is rare (13% of cases only).^{108,109} The majority of patients, as in the two cases quoted above, developed their symptoms within 2 weeks of the commencement of steroid treatment and in most (77%) the changes developed on doses greater than 40 mg. The mental changes resolved after between 2 and 60 days (with a mean of 24 days) following tapering of steroid dosage. In contrast to steroid-induced psychiatric syndromes, SLE patients have a high incidence of psychosis (24%), the majority (61%) of neuropsychiatric manifestations occur within the first year after the initial diagnosis of SLE and their frequency tends to decrease with time, but usually lasts longer than the steroid-induced psychotic conditions.¹¹⁰

In summary therefore, NP-SLE still remains a complex clinical situation with no single pathogenetic cause. The estimation of autoantibodies particularly those directed against cardiolipin, ribosomal-P and certain shared lymphocyte/brain antigens might assist in defining 'subsets'. Therapy still is individually 'tailored', although guiding principles enumerated in this article may certainly be of assistance in a particular case.

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