Neuropsychiatric syndromes in systemic lupus erythematosus: A new look

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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 neuro-pathological 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 pathophysiological 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, mammillary 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-
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...tion, 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, hypososexuality, 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
construcational 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 neuropsychological and neurophysiological 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