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Neuropsychiatric syndromes in systemic lupus erythematosus: A new look

S. Khoshbin[1], B.I. Glanz[1], P.H. Schur[2]

[1]Department of Neurology and [2]Division of Rheumatology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Shahram Khoshbin, M.D., Associate Professor of Neurology; Bonnie I. Glanz, Ph.D., Research Fellow in Neurology; Peter H. Schur, M.D., Professor of Medicine, Harvard Medical School.

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Please address correspondence and reprint requests to: Shahram Khoshbin, M.D., Department of Neurology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
E-mail: skhoshbin@bics.bwh.harvard.edu

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Introduction

Neuropsychiatric disease in systemic lupus erythematosus (SLE) includes diverse neurologic and psychiatric manifestations such as stroke, seizures, psychosis, depression, and cognitive dysfunction (1). The reported prevalence of neuropsychiatric disease varies from 25-75% (2-4). Neuropsychiatric symptoms are associated with significant morbidity and poor long term outcome in patients with SLE (2, 5-7).

Neuropsychiatric involvement in SLE was first described by Kaposi (8) in 1872. He reported disturbed cerebral function or delirium in two of 11 patients with SLE. Between 1895 and 1903, Osler (9-11) published three articles on the systemic nature of SLE, including the neuropsychiatric manifestations of the disease. Osler believed that the pathogenesis of neuropsychiatric involvement in SLE was similar to the pathogenesis of other organ system involvement, namely vasculitis. In 1968, Johnson and Richardson (6) investigated the neuropathological changes associated with SLE, and found that true vasculitis was rare. Instead, they observed destructive lesions in the walls of small vessels and the presence of multiple microinfarcts; however, even this vasculopathy did not correlate well with the severity of neuropsychiatric symptoms.

The failure to find a clear association between neuropsychiatric disease and vasculopathy prompted the examination of other potential pathogenic mechanisms of disease. In 1981, Bluestein *et al.* (12) proposed that antibodies against nervous system tissue accounted for the diverse neuropsychiatric manifestations of SLE. They identified neuron-reactive antibodies in the cerebrospinal fluid of SLE patients. Antineuronal activity was found to be greater in patients with psychosis, cognitive dysfunction, and generalized seizures than in patients with hemiparesis. These antibodies were believed to enter the brain through an impaired blood-brain barrier. Numerous studies followed, attempting to correlate neuropsychiatric syndromes with the presence of specific antibodies, including antineuronal, antiphospholipid, lymphocytotoxic, and antiribosomal P antibodies (13-18). More recently, increased cytokine production has been suggested to account for the neuropsychiatric manifestations of SLE (19-20).

Taken together, these etiologic studies have yielded frustrating and inconsistent results, partly as a result of the poor definition and classification of neuropsychiatric syndromes. In addition, researchers have failed to recognize that different pathophysiologic mechanisms may be responsible for the different neuropsychiatric manifestations of SLE. Vascular disease, for example, may explain manifestations such as stroke, but is unlikely to account for cognitive dysfunction, all seizures disorders, and psychosis in the absence of vascular lesions. Researchers have also relied on small sample sizes that do not allow for meaningful statistical comparisons between subgroups of patients with different neuropsychiatric symptomatology. Finally, previous studies may be flawed by the inclusion of patients with neuropsychiatric disease secondary to other organ system involvement such as renal disease and hypertension, and neuropsychiatric disease secondary to drug therapy.

Temporolimbic dysfunction in SLE

Based on preliminary neuropsychological and neurophysiological data, we are proposing that localizable left temporolimbic hypothalamic dysfunction accounts for specific neuropsychiatric symptoms in patients with SLE. The limbic system is a complex system of structures that includes the hippocampus, fornix, mamillary bodies, thalamus, and amygdala (21). These structures are contained in the temporal lobe, subcortical forebrain, and midbrain. The hippocampal formation projects directly to the hypothalamus.

Temporolimbic dysfunction may explain cognitive dysfunction, complex partial seizures, and psychosis in patients with SLE. Patients with SLE demonstrate a pattern of performance on neuropsychological testing that is consistent with unilateral lesions of the left temporal lobe (22). Patients with SLE also demonstrate predominantly left temporolimbic abnormalities on electroencephalography (EEG) that include slowing and sharp wave activity (23).

Cognitive deficits include decreased at-

tention, impaired memory, and poor word-finding ability. These deficits occur in up to 75% of patients with SLE (24-27). Previous studies have failed to identify a single pattern of cognitive dysfunction associated with SLE. This may reflect the use of unselected patient groups with diverse neuropsychiatric symptomatology. In a study of cognitive functioning in SLE patients with inactive disease at the time of neuropsychological testing, Glanz (28) reported that the cognitive variables that best discriminated between SLE patients and healthy controls were high scores on tests of verbal speed/fluency and low scores on measures of immediate and rote auditory verbal memory and cognitive flexibility. Poor performance on these tests of verbal attention and memory has been associated with left hemisphere brain disease. Glanz *et al*. (22) recently reported that SLE patients did not demonstrate a significant right-ear advantage on a dichotic listening task. This pattern of performance has previously been described in patients with unilateral lesions of the left temporal lobe (29).

Seizure disorders have been reported in 15-20% of patients with SLE (3, 6). The precise prevalence of generalized (e.g., tonic-clonic and minor motor seizures) versus focal seizures (simple partial and complex partial seizures) is unknown. Generalized seizures tend to occur secondary to other disease manifestations such as renal dysfunction or hypertension. We believe that complex partial seizures are a primary neuropsychiatric manifestation of SLE. Complex partial seizures usually originate in the temporal lobes, and may involve the hippocampus, amygdala, and uncus (21). They are associated with psychomotor, psychosensory, cognitive, and affective symptoms, including hallucinations, visual distortions, fear, and anxiety (30). The interictal personality disorder that has been associated with complex partial seizures also occurs in patients with SLE (30, 31). Waxman and Geschwind (32) described five distinct symptoms, hypergraphia, religiosity, hyposexuality, aggressivity, and viscosity, in patients with complex partial seizures. Viscosity refers to stickiness of thought and enhanced social cohesion. The seizures and behavioral disturbances are believed to result from the same underlying temporolimbic pathology. Rao *et al.* (33) pointed out that different personality traits may be associated with lateralized epileptogenic foci. They found that viscosity, for example, was more commonly observed in patients with left than right temporal lobe seizures.

In a retrospective review of electroencephalogram (EEG) abnormalities in patients with SLE and seizure disorders, Glanz *et al.* (23) reported left hemisphere abnormalities in 80%, right hemisphere abnormalities in 7%, and bilateral abnormalities in 13% of patients. Abnormalities included theta and delta slowing and sharp wave activity. In 74% of patients with left hemisphere EEG abnormalities, the abnormalities were localized to the left temporal leads. These findings suggest selective damage to the left temporolimbic region in patients with SLE. Psychosis involves a loss of reality testing and impairment of mental functioning that may include delusions and hallucinations. Psychosis has been reported in 20-30% of patients with SLE (34). Corticosteroid-induced psychosis is believed to occur in less than 5% of patients (35, 36). There is growing evidence to implicate left temporolimbic dysfunction in the pathogenesis of psychotic disorders (37-39). Jibiki *et al.* (40) reported that delusional patients with seizure disorders demonstrated epileptic EEG foci in the left temporal lobe. In addition, Bogerts *et al.* (41) measured the volumes of the hippocampus-amygdala complex and adjoining temporal horns in patients with first episode schizophrenia and healthy controls, and found a selective volume reduction in the left hippocampal region in patients with schizophrenia.

In addition to cognitive dysfunction, complex partial seizures, and psychosis, patients with SLE demonstrate fever, fatigue, and migraine (6, 42, 43). These disturbances are consistent with hypothalamic dysfunction (21). The hypothalamus regulates autonomic functions including body temperature, food intake, and autonomic aspects of emotion. Limbic structures modulate the endocrine function of the hypothalamic pituitary axis. There is some evidence to suggest that there are lateralized asymmetries in temporolimbic and hypothalamic influences on hormonal secretion. Herzog (44) reported a significant relationship between the laterality of epileptiform discharges and endocrine disorders in patients with complex partial seizures. Patients with left-sided discharges demonstrated polycystic ovarian syndrome, while patients with right-sided discharges demonstrated hypogonadotropic hypogonadism.

Temporolimbic syndromes

Selective damage to the temporolimbic region has been demonstrated in other immune-mediated disorders. First, paraneoplastic limbic encephalopathy (PLE) occurs as a remote non-metastatic effect of cancer. It presents with a variety of symptoms that reflect limbic system dysfunction, including confusion, memory loss, agitation, hallucinations, and seizures (45-49). PLE is believed to result from an immune response to limbic neurons triggered by tumor antigens that crossreact with similar antigens in the central nervous system (CNS) (50). Although it appears that PLE more commonly affects the left than right temporolimbic region (45, 47, 51, 52), the small number of cases reported in the literature makes it difficult to substantiate this claim.

Second, herpes simplex virus encephalitis (HSVE) is a common form of viral encephalitis. Patients display disturbances in affect and behavior including delusions and hallucinations (53-55). Computed tomography (CT), magnetic resonance imaging (MRI), EEG, and postmortem studies have demonstrated involvement of the temporal lobe and limbic structures in HSVE (56-58). Caparros-Lefebvre *et al*. (59) identified impairment of left amygdalofrontal pathways in patients with HSVE.

Finally, Lyme encephalopathy is a disorder seen in patients with Lyme disease. These patients present with neuropsychiatric symptoms including fatigue, headache, psychosis, and cognitive dysfunction (60, 61). Benke *et al*. (62) reported poor performance on tests of verbal memory and verbal associative functions and adequate performance on tests of sustained attention, mental speed, and

constructional ability in patients with Lyme encephalopathy. This pattern of performance on neuropsychological testing is consistent with damage to the left temporolimbic region.

There are animal and human studies to support the notion that hippocampal and hypothalamic cells are particularly vulnerable to immune diseases. Increased cytokine production, for example, has been reported in patients with neuropsychiatric manifestations of SLE (19, 20). Breder *et al*. (63) demonstrated that IL-1 was present in regions of the human hypothalamus and thalamus. Lechan *et al.* (64) identified IL-1 in the hypothalamus, hippocampus, and olfactory tubercle of the rat.

Conclusions

We propose that cognitive dysfunction, complex partial seizures, and psychosis are common manifestations of SLE with the same or similar underlying left temporolimbic pathophysiology. These manifestations are distinct from the neurovascular manifestations, such as stroke. Future research is needed to confirm the pattern of left temporolimbic neuropsychologic and neurophysiologic dysfunction in this subset of patients with SLE. Future research is also needed to elucidate possible mechanisms of immune-mediated damage to specific neural structures in patients with SLE and other temporolimbic syndromes.

References

1. ACR AD HOC COMMITTEE ON NEUROPSYCHIATRIC LUPUS NOMENCLATURE: The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42: 599-608.
2. ESTES D, CHRISTIAN CL: The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 1971; 50: 85-95.
3. FEINGLASS EJ, ARNETT FC, DORSCH CA, ZIZIC T, STEVENS MB: Neuropsychiatric manifestations of systemic lupus erythematosus: Diagnosis, clinical spectrum, and relationship to other features of the disease. *Medicine* 1976; 55: 323-39.
4. KOVACS J, UROWITZ MB, GLADMAN DD: Dilemmas in neuropsychiatric lupus. *Rheum Dis Clin North Am* 1993; 19: 795-814.
5. ABEL T, GLADMAN DD, UROWITZ MB: Neuropsychiatric lupus. *J Rheumatol* 1980; 7: 325-33.
6. JOHNSON RT, RICHARDSON EP: The neurological manifestations of systemic lupus erythematosus: A clinical-pathological study of 24 cases and review of the literature. *Medicine* 1968; 47: 337-69.
7. LEE P, UROWITZ MB, BOOKMAN AAM, *et al*.: Systemic lupus erythematosus: A review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis and prognosis. *Q J Med* 1977; 46: 1-32.
8. KAPOSI M: Neue beitrage zur kenntnis des lupus erythematosus. *Arch Dermat Syph* 1872; 4: 36-79.
9. OSLER W: On the visceral complications of erythema exudativum multiforme. *Am J Med Sci* 1895; 110: 629-46.
10. OSLER W: The visceral lesions of the erythema group. *Br J Dermatol* 1900; 12: 228-45.
11. OSLER W: On the visceral manifestations of erythema group of skin diseases. *Trans Assoc Am Physicians* 1903; 18: 599.
12. BLUESTEIN HG, WILLIAMS GW, STEINBERG AD: Cerebrospinal fluid antibodies to neuronal cells: Association with neuropsychiatric manifestations of systemic lupus erythematosus. *Am J Med* 1981; 70: 240-6.
13. DENBURG SD, BEHMANN SA, CARBOTTE RM, DENBURG JA: Lymphocyte antigens in neuropsychiatric systemic lupus erythematosus: Relationship of lymphocyte antibody specificities to clinical disease. *Arthritis Rheum* 1994; 37: 369-75.
14. HANLY JG, WALSH NM, FISK JD, *et al*.: Cognitive impairment and autoantibodies in systemic lupus erythematosus. *Br J Rheumatol* 1993; 32: 291-6.
15. HANLY JG, FISK JD, EASTWOOD B: Brain reactive antibodies and cognitive impairment in systemic lupus erythematosus. *Lupus* 1994; 3: 193-9.
16. SCHNEEBAUM AB, SINGLETON JD, WEST SG, *et al*.: Association of psychiatric manifestations with antibodies to ribosomal P proteins in systemic lupus erythematosus. *Am J Med* 1991; 90: 54-62.
17. TOUBI E, KHAMASHTA MA, PANARRA A, HUGHES GRV: Association of antiphospholipid antibodies with central nervous system disease in systemic lupus erythematosus. *Am J Med* 1995; 99: 397-401.
18. YOSHIO T, MASUYAMA J-I, IKEDA M, *et al*.: Quantification of antiribosomal PO protein antibodies by ELISA with recombinant PO fusion protein and their association with central nervous system disease in systemic lupus erythematosus. *J Rheumatol* 1995; 22: 1681-7.
19. HIROHATA S, MIYAMOTO T: Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus. *Arthritis Rheum* 1990; 33: 644-9.
20. SUZUKI H, TAKEMURA H, KASHIWAGI H: Interleukin-1 receptor antagonist in patients with systemic lupus erythematosus. *Arthritis Rheum* 1995; 38: 1055-9.
21. ADAMS RD, VICTOR M, ROPPER AH: *Principles of Neurology* (6th ed). McGraw-Hill: New York, 1997.
22. GLANZ BI, MURAWSKI BJ, SCHUR PH, KHOSHBIN S: Dichotic listening in SLE. *Soc Neurosci Abstr* 1997; 23: 497.
23. GLANZ BI, SCHUR PH, KHOSHBIN S: EEG abnormalities in systemic lupus erythematosus. *Clin Electroencephalogr* 1998; 29: 128-31.
24. CARBOTTE RM, DENBURG SD, DENBURG JA: Prevalence of cognitive impairment in systemic lupus erythematosus. *J Nerv Ment Dis* 1986; 174: 357-64.
25. GINSBURG KS, WRIGHT EA, LARSON MG, *et al*.: A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. *Arthritis Rheum* 1992; 35: 776-82.
26. GLANZ BI, SLONIM D, UROWITZ MB, GLADMAN DD, GOUGH J, MACKINNON A: Pattern of neuropsychological dysfunction in inactive systemic lupus erythematosus. *Neuropsychiatry Neuropsychol Behav Neurol* 1997; 10: 232-8.
27. HANLY JG, FISK JD, SHERWOOD G, JONES E, VERRIER JONES J, EASTWOOD B: Cognitive impairment in patients with systemic lupus erythematosus. *J Rheumatol* 1992; 19: 562-7.
28. GLANZ B: *Neuropsychological deficits in inactive systemic lupus erythematosus*. Unpublished doctoral dissertation, York University, Toronto, 1995.
29. MILNER B, TAYLOR L, SPERRY RW: Lateralized suppression of dichotically presented digits after commissural section in man. *Science* 1968; 161: 184-6.
30. KHOSHBIN S: Epilepsy and behavior. *In:* SAMUELS M and FESKE S (Eds.): *Office Practice of Neurology*. New York, Churchill Livingstone 1996; 773-9.
31. KHOSHBIN S: Van Gogh's malady and other cases of Geschwind's syndrome. *Neurology* 1986; 36 (Suppl. 1): 213-4.
32. WAXMAN SG, GESCHWIND N: Hypergraphia in temporal lobe epilepsy. *Neurology* 1974; 24: 629-36.
33. RAO SM, DEVINSKY O, GRAFMAN J, *et al*.: Viscosity and social cohesion in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 1992; 55: 149-52.
34. ROGERS MP, KELLY MJ: Psychiatric aspects of lupus. *In* SCHUR PH (Ed.): *The Clinical Management of Systemic Lupus Erythematosus* (2nd ed.). Philadelphia, Lipincott-Raven 1996; 155-74.
35. STERN M, ROBBINS ES: Psychoses in systemic lupus erythematosus. *Arch Gen Psychiatry* 1960; 3: 205-12.
36. WALLACE DJ, DUBOIS EL: Psychopathology of the lupus patient. *In* DUBOIS EL (Ed.): *Lupus Erythematosus* (3rd ed). Philadelphia, Lea & Fibiger 1987; 488-98.
37. RENSHAW PF, YURGELUN-TODD DA, TOHEN M, GRUBER S, COHEN BM: Temporal lobe proton magnetic resonance spectroscopy of patients with first-episode psychosis. *Am J Psychiatry* 1995; 152: 444-6.
38. STEVENS JR: Psychosis and the temporal lobe. *Adv Neurol* 1991; 55: 79-96.
39. TUCKER GJ, PRICE TR, JOHNSON VB, MCALLISTER T: Phenomenology of temporal lobe dysfunction: a link to atypical psychosis - A series of cases. *J Nerv Ment Dis* 1986; 174: 348-56.
40. JIBIKI I, MAEDA T, KUBOTA T, YAMAGUCHI N: ^{123}I-IMP SPECT brain imaging in epileptic psychosis: A study of two cases of temporal lobe epilepsy with schizophrenia-like syndrome. *Neuropsychobiology* 1993; 28: 207-11.

41. BOGERTS B, ASHTARI M, DEGREEF G, ALVIR JMJ, BILDER RM, LIEBERMAN JA: Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Res* 1990; 35: 1-13.
42. WYSENBEEK AJ, LEIBOVICI L, WEINBERGER A, GUEDJ D: Fatigue in systemic lupus erythematosus. Prevalence and relation to disease expression. *Br J Rheumatol* 1993; 32: 633-5.
43. ISENBERG DA, MEYRICK-THOMAS D, SNAITH ML, MCKERAN RO, ROYSTON JP: A study of migraine in systemic lupus erythematosus. *Ann Rheum Dis* 1982; 41: 30-2.
44. HERZOG AG: A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. *Neurology* 1993; 43: 1907-10.
45. AMIR J, GALBRAITH RC: Paraneoplastic limbic encephalopathy as a non-metastatic complication of small cell lung cancer. *South Med J* 1992; 85: 1013-4.
46. CAMARA EG, CHELUNE GJ: Paraneoplastic limbic encephalopathy. *Brain Behav Immun* 1987; 1: 349-55.
47. LACOMIS D, KHOSHBIN S, SCHICK RM: MR imaging of paraneoplastic limbic encephalitis. *J Comput Assist Tomogr* 1990; 14: 115-7.
48. POSNER JB: Paraneoplastic syndromes. *Neurol Clin* 1991; 9: 919-36.
49. POSNER JB, DALMAU J: Clinical enigmas of paraneoplastic neurologic disorders. *Clin Neurol Neurosurg* 1995; 97: 61-70.
50. FELTEN DL, FELTEN SY: Immune interactions with specific neural structures. *Brain Behav Immun* 1987; 1: 279-83.
51. BAKHEIT AMO, KENNEDY PGE, BEHAN PO: Paraneoplastic limbic encephalitis: Clinicopathological correlations. *J Neurol Neurosurg Psychiatry* 1990; 53: 1084-8.
52. FRANCK G, SADZOT B, SALMON E, *et al*.: Encephalopathie limbique paraneoplasique secretion inapropriée d'ADH, et crises epileptiques subintrantes infracliniques: Correlations cliniques, anatamo-pathologiques et metaboliques par tomographie à emission de positons. *Rev Neurol* 1987; 143: 657-69.
53. SCHLITT M, LAKEMAN FD, WHITLEY RJ: Psychoses and herpes simplex encephalitis. *South Med J* 1985; 78: 1347-50.
54. OOMMEN KJ, JOHNSON PC, RAY CG: Herpes simplex type 2 virus encephalitis presenting as psychosis. *Am J Med* 1982; 73: 445-8.
55. WILSON LG: Viral encephalopathy mimicking functional psychosis. *Am J Psychiatry* 1976; 133: 165-70.
56. HIERONS R, JANOTA I, CORSELLIS JAN: The late effects of necrotising encephalitis of the temporal lobes and limbic areas: A clinicopathological study of ten cases. *Psychol Med* 1978; 8: 21-42.
57. KAPUR N, BARKER S, BURROWS EH, *et al*.: Herpes simplex encephalitis: Long term magnetic resonance imaging and neuropsychological profile. *J Neurol Neurosurg Psychiatry* 1994; 57: 1334-42.
58. PIETRINI V, NERTEMPI P, VAGLIA A, REVELLO MG, PINNA V, FERRO-MILONE F: Recovery from herpes simplex encephalitis: Selective impairment of specific semantic categories with neuroradiological correlation. *J Neurol Neurosurg Psychiatry* 1988; 51: 1284-93.
59. CAPARROS-LEFEBVRE D, GIRARD-BUTTAZ I, REBOUL S, *et al*.: Cognitive and psychiatric impairment in herpes simplex virus encephalitis suggest involvement of the amygdalofrontal pathways. *J Neurol* 1996; 243: 248-256.
60. AWAN ZF, BHARATH AB: Psychiatric symptoms and memory impairment in a patient with Lyme encephalitis. *Resident Staff Physician* 1996; 42: 25-6.
61. KAPLAN RF, MEADOWS M-E, VINCENT LC, LOGIGIAN EL, STEERE AC: Memory impairment and depression in patients with Lyme encephalopathy: Comparison with fibromyalgia and non-psychotically depressed patients. *Neurology* 1992; 42: 1263-7.
62. BENKE T, GASSE T, HITTMAIR-DELAZER M, SCHMUTZHARD E: Lyme encephalopathy: Long-term neuropsychological deficits years after acute neuroborreliosis. *Acta Neurol Scand* 1995; 91: 353-7.
63. BREDER CD, DINARELLO CA, SAPER CB: Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* 1988; 240: 321-4.
64. LECHAN RM, TONI R, CLARK BD, *et al.*: Immunoreactive interleukin-1β localization in the rat forebrain. *Brain Res* 1990; 514: 135-40.