Neuropsychiatric Lupus (NPL) is the term for the presenting manifestations of psychologic, central nervous system (CNS) or peripheral nervous system (PNS) abnormality arising out of systemic lupus erythematosus (SLE). The prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) in SLE ranges widely between 14 and 75%. As a general term, it has brought the previously used terms like CNS lupus, neurolupus, CNS vasculitis or Organic Brain Syndrome to include a plethora of clinical manifestations under one umbrella. Even there may be cranial or peripheral neuropathy as a result of vasculitis of vasa nervosum. The retinopathy may present as cotton wool spots (cytoid bodies) is also due to vasculitis.

The etiology of NPL is likely to be multifactorial, and includes microangiopathy, autoantibody production and intrathecal production of pro-inflammatory cytokines. Newer imaging modalities of brain structure and function provide novel ways of understanding its pathogenic mechanisms. The most probable pathomechanism is the existence of a vasculopathic state (abnormal vessel walls without inflammatory cell infiltrates) of small vessels which alters cerebral microcirculation. A true vasculitic process occurs much less often. The finding of elevated IgG anticardiolipin antibodies in CSF, greater than expected from a vascular supply alone, suggests central production of this potentially pathologic element. Metabolic abnormalities, as a consequence of other organ dysfunction, could play a role in changing the metabolic capability of neurons and their axons, dendrites and synapses. Alteration of balance of neurotransmitters of hindbrain, like serotonin, could be altered by lupus or drugs used for lupus.

The 1999 ACR Nomenclature Committee has identified 19 different NPL conditions those are part of lupus complex of which 12 are CNS-related and 7 are PNS-related. This new set of 19 NP definitions with proper clinical judgment could be used to expand the neuropsychiatric criteria of the ACR classification criteria of SLE from just seizures and psychosis. These NPL case definitions are:

1. Acute confusional state
2. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre Syndrome) [AIDP]
3. Anxiety disorder
4. Aseptic meningitis
5. Autonomic disorder
6. Cerebrovascular disease
7. Cognitive dysfunction (most common manifestation of diffuse CNS lupus)
8. Demyelinating syndrome
9. Headache
10. Mononeuropathy (single/ multiplex)
11. Mood disorders
12. Movement disorder (chorea)
13. Myasthenia gravis
14. Myelopathy
15. Neuropathy, cranial
16. Plexopathy
17. Polymyositis
18. Psychosis
19. Seizure and seizure disorder

**PNS-related:** 2, 5, 10, 13, 15-17; **CNS-related:** rest; No. 8, 12, 14 are rare

Each syndrome is described below chronologically:

1. **ACUTE CONFUSIONAL STATE:**
   Disturbance of consciousness or level of arousal varying from delirium to coma.
   **DIAGNOSTIC CRITERIA:**
   Disturbance of consciousness or level of arousal with reduced ability to focus, maintain, or shift attention, and one or more of the following developing over a short period of time (hours to days) and tending to fluctuate:
   - A. Acute or subacute change in cognition, memory deficit and disorientation.
   - B. A change in behavior, mood, or affect.
   **EXCLUSIONS:**
   - Primary mental/neurologic disorder not related to SLE.
   - Metabolic disturbances
   - Substance or drug-induced delirium (including withdrawal)
   - Cerebral infections
   **N.B.:** Preexisting cognitive deficit is not an exclusion.
   **ASSOCIATIONS:**
   - Marked psychosocial stress
   - Corticosteroid use
   - TTP (thrombotic thrombocytopenic purpura) / HUS (hemolytic-uremic syndrome)

2. **AIDP:**
   Acute, inflammatory, and demyelinating syndrome of spinal roots, peripheral, and occasionally cranial nerves.
   **DIAGNOSTIC CRITERIA:**
   - A. Clinical Features:
     - Progressive polyradiculoneuropathy, which peaks usually within ≤ 21 days
     - Reflex loss
     - Symmetric
   - B. C.S.F: albumino-cytological dissociation
   - C. Nerve conduction study abnormality in 3 nerves
   The abnormalities are:
   - 1. Conduction block in which the amplitude of compound muscle action potential diminishes with more proximal sites of nerve stimulation
   - 2. F-waves may be absent or prolonged
   - 3. Slowing of conduction velocity
   - 4. Prolongation of distal latencies
   **N.B.:** Nerve conduction abnormalities may be subtle in early stages
   **EXCLUSIONS:**
   - Acute spinal cord, anterior horn cell or neuromuscular junction disease

3. **ANXIETY DISORDER**
   Anticipation of danger or misfortune accompanied by apprehension, dysphoria, or tension.
   **N.B.:** In most SLE patients, anxiety is a secondary stress reaction
   **DIAGNOSTIC CRITERIA:**
   Both of the following:
   - Prominent anxiety, panic disorder, panic attacks, or obsessions or compulsions
   - Disturbance causes clinically significant distress or impaired social, occupational, or other important functioning
   **EXCLUSIONS:**
   - Adjustment disorder with anxiety
   - Substance- or drug-induced anxiety
   - Anxiety occurring exclusively during the course of an acute confusional state, a mood disorder, or psychosis
   **ASSOCIATIONS:**
   - Metabolic disorders
• Psychosocial stress
• Corticosteroid use

4. ASEPTIC MENINGITIS

Syndrome of fever, headache, and meningeal irritation with CSF pleocytosis, and negative CSF cultures.

DIAGNOSTIC CRITERIA:
All of the following:
• Acute or subacute onset of headache with photophobia, neck stiffness, and fever
• Meningism
• Abnormal CSF

EXCLUSION CRITERIA:
CNS or meningeal inflammation due to:
• Infection
• Subarachnoid hemorrhage
• Malignancy or granulomatous disease
• Medications: NSAIDs, intravenous immunoglobulin, azathioprine etc.

5. AUTONOMIC DISORDER:

Disorder of the autonomic nervous system with orthostatic hypotension, sphincteric erectile/ejaculatory dysfunction, anhidrosis, heat intolerance, or constipation.

DIAGNOSTIC CRITERIA:
Symptoms and abnormal response to provocative tests:
Normal range of tests:
• Blood pressure response to ‘standing Fall’ in BP 30/15 mm Hg
• Heart rate response to ‘standing Increase’ 11-29 beats/minute
• Heart rate variation with respiration Max.—min. heart rate 15 beats/min; Expiration: Inspiration ratio 1.2
• Valsalva ratio 1.4
• Sweat test – Sweating over all body and limbs

EXCLUSIONS:
• Autonomic dysfunction with Lambert-Eaton syndrome
• Medications: tricyclic antidepressants
• Poisons: organophosphates
• Shy-Drager syndrome

6. CEREBROVASCULAR DISEASE

Neurologic deficits due to arterial insufficiency or occlusion, venous occlusive disease, or hemorrhage; these are mainly focal but may be multifocal in recurrent disease.

DIAGNOSTIC CRITERIA:
One of the following and supporting radioimaging study:
• Stroke syndrome
• Transient ischemic attack
• Chronic multifocal disease
• Subarachnoid and intracranial hemorrhage
• Sinus thrombosis

EXCLUSIONS:
• Infection with space occupying lesions in the brain
• Trauma
• Vascular malformation
• Hypoglycemia

7. COGNITIVE DYSFUNCTION

Significant objective deficits in any or all of the following cognitive or higher functions; it may or may not impede social, educational, or occupational functioning.

DIAGNOSTIC CRITERIA:
A. Documented impairment of one or more of the following cognitive domains:
1. Simple / complex attention
2. Memory
3. Visual-spatial processing
4. Language
5. Reasoning/problem solving
6. Psychomotor speed
7. Executive functions
B. The cognitive deficits represent a significant decline from a former level of functioning (if known).
C. The cognitive dysfunction may cause varying degrees of impairment of social, educational or occupation function depending on the degree of function(s) impaired.

8. DEMYELINATING SYNDROME:

Acute or relapsing demyelinating encephalomyelitis
with evidence of discrete neurologic lesions distributed in place and time.

**DIAGNOSTIC CRITERIA:**

Two or more of the following, each occurring at different times,

Or, one of the following occurring on at least two different occasions

1. Multiple areas white matter damage within CNS, causing weakness/sensory loss in ≥1 limbs
2. Transverse myelopathy
3. Optic neuropathy
4. Diplopia due to isolated nerve palsies or internuclear ophthalmoplegia
5. Brain stem disease with vertigo, vomiting, ataxia etc.
6. Other cranial nerve palsies

**EXCLUSIONS:**

1. Infections
2. Vitamin B₁₂ deficiency

**N.B.:** Clinical and neuroimaging evidences may be indistinguishable from multiple sclerosis

9. **HEADACHE:**

Discomfort in the region of the cranial vault.

**I. Migraine:**

**Migraine without aura:**

- Idiopathic, recurrent unilateral, pulsating headache, with nausea/vomiting manifested by attacks lasting 4-72 hours, aggravated by activity or light
- At least 5 attacks

Migraine with aura:

- Idiopathic, recurrent disorder manifested by attacks of neurologic symptoms localizable to cerebral cortex or brain stem
- Gradually developing over 5-20 minutes and lasting less than 60 minutes

**II. Tension headache (episodic tension type headache):**

- Recurrent episodes of bilateral headaches, not associated with activity or photo-exposure lasting minutes to days
- At least 10 previous headaches

**III. Cluster headache:**

- Attacks of severe, strictly unilateral pain, orbital, supraorbital, and/or temporal, usually lasting 15-180 minutes, occurring in clusters
- Associated with ≥1 of the following: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, myosis etc.

**IV. Headache from intracranial hypertension (pseudotumor cerebri, benign intracranial hypertension):**

All of the following:

- Increased intracranial pressure (200 mm of H₂O) without mass/ventriculomegaly/venous sinus thrombosis
- Normal neurologic findings except for papilledema and possible VI nerve palsy
- Normal CSF

**V. Intractable headache, nonspecific:**

**EXCLUSIONS:**

- Aseptic meningitis
- Drug-induced pseudotumor cerebri
- CNS infection
- Structural lesions
- Low intracranial pressure
- Trauma
- Intracranial hemorrhage or vascular occlusion

10. **MONONEUROPATHY (SINGLE / MULTIPLEX)**

Disturbed function of one or more peripheral nerve(s) due to axonopathy or demyelination.

**DIAGNOSTIC CRITERIA:**

1. Clinical demonstration of motor/sensory disturbances in one peripheral nerve and/or
2. Abnormalities on nerve conduction studies or EMG

11. **MOOD DISORDERS**

Prominent and persistent disturbance in mood characterized by

- Depressed mood or markedly diminished interest or pleasure in almost all activities, or
- Elevated, expansive or irritable mood

**DIAGNOSTIC CRITERIA:**

**I. Major depression-like episode**
One or more major depressive episodes with at least five of the following symptoms, including either A or B or both, during a 2-week period and nearly every day:

A. Depressed mood most of the day.

B. Markedly diminished interest in all / almost all, activities most of the day observation.

C. Following symptoms like:
   1. Significant weight loss without dieting or weight gain (>5% of body weight in one month)
   2. Insomnia or hypersomnna; psychomotor agitation or retardation
   3. Fatigue
   4. Feelings of worthlessness or inappropriate guilt
   5. Diminished ability to think or concentrate
   6. Recurrent thoughts of death / recurrent suicidal ideation without a specific plan, or a suicide attempt.

II. Mood disorder with depressive feature
Prominent and persistent mood disturbance characterized by predominantly depressed mood or diminished interest or pleasure in activities

III. Mood disorder with manic feature

IV. Mood disorder with mixed feature
EXCLUSIONS:
   • Primary mental disorders
   • Substance-induced mood disorder

NB.: If mood disturbance occurs exclusively during an acute confusional state: classify as acute confusional state, and if mood disturbance occurs exclusively during a psychotic disorder: classify as psychosis.

12. MOVEMENT DISORDER (CHOREA)
Chorea
Irregular, involuntary, quasi-purposive and jerky movements that may involve any portion of the body in random sequence; each movement is brief and unpredictable.

DIAGNOSTIC CRITERIA
Both of the following:
   • Observed abnormal movements
   • Random, unpredictable sequence of movements

EXCLUSIONS
   • Wilson’s disease
   • Huntington’s/any hereditary disease
   • Medications

13. MYASTHENIA GRAVIS
Neuromuscular transmission disorder characterized by fluctuating weakness and fatigability of bulbar and voluntary muscles without areflexia or sensory loss.

DIAGNOSTIC CRITERIA:
A. CHARACTERISTICS SIGN AND SYMPTOMS:
   One of the following:
   1. Diplopia, ptosis, dysarthria, weakness in chewing, difficulty in swallowing, muscle weakness with preserved deep tendon reflexes, and
   2. Increased weakness during exercise and repetitive use with at least partially restored strength after periods of rest
   3. Dramatic improvement in strength following administration of anticholinesterase drug
   And one or more of the following:

B. EMG and repetitive stimulation of a peripheral nerve at a rate of 2/second shows characteristic decremental response which is reversed by edrophonium or neostigmine.

C. Antibodies to Acetylcholine Receptors.

EXCLUSIONS:
   • Congenital myasthenic syndrome, progressive restricted myopathies, steroid and inflammatory myopathies, motor neuron disease
   • Organophosphate toxicity, botulism
   • Lambert-Eaton syndrome
   • Medications: neuromuscular blocking agents
   • Hypokalemia, hypophosphatemia

ASSOCIATIONS:
   • Pure red cell aplasia
   • Thyroid abnormalities
14. **MYELOPATHY**
Disorder of the spinal cord characterized with a demonstrable motor and/or sensory cord level (may be transverse) and/or sphincter involvement.

**DIAGNOSTIC CRITERIA**
Usually rapid onset (hours or days) of one or more of the following
- Bilateral weakness of legs with or without arms
- Sensory impairment with cord level similar to that of motor weakness; with or without bowel and bladder dysfunction.

**EXCLUSIONS**
- Mass lesion causing compression of or within spinal cord
- Cauda equina lesion

15. **NEUROPATHY, CRANIAL**
Disorder of sensory and/or motor function of a specific cranial nerve(s).

**DIAGNOSTIC CRITERIA:**
Any documentation of any cranial nerve deficit.

**EXCLUSIONS:**
- Skull fracture
- Tumor
- Infection
- Miller Fisher syndrome

16. **PLEXOPATHY**
Disorder of brachial or lumbo-sacral plexus not corresponding to the territory of single root or nerve.

**DIAGNOSTIC CRITERIA:**
All of the following:
- Characteristic sign and symptoms of:
  - **Brachial plexus:** deep pain in shoulder, muscle weakness, sensory deficit and/or reflex impairment of arm
    Or,
  - **Lumbo-sacral plexus:** deep boring pain in thigh, muscle weakness, sensory deficit and/or reflex impairment of leg
- Positive EMG finding and/or nerve conduction studies for EMG: >1 root or nerve abnormalities with sparing of paraspinal muscles
- Normal MRI or CT scan (optional: myelogram) to rule out a higher neurologic lesion

**EXCLUSIONS:**
- Damage from injury, compression, tumor, aneurysm, radiation
- Cervical rib, thoracic outlet syndrome

17. **POLYNEUROPATHY**
Acute or chronic disorder of sensory and motor peripheral nerves with variable tempo characterized by symmetry of symptoms and physical findings in a distal distribution.

**DIAGNOSTIC CRITERIA:**
One or both of the following:
- Clinical feature:
  1. Clinical demonstration of distal symmetrical sensory and/or motor deficit
- Confirmation by EMG:
  1. Denervation of muscle, or
  2. Demyelinating neuropathy

**EXCLUSIONS:**
- Vitamin deficiencies
- Hypothyroidism

18. **PSYCHOSIS:**
Severe disturbance in the perception of reality characterized by delusions and/or hallucinations; psychosis has been associated with anti-ribosomal P antibody.

**DIAGNOSTIC CRITERIA:**
All of the following:
- At least one of the following:
  1. Delusions
  2. Hallucinations without insight
- The disturbance causes clinical distress or impairment in social, occupational, or other relevant areas of functioning.
- The disturbance does not occur exclusively during the course of a delirium.
- The disturbance is not better accounted for by another mental disorder (e.g., mania).
EXCLUSIONS:
• Primary or drug-induced psychotic disorder unrelated to SLE (e.g., schizophrenia)
• Steroid psychosis or CNS infections (after the steroids are stopped, lupus psychosis get worse and confirms that it is lupus psychosis, and is not steroid psychosis. Steroid psychosis improves after stoppage of steroid)

19. SEIZURE AND SEIZURE DISORDER
Generalized and focal seizures are reported in 6-51% pts of SLE.
1. Primary generalized seizures
2. Partial or focal seizures

DIAGNOSTIC CRITERIA:
A. Independent description by a reliable witness
B. EEG abnormalities

EXCLUSIONS:
Seizure-like sign and symptoms or seizure from:
• Vasovagal syncope
• Cardiac syncope
• Hysteria
• Alcohol, drugs or, drug withdrawal
• Panic attacks, conversion disorders, and malingering

MANAGEMENT
• As a life threatening condition, NPL needs aggressive immunosuppression with high-dose glucocorticoids and cyclophosphamide, but vascular occlusive CNS insults are steroid-nonresponsive. Seizures require anticonvulsants. Antipsychotic drugs are instituted in behavioral disorders and psychosis. Mild cognitive disorder requires a low to moderate dose of steroids.
• After controlling the life-threatening condition, maintenance therapy is done with steroid and/or other immunosuppressants with careful attention to their side effects.

REFERENCES