

REVIEW ARTICLE

Diagnosis of Central Nervous System Lupus

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ABSTRACT: Central nervous system (CNS) involvement in systemic lupus erythematosus is a major source of patient morbidity and mortality. The recognition of nervous system lupus is hampered by the diagnostic insensitivity and non-specificity of the various testing modalities that are currently available. A review of the effectiveness of diagnostic tests for CNS lupus is presented. Areas of current research in this area are examined. Because of the diversity of neurologic manifestations in this disorder and their complex pathogenesis, no single test is sufficient to establish the diagnosis rapidly and accurately in all cases, now or for the foreseeable future.

RÉSUMÉ: Le diagnostic d'atteinte lupique du système nerveux central L'atteinte du système nerveux central (SNC) dans le lupus érythémateux aigu disséminé est une source importante de morbidité et de mortalité chez ces patients. L'identification d'une atteinte lupique du système nerveux est entravée par le peu de sensibilité et la non-spécificité diagnostique des différents modes d'exploration actuellement disponibles. Nous présentons une revue de l'efficacité des épreuves diagnostiques pour détecter le lupus du SNC. Nous examinons également les différents points à l'étude dans ce domaine. A cause de la diversité des manifestations neurologiques dans cette maladie et de la complexité de leur pathogénèse, il n'existe pas à l'heure actuelle ou dans un avenir prochain, d'épreuve diagnostique unique pouvant établir le diagnostic rapidement et fidèlement dans tous les cas.

Can. J. Neurol. Sci. 1988; 15:257-260

Central nervous system manifestations occur in 25%-75% of cases of systemic lupus erythematosus.^{1,2,3} After renal failure they are the second most common cause of death accounting for 13% of all deaths in lupus according to one series.¹ Moreover, such nervous system complications in lupus are a major cause of patient morbidity and give rise to a wide variety of neurologic and psychiatric symptoms and signs (see Table 1) including particularly seizures, hemiparesis, headache, psychosis, and cognitive impairment.^{1,2,3,4,5}

Despite these protean CNS manifestations, there remains no simple method to diagnose CNS involvement in lupus. To date, methods used to detect this process have been restricted by problems of inadequate sensitivity or specificity or both.

Clinical assessment using history and physical examination remains the cornerstone of diagnosis in CNS lupus. However, up to 2/3 of nervous system manifestations in lupus are not due to direct brain involvement in this disease process but rather are a consequence of metabolic, hypertensive, or drug-related dysfunction occurring in a setting of systemic lupus erythematosus.⁶ History and physical examination is often unable to clearly distinguish between such "primary" and "secondary" nervous system manifestations. For findings such as cognitive deterioration or other early manifestations of CNS lupus, history and physical examination is also an insensitive diagnostic tool.⁷

Neuropsychiatric manifestations may reflect either diffuse or focal involvement of the central nervous system.⁵ Diffuse involvement of the central nervous system gives rise to the most common neuropsychiatric manifestations including cognitive impairment with or without psychosis, cognitive deterioration, and generalized seizures. Focal involvement of the nervous system gives rise to such common manifestations as cranial or peripheral neuropathy, stroke syndromes, chorea, or transverse myelitis. Most patients with nervous system involvement have more than one manifestation and half have psychiatric, as well as neurologic, symptoms with the two frequently present at the same time.⁵

Cognitive impairment is the most common neuropsychiatric manifestation of SLE, and psychiatric symptoms are in general more common than neurological symptoms in SLE. Cognitive dysfunction as diagnosed by abnormalities on neuropsychological testing may occur in up to 80 percent of cases.⁷ Difficulties in this area of research, however, include the fact that accurate neuropsychological testing requires patient motivation, cooperation, and concentration, all of which may be affected by a variety of functional psychological factors. Moreover, the correlation between neuropsychological test abnormalities and CNS pathological changes in lupus is not well documented to date.

A particularly difficult diagnosis is that of SLE-related psychosis versus steroid-induced psychosis. This difficulty is com-

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Received September 1, 1987. Accepted in final form February 11, 1988

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Table 1: Neuropsychiatric Manifestations of SLE^{1,2,3,4,5}

	Psychiatric
	Cognitive dysfunction
	Schizophreniform psychosis
	Affective disorder
	Adjustment disorder
	Neurologic
	Headache
	Seizure
	Hemiparesis
	Coma
	Movement disorder
	Ataxia
	Cranial neuritis
	Optic neuritis
	Meningitis
	Pseudotumor cerebri
	Neurophathy
	Myelitis
	Neuromuscular junction disorders
	Cerebral hemorrhage/infarction

pounded by the fact that such patients usually have serious SLE requiring high dose steroid therapy to control the disease systemically. Moreover, focal neurological findings, which would tend to point away from a drug-induced etiology are often absent during such psychotic episodes.

Less dramatic presentations of psychiatric symptoms such as cognitive dysfunction or adjustment disorder are also difficult to diagnose etiologically because of their insidious onset, paucity of associated laboratory abnormalities, and slowness of evolution.

The differential diagnosis of suspected primary CNS lupus is extensive. Clearly, almost any neuropsychiatric symptom may be attributable to secondary involvement of the nervous system because of infectious, metabolic, hypertensive, drug-related, or hematologic derangements occurring in the course of SLE. However, other primary CNS disorders may also occur in SLE and must be excluded, particularly CNS infections.

The combination of both generalized and focal nervous system involvement has led to the concept of two pathogenetic mechanisms in nervous system lupus: immune-mediated vascu-

lopathy and antineuronal antibodies. An autoantibody-mediated process is a possible explanation for the diffuse and partially reversible manifestations of the more common neuropsychiatric features of SLE.⁵

Contributing to the immune-mediated vascular dysfunction in cerebral lupus is the circulating lupus anticoagulant. Paradoxically, it may give rise to thrombotic complications in SLE and is present in about 10% of SLE patients. Conversely, 34% of patients with this antibody have SLE.²⁹

Serological diagnosis of CNS lupus has long been attempted. Autoimmune hematologic problems occur more frequently in patients with neuropsychiatric involvement than in other patients with SLE.⁵ Neuron-reactive antibodies are also frequently detected in serum from patients with SLE, and there is some evidence that the titers of these antibodies vary with lupus activity in the nervous system.^{8,9,10,11}

Unfortunately, serological diagnosis of nervous system lupus has been restricted by the failure to find a marker of nervous system disease that is of both high sensitivity and specificity. This situation is complicated by the fact that CNS antibodies in SLE have a number of different antigenic specificities. Different antigens on glial, neuronal, or vascular endothelial components may be involved, and as such there is no single CNS antibody in SLE.

Cerebrospinal fluid analysis has been used for a number of years in an attempt to diagnose CNS lupus. Findings such as CSF pleocytosis or increased protein have a sensitivity of about 33%,⁴ and lowered complement or antineuronal antibodies are detected even less frequently in most series.^{4,8,9,10,11,12} Promising results with the use of CSF IgG, IgA or IgM indices have been recently reported but these findings await further confirmation.^{13,14}

Neuron-reactive antibodies appear to occur most frequently in patients with cognitive deterioration, psychosis, or seizures. The reversibility of these findings may be attributable to the binding of autoantibodies to molecules on neuronal membranes, which interferes with neuronal function without actually destroying the nerve cells. Immune-mediated vasculopathy could cause an alteration of the blood-brain barrier allowing such autoantibodies to enter the central nervous system.⁵

In a recent study,¹⁵ 18 of 20 patients with psychosis secondary to systemic lupus erythematosus were found to have

Table 2: Diagnostic Tests in CNS Lupus

Test	Sensitivity	Specificity	References
(1) Serological:			
Neuron-reactive antibodies	Variable	Low	8, 9, 10, 11
Anti-ribosomal P protein antibody	90% (psychosis only)	Low	15
(2) CSF exam:			
Pleocytosis	33%	Low	4
Low complement or antineuronal antibodies	Low	Low	4, 8, 9, 10, 11, 12
(3) Serum/CSF:			
IgG, IgA, or IgM indices	High	Under study	13, 14
(4) Radionuclide brain scanning	8-100%	Low	4, 18, 20
(5) EEG	70-80% (major neurologic deficit)	Low	17, 18, 19
(6) Cerebral angiography	Low	Low	20
(7) CT scan	66-75% (major neurologic deficit)	Low	21, 22, 23, 24, 25
(8) MRI scanning	High	Under study	27, 28

serum autoantibodies to ribosomal P proteins. The anti-P antibodies are of interest inasmuch as they are directed towards an antigenic determinant of three subunit ribosomal phosphoproteins. Positive cytoplasmic staining of neurons by serum from patients with cerebral lupus may, in some cases, have been due to unrecognized anti-P activity,^{10,15} and as such, anti-P antibodies may function as antineuronal antibodies. The autoantibodies were detected by immunoblotting and measured with a radioimmunoassay using a synthetic peptide as antigen.¹⁵ The anti-P antibody was found in only 3 of 20 lupus patients with other CNS manifestations, 0 of 8 SLE patients with transient behavioural abnormalities, 0 of 13 psychotic non-SLE patients, and 0 of 20 normal controls. In 2 patients anti-P levels appeared to increase before and during the active phase of the psychosis while remaining relatively unchanged during other exacerbations of the disease including sepsis, rash, and arthritis.¹⁵

However, the diagnostic specificity of anti-P antibodies in SLE psychosis appears low. Unselected SLE patients have a frequency of anti-P antibodies of 12%, and in SLE patients with non-psychotic neurologic disease, the prevalence of antibodies is 15%.¹⁶ Fourteen of the 32 patients identified with elevation of anti-P antibody levels had no psychosis. The average elevation of anti-P levels in non-psychotic SLE patients was at least as high as that in psychotic SLE patients.¹⁵ Substantial fluctuation (>5-fold) in anti-P levels appeared to be associated with psychosis.¹⁵ Nonetheless, a single measurement of serum anti-P antibody levels is not useful in the diagnosis of lupus psychosis, and this hampers the use of this measure as a diagnostic test.

In the presence of SLE-associated encephalopathy or focal neurological deficits, the EEG shows abnormalities in 70-80% of patients.^{17,18,19} Abnormalities are seen much less frequently with other manifestations of CNS lupus. Moreover, all of these EEG findings are completely nonspecific.

The utility of radionuclide brain scanning in the diagnosis of CNS lupus has been a source of controversy in the past. In reported series, the sensitivity of this test has varied from 8% to 100%.^{4,18,20} These discrepant results may be attributable to a number of factors including variation in the neurological symptoms of the patients under study, variation in scanning equipment and technique, and variation in the criteria used to read a scan as normal or abnormal.

To date, radiologic assessment of this disorder has produced somewhat mixed results. Cerebral angiography is generally not useful as it is both an insensitive and non-specific diagnostic tool here. The diagnostic insensitivity of cerebral angiography is unsurprising given the fact that SLE-related vasculopathy primarily involves small vessels, whereas angiography reliably images large- and medium-sized vessels. Although occlusion of these larger vessels has been reported in lupus, this occurrence is extremely uncommon.²⁰

CT scanning of the brain shows abnormalities in 66% to 75% in CNS lupus patients,^{21,22,23} although the patients reported in these series had evidence of severe neurological involvement at the time of CT scanning. The sensitivity of this test for patients with less florid CNS involvement is unclear. Moreover, changes on CT scanning may not become evident until months after the onset of neurological symptoms and signs.^{21,22,23}

Compounding this problem is the non-specificity of the most common CT finding in CNS lupus, namely cerebral atrophy. It

is accepted that both CNS lupus and steroids may cause slight cerebral atrophy.²⁴ It is argued by some^{22,24,25} that more severe degrees of atrophy are never attributable to steroid effects (and are thus attributable presumably to CNS lupus), whereas other authors^{23,26} argue that any degree of atrophy on CT scanning may be attributable either to steroid or lupus effects. If the latter proposition is correct, the usefulness of CT scanning in the diagnosis of CNS lupus is greatly reduced as most patients with possible CNS lupus have been on steroids for some time when they first undergo CT scanning of the brain.

Magnetic resonance imaging (MRI) may be more sensitive than CT scanning for the detection of some of the lesions occurring in CNS lupus. Vermess et al²⁷ compared the sensitivity of MRI to CT in a small series of lupus patients who had abnormal CT scans. A substantially greater number of lesions were found on MRI scanning. Aisen et al²⁸ compared the sensitivity of CT to MRI in a series of 8 patients with a clinical diagnosis of CNS lupus. CT scanning was abnormal in 2 of 7 patients, whereas all 7 of the patients (plus one other patient who only underwent MRI scanning) showed abnormalities on the MRI scans. Lesions, single or multiple, were noted in both white matter or grey matter, and these lesions often appeared to be unassociated with the clinical signs. Of particular interest were the presence of small grey matter lesions that appeared at the time of development of neurological symptoms and which disappeared on subsequent MRI scans performed several months later. These reversible grey matter lesions may be markers of acute CNS lupus.

In summary, the diagnosis of CNS lupus is difficult. Clinical assessment remains the cornerstone of diagnosis but, by itself, may either underdiagnose nervous system manifestations in SLE or fail to discern their etiology. No broadly applicable set of diagnostic criteria that promptly and reliably confirm the diagnosis have been developed to date. Obviously, primary CNS lupus cannot be diagnosed until other causes of nervous system dysfunction have been ruled out.

Yet, the diagnosis of primary CNS lupus is important because it may affect patient treatment, it signifies a more serious phase in the disease, and, unless detected promptly, may be associated with the development of irreversible CNS changes. It seems likely that reliance on a multiplicity of diagnostic tests together with clinical judgement in this situation will be necessary for the foreseeable future.

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