Chapter 9: Systemic Lupus Erythematosus (SLE) and Neuropsychiatry

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Introduction

SLE is an autoimmune, connective tissue disorder which affects multiple organ systems including the CNS. The exact pathophysiology is not well understood but can be simplified as the formation of pathological antinuclear antibodies (ANA) which binds with antigens in to form *immune complexes* (IC). ICs deposit in tissue and trigger an inflammatory cascade resulting in tissue damage.

A variety of ANA are produced with varying levels of sensitivity and specificity for SLE (anti-PL, Anti-rib P, anti-ss DNA, anti-ds DNA, anti-SM, anti-Ro, anti-La etc.). Both genetic and environmental factors are important in the development of SLE.

The risk of developing SLE is 5-10 times higher in females. It is more prevalent in African patients. Involvement of the nervous system (central, peripheral, cognitive as well as psychiatric manifestations) is referred to as neuro-lupus, and Neuropsychiatric manifestations of lupus are common.

Clinical features of SLE

Insidious onset of constitutional symptoms; malaise, low grade fever, migratory arthritis, diffuse muscle ache. There is lymphadenopathy, as well as anorexia, nausea, abdominal pain. Haematological manifestations include haemolytic anaemia. SLE most commonly presents with skin manifestations, namely butterfly rash, purpura, alopecia

The systemic manifestations include kidney, cardiac, lung, and then Central Nervous System.

Neuro-lupus

The cardinal features of neuro-lupus including the neuropsychiatric manifestations are listed in Table 1 below.

Table 1 – Neuropsychiatric syndromes in SLE as defined by ACR nomenclature

CNS	Peripheral nervous system
Acute confusional state	Autonomic neuropathy
Anxiety disorder	Cranial neuropathy
Aseptic meningitis	Guillain-Barré syndrome
Cerebrovascular disease	Mononeuropathy
Cognitive dysfunction	Myasthenia gravis
Demyelinating syndrome	Plexopathy
Headache	Polyneuropathy
Mood disorder	
Movement disorder	
Myelopathy	
Psychosis	
Seizure disorders	

SLE, systemic lupus erythematosus; ACR, American College of Rheumatology.

Adapted from American College of Rheumatology Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. *Arthritis Rheum*. 1999.[2]

From: Neuro-lupus, A Review. Practical Neurology 2010;10

The development of Neuro-lupus is not well understood. It is most likely based on autoantibodies within the CNS causing Immune Complex aggregation and inflammatory changes. A vasculopathy leading to thrombosis and ischemia (infarctions) may occur. Psychosocial factors may play a role, independently of other factors.

The acute neuropsychiatric syndromes secondary to SLE usually occur within 2 years following the onset of the disease. These may be due to one or more of:

- Active CNS Lupus
- Persistent neurological deficits from previous infarcts
- Complications from other affected systems (nephropathy, metabolic abnormalities, anaemia etc.)
- Psychosocial stressors
- Medication side-effects (particularly steroids but cyclophosphamide, azathioprine and opioids are all potential culprits)

See Kivity, S *et al.* Neuropsychiatric lupus: a mosaic of clinical presentations. *BMC Med* **13,** 43 (2015).

Neuropsychiatric Symptoms

1. Cognitive Impairment / Disorders

Acute confusional state / encephalopathy (delirium) may have multiple possible etiologies. If the encephalopathy is due to an acute exacerbation of the primary disease (lupus cerebritis), one would expect the CSF to show an inflammatory profile. Note that active CNS lupus (lupus cerebritis rarely occurs in the absence of other acute systemic manifestations of SLE.

Neurocognitive disorders occur frequently (incidence 20-80%) but major neurocognitive disorders are rare. They are characterized by executive dysfunction (processing speed, attention and retrieval memory deficits). There are again multiple possible etiologies (small vessel disease, residual neurological deficits from previous large vessel infarcts, acute/active CNS lupus flare-up, medication effects)

Treatment is based on the presumed etiology. In the case of cognitive impairment secondary to an acute flare-up, the treatment would be with immune suppressants. If cognitive symptoms are thought to be due to medication side-effects, one would lower the dose of the offending immune suppressant

2. Mood Disorders

Depression is common in patients with SLE. Depressed mood may reflect the reaction to living with a chronic disease or may have an organic basis. Some patients have shown elevated levels of antibodies, but the evidence is not conclusive. If mania does occur, it is most likely secondary to the use of corticosteroids.

3. Psychosis

Occurs in < 5% of patients with SLE. Psychotic symptoms may be caused by steroid therapy or active CNS Lupus- this is the clinical dilemma because the treatment of SLE is corticosteroids and disease-modifying agents, while the treatment of medication-induced illness is medication reduction. CNS Lupus psychosis usually occurs within the first year of diagnosis. It hss been associated with the presence of anti-ribosomal P anti-bodies. The clinical features include Delusions, Visual Hallucinations, Tactile Hallucinations, and Disorganized thought form. On the other hand, Steroid induced psychotic episodes are usually dose dependent, occurring at prednisone doses >40mg daily. In this form of psychosis, auditory hallucinations are common.

4. Other neurologic manifestations of Neuro-lupus:

Seizures are common (up to 20% of patients). They may occur in an acute inflammatory episode or due to old scarring from vascular insults. One must exclude metabolic/electrolyte imbalance as possible cause.

Movement Disorders are rare, and usually occur in the context of an acute episode. The most common form consists of choreiform movements

Investigations in SLE

The false positive anti-body rate rate is high, as 30% of the general population will have a positive ANA, therefore, titers are useful. In this regard, an ANA titer >1:160 is significant. If it is positive, follow up with more specific tests, such as anti-ds DNA or anti-SM antibodies. There are no specific antibodies which are used in clinical practice to make a diagnosis of neurolupus.

Within the CSF, a broadly inflammatory picture is usually seen, with lymphocytic pleocytosis, mildly elevated protein, elevated IgG index and oligo-clonal bands. The EEG in acute CNS lupus may reveal diffuse slowing in 80% of cases.

Imaging is non-specific. One may see evidence of cerebrovascular disease and small vessel disease. There may be One may see periventricular hyperintensities on T2 MRI. Functional imaging such as PET and SPECT are sensitive but nonspecific diagnostic imaging tools.

References

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