NEUROPSYCHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS
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ABSTRACT
In systemic lupus erythematosus, many neuropsychiatric symptoms are related to the impact on the central nervous system. The complex symptomatology includes neurological symptoms and psychiatric manifestations. Neurological symptoms include headache, seizures, focal signs, chorea, parkinsonism, and peripheral neuropathy. Psychiatric manifestations include depression, mania, psychosis, delirium, dementia, and cognitive slowing.

Although these findings may occur independently, patients will usually have a mixture. Psychosis and altered mental status are among the most common symptoms, and these can develop in the absence of active disease. When providing symptomatic relief for these patients, the clinician would need to avoid antipsychotics and antidepressants that may lower the seizure threshold.

Keywords: anxiety, neuropsychiatric sequelae, anti-phospholipid syndrome, cerebral lupus, steroids

INTRODUCTION
Systemic lupus erythematosus (SLE) is a primarily antibody-mediated autoimmune disease that can have significant psychiatric sequelae. Many neuropsychiatric symptoms are related to the impact on the central nervous system. In SLE, there are multiple different antibodies directed at multiple targets, including vascular endothelium, neurons, and phospholipids. The anti-phospholipid antibodies, which include the 'lupus anticoagulant,' may be particularly important as they predispose to cerebral infarction. Autopsy studies have revealed multiple small infarctions located in the cerebral cortex and subcortical white matter. Also, immune complexes have been found in the choroid plexus, and it is possible that direct neuronal damage by anti-neuronal antibodies may contribute to the overall symptomatology.

In general, the occurrence of neuropsychiatric symptomatology in the setting of constitutional symptoms, arthralgia, myalgia, or rashes should raise the suspicion of SLE. Noncaucasian races have a higher prevalence of SLE than Caucasians. Asians are at three times the risk of Caucasians. Chang et al (1995) in a review of 61 ethnic Chinese male lupus patients, found a higher frequency of renal disease, malar rash and photosensitivity, but a lower frequency of arthritis and lymphadenopathy, compared to previous reports of caucasians. In Chang's series, 26% of patients have neuropsychiatric disease. Though there is no nation-wide epidemiologic survey of SLE in Singapore, a conservative estimate had put the number of sufferers at 1,000. This yielded a prevalence rate of approximately 33 per 100,000 individuals.

On the whole, the literature on psychiatric aspects of SLE is confusing; many authors fail to use standardised definitions for the terms psychosis, organic brain syndrome, delirium and toxic reactions. Few studies are prospective, and many are simple chart reviews. Some studies even omit mood disturbances, which are likely to be common given the chronic nature of the illness. The complex neuropsychiatric symptomatology includes depression, mania, psychosis, delirium or dementia, cognitive slowing, headache, seizures, focal signs, chorea, parkinsonism, and a peripheral neuropathy. Although these findings may occur independently, patients will usually have a mixture. Three categoric presentations are recognised: direct involvement of the central nervous system, with mood disturbances, delirium, or other cognitive impairment disorders; psychological sequelae of the patient's awareness of the illness or its impact; and psychiatric side effects of the drugs used to treat the illness. Clinical manifestations are protean but can be divided into 3 basic groups: (1) neurologic, (2) psychiatric, (3) psychologic. These groupings are artificial as they are not mutually exclusive.

The American College of Rheumatology has revised the clinical nomenclature for neuropsychiatric SLE (N-P-SLE), providing case definitions for 19 neuropsychiatric syndromes seen in SLE, with reporting standards and recommendations for laboratory and imaging tests. The nomenclature is intended to facilitate communication and enhance clinical research, particularly multicenter studies, and reporting. It is useful for didactic purposes but should not be used uncritically or as a substitute for a clinical diagnosis. In clinical settings, consultation with other specialists are often required.

Hugo et al (1996) applied DSM-III-R criteria in the evaluation of 88 SLE patients and found a point prevalence rate of 18.2% for psychiatric disorders, the most common diagnosis being adjustment disorder (11.4%). No patients had mood disturbances compatible with a functional psychosis. High scores on a life event scale were associated with psychiatric disorders, suggesting that psychosocial stress is etiologically important. A limitation of the study is the failure to distinguish between stresses that are consequent to SLE and those that are not related to SLE.

The prospective prevalence risk for SLE patients to develop behavioural disturbances over 1 to several years approaches 50% in studies that have included longitudinal follow-up. Some of these mood disturbances may be related to the variety of...
circulating anti-self-antibodies that occur in SLE. The data from many studies are too preliminary to allow an understanding of specific connections between circulating autoantibodies in these patients and behavioural disturbance.

NEUROPSYCHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Neurological involvement

Headache is common and may resemble that seen in migraine. Seizures are relatively common and may be either partial or grand mal. Focal deficits may also occur, e.g., hemiplegia. Chorea may occur and has constituted the presentation of SLE. Parkinsonism is a rare symptom of SLE. A peripheral neuropathy may occur and may be either of the polyneuropathy or mononeuritis complex variety. Cerebrovascular accidents, transverse myelitis, seizures and aseptic meningitis may necessitate monitoring and treatment in the intensive care setting.

Psychiatric manifestations

Possible presentations include psychosis, depression, change in behaviour, change in personality, and delirium. For the recent definition of neuropsychiatric lupus, a multidisciplinary committee recommended using DSM-IV criteria to diagnose psychosis, mania, depression, and delirium. Depression and anxiety were thought to be predominantly psychological in origin in most patients; other syndromes were biological.

Neuropsychiatric symptoms often occur in the first year of SLE, but are rarely the presenting symptoms of the disease. The etiology for the neuropsychiatric sequelae could be primary or secondary events. Primary events result directly from immune-mediated injury to the CNS, e.g., vascular occlusion from immune-complex-mediated or antibody-mediated vasculopathy; cerebral dysfunction from antibodies to brain tissue. Secondary events result from disease in other organs, complications of therapy, or both. Examples include infection (meningitis, abscess, discitis), cerebrovascular accidents due to accelerated atherosclerosis, metabolic encephalopathy, hypercoagulable state due to nephrotic syndrome and drugs.

Lupus cerebritis and organic brain syndrome

Psychosis and altered mental status are among the most common symptoms, and these can develop in the absence of active disease. Reported in as many as 20% of patients with SLE, organic brain syndrome usually manifests with various degrees of memory impairment, apathy, and loss of orientation, intellect or judgment. Agitation, delirium, stupor, or coma may occur in severe cases. Lupus cerebritis, in the full-blown presentation, would be seen as classic delirium with disturbance of consciousness, disorientation, and even hallucinations (visual more likely than auditory). The patient also can present with depressive symptoms, including insomnia, irritability, emotional lability, and suicidal ideation.

It is important to realise that terms like lupus cerebritis and lupus vasculitis are inaccurate simplifications of the complex cerebral disease found in SLE patients. The clinical presentation, serologic tests and neuroimaging techniques have to be considered to support the diagnosis of cerebral lupus. Although some reports have suggested a close relationship between psychosis and the presence of anti-ribosomal P protein antibodies, others have not agreed, its status being unclear. Delirium may not be due to lupus cerebritis, but it may be due to renal failure and uremia. Lupus psychosis should be differentiated from steroid psychosis, which is uncommon and affects only 10% of patients on steroid and occurs almost exclusively at prednisolone dose higher than 20 mg a day for prolonged periods.

Anxiety and mood disorders

Depression, in some cases accompanied by hallucinations or delusions, has been found commonly by some, but not all authors. Mania, though reported, is far less common than depression. Lim and colleagues (1988) made ‘lifetime’ (i.e., since onset of lupus) diagnoses of major depression in 16 of 40 (40%) patients and found anxiety disorders in an additional 4 of 40 (10%). Miguel and colleagues (1994) diagnosed organic mood disorder, in all cases depressive, in 19 of 43 (44%) patients. Hugo and colleagues (1996) found only one case of major depression and one case of organic mood disorder among their 88 carefully assessed patients; by contrast, 10 (11%) had adjustment disorders, with depressive symptoms often prominent and a trend toward higher scores on ratings of stressful life events.

The origin of the depressive symptoms is what causes debate. Miguel and colleagues (1994) argued that the timing, association with neurobiological and neuroimaging findings, and phenomenology of the psychiatric features proved an organic cause. Utset et al (1994) argues that discrete associations of depressive symptoms with neuropsychiatric lupus and secondary Sjogren’s syndrome suggest that depression does not occur purely as a response to social stresses, and may be a manifestation of autoimmune disease in some patients. Moran et al (2000) opine that depression may not be due to the direct effect of the medical condition, but could be a psychological reaction to the illness.

Steroids are used to treat acute episodes of SLE and can themselves cause significant changes in mood. A very close look at the timeline of the symptoms and treatment may provide some clues. Increasing the corticosteroid dose will usually improve symptoms due to an underlying disease but will generally worsen a corticosteroid-induced disorder. This entity is usually suspected when symptoms occur within 15 days of initiation of corticosteroids or after an increase in corticosteroid dosage.

Rapid tapering of steroids can produce a withdrawal syndrome consisting of flu-like symptoms (myalgias, low grade fever, anorexia) and even joint effusions and postural hypotension. By holding the steroid dose constant, one can generally distinguish between the withdrawal symptoms, which go away in a few days to a week or two, and the underlying...
illness, which persists or worsens. Low doses of sedating antidepressants may help with symptoms of anxiety and insomnia.

Cognitive symptoms
SLE can be complicated by the antiphospholipid syndrome, which is characterized by antiphospholipid antibodies and specific thromboembolic phenomena, including pulmonary emboli, recurrent miscarriages, thrombocytopenia, and arterial or venous thrombosis. SLE-antiphospholipid syndrome is a particularly debilitating form of neuropsychiatric SLE that is characterized by focal neurological deficit, epilepsy, recurrent strokes and multi-infarct dementia.

Minor psychiatric symptoms and abnormalities on neuropsychological testing are being detected with increasing frequency. Neurocognitive dysfunction has been reported in patients with antiphospholipid syndrome even in the absence of obvious focal lesions, indicating substantial microscopic disease. Migraine, dementia, delusional states, and depression, each of which can be symptoms of NPSLE, have been associated with antiphospholipid syndrome.

Neuropsychiatric symptoms improved or resolved in most children within 6 months. Several children were left with chronic sequelae, including residual neuropathy and cognitive problems. So far the data on cognitive impairment in lupus raise the possibility of multiple origins of cognitive impairment, including both reversible effects of systemic or cerebral inflammation and irreversible structural cerebral activity.

TREATMENT OF NEUROPSYCHIATRIC SEQUELAE

Medications
The treatment of cerebral lupus is empiric, due to a lack of randomized studies. The best available evidence for treatment of CNS lupus is largely based on retrospective series, case reports and expert opinion. Inflammatory brain lesions are treated with corticosteroids and immunosuppressive drugs (e.g., cyclophosphamide). Anticoagulant therapy with coumarins is recommended in cases of thrombotic events associated with antiphospholipid antibodies.

In cases in which depression, mania, psychosis, delirium, or dementia persists despite treatment, symptomatic treatment is justified. One would need to avoid antipsychotics and antidepressants that may lower the seizure threshold. When choosing an antipsychotic, conventional antipsychotics may be avoided because of the higher risks of extrapyramidal side effects; risperidone and olanzapine are the preferred agents for organic psychosis. Of the antidepressants, a selective serotonin reuptake inhibitor (SSRI) is probably appropriate, and if a mood stabilizer is required, consideration may be given to sodium valproate.

The S-enantiomer of warfarin, the more active isomer, is metabolized at liver cytochrome enzyme 2C9, whereas R-Warfarin is metabolized at 1A2. It is because of this complicated metabolism that warfarin is sensitive to inhibition and induction by many drugs. Fluvoxamine (an SSRI) elevates S-warfarin levels through inhibition of 2C9, increasing the risk of bleeding. Other drugs that increase warfarin levels through this mechanism may be the SSRIs fluoxetine, paroxetine, and sertraline. These agents are all fairly modest 2C9 inhibitors.

Psychosocial interventions
In Savelkoul et al (2001)'s study, the effects of a coping intervention aimed at teaching patients active problem-focused coping in the form of action-directed coping and coping by seeking social support were investigated in a randomized controlled trial. The study suggests that patients who attend at least half of all sessions of the coping intervention obtain additional benefits in that loneliness and negative social interactions decrease and life satisfaction improves.

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