Review Article

iMedPub Journals
www.imedpub.com

Medical & Clinical Reviews
ISSN 2471-299X

2025
Vol.11 No.1:076

Neuropsychiatric Lupus-Review and New Models for Its Classi ication and Diagnostic Approach

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Received date: September 28, 2023, Manuscript No. IPMCR-23-17960; **Editor assigned date:** October 02, 2023, PreQC No. IPMCR-23-17960 (PQ); **Reviewed date:** October 16, 2023, QC No. IPMCR-23-17960; **Revised date:** January 03, 2025, Manuscript No. IPMCR-23-17960 (R); **Published date:** January 10, 2025, DOI: 10.36648/2471-299X.11.1.076

Citation: Palacios SCD, Coronado MDLAA (2025) Neuropsychiatric Lupus-Review and New Models for Its Classification and Diagnostic Approach. Med Clin Rev Vol:11 No:1

Abstract

The objective of the study is to review current concepts about neuropsychiatric lupus, emphasizing new proposals for its diagnostic approach. An advanced search was carried out in the PubMed database to finally include and make an exhaustive review of 59 articles. The manifestations of Neuropsychiatric Lupus (NPSLE) have been described in a wide way and in a wide spectrum; at present it is known that some associations made previously do not actually have to do directly with the pathogenesis of Systemic Lupus Erythematosus (SLE), on the other hand we make a contribution in the review of the literature that we consider essential for clinicians, since have described new models and algorithms to objectively establish whether or not a patient has PNLL, advances have also been described in the discovery of new biomarkers and imaging techniques, especially nuclear magnetic resonance imaging, which can be decisive in the management and prognosis of patients affected by this sometimes forgotten entity.

Keywords: Lupus erythematosus; Systemic; Nervous system; Neuropsychiatric lupus, Biomarkers

Introduction

The involvement of the nervous system in SLE encompasses any level of the nervous system, and is not only due to pathogenic mechanisms mediated by the immune system but also eventually to the effects of therapy [1]. Therefore, the term “neurolupus” is quite broad and nonspecific and is sometimes used interchangeably to include neuropsychiatric manifestations, although it is worth clarifying that other authors include all of these manifestations in the so-called “Neuropsychiatric Lupus” (NPLES).

In 1999, the American college of rheumatology proposed the well-known definition of NPLES that is still in force, which covers manifestations in the Central Nervous System (CNS), peripheral, autonomic, in addition to psychiatric ones (**Table 1**), however there are new models that are proposed and that also provide a score that, through a score, establishes the probability of studying with SLENP [2].

Table 1: Clinical manifestation.

	Central nervous system	Peripheral nervous system
Diffuse manifestations	Delirium	-
	Anxiety	-
	Cognitive impairment	-
	Mood disorder	-
	Psychosis	-
Focal manifestations	Aseptic meningitis	Guillain barre
	Cerebrovascular disease	Autonomic disorders

	Headache	Myasthenia gravis
	Movement disorders	Neuropathy
	myelopathy	polyneuropathy
	Seizures	

On the other hand, in 2019, the League European Against Rheumatism and the American College of Rheumatology (EULAR/ACR) published new criteria for the classification of SLE, reporting a sensitivity of 96.1% and a speci icity of 93.4% with better performance compared to previous ones (sensitivity of 82.8% and speci icity of 93.4% (ACR-1997) (**Tables 2 and 3**) [3].

Table 2: Spanish adaptation of EULAR/ACR 2019 criteria for SLE.

Entry criteria	**ANA) titer ≥ 1:80 in HEp-2 cells or a positive equivalent test**
Additional criteria	Do not count the criterion if there is a more probable explanation than SLE.
	The appearance of a criterion on at least one occasion is sufficient, it is not necessary for the criteria to occur simultaneously.
	At least one clinical criterion and >10 points are required.
	Within each domain only the highest criterion is counted for the score.
Clinical and immunological criteria	*Classify as SLE with a score of 10 or more if the entry criterion is met.

Table 3: Clinical and immunological criteria.

Clinical criteria		**Immunological criteria**	
Constitutional		Antiphospholipid antibodies	
Fever	2	Anticardiolipin-O antibodies	
		Beta 2 antibodies	
		glycoprotein	
Hematological		or lupus anticoagulant	2
Leukopenia	3		
Thrombocytopenia	4		
autoimmune hemolysis	4		
Neuropsychiatric		Complement proteins	
Delirium	2	C3 low or C4 low	3

Psychosis	3	C3 low and C4 low	4
Seizure	5		
Mucocutaneous		SLE-specific antibodies	
Non-scarring alopecia	2	dsDNA antibodies or	
Oral ulcers	2	Anti-Smith antibodies	
Subacute cutaneous lupus	4		6
Acute cutaneous lupus	6		
Serous			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria > 0.5 g/24 h	4		
Class II or V lupus nephritis	8		
Class III or IV lupus nephritis	10		

Literature Review

An advanced search was performed in the PubMed database from 1990 to October 2021 including the following terms mesh (systemic lupus erythemathosus) AND (central nervous system) AND (biomarkers) obtaining 133 articles of which 74 results were excluded due to repeated articles, languages other than Spanish and English, full text not available and not relevant topic; to finally include and make an exhaustive review of 59 articles.

Epidemiology

In hospitalized patients with a diagnosis of SLE, neuropsychiatric manifestations can occur in up to 26% of cases; the most common are headache, cerebrovascular disease, acute confusional state, seizures and aseptic meningitis [4]. The risk factors that have been associated with the presence of these manifestations are the systemic activity of SLE and organ damage with high severity indices, serological activity and treatment with high doses of steroids; history of neuropsychiatric events, and the presence of persistently positive anti-phospholipid antibodies (anti-cardiolipins, anti-2 glycoprotein or lupus anticoagulant) [5].

Pathophysiology

The pathophysiology could be divided into two axes; that mediated by non-immunological mechanisms or triggers, among which are therapy with steroids and immunosuppressants that produces metabolic alterations such as hyperglycemia and uremia, in addition to infections in the central nervous system associated with opportunistic germs [5–7]. On the other hand, immunological mechanisms have been proposed to explain the pathogenesis in NPSLE, however several theories have been the subject of controversy; however, there are several aspects that have been documented, among them the most relevant are micro-infarcts in territories of small vessels, mainly in the cerebral cortex and brain stem. Associated with this, deposits of components of the classical pathway of the brain have been found. Complement such as C1q, C4d as well as those that are part of the membrane attack complex (C5b-9) with the consequent formation of microthrombi [8,9]. A minor association has been found in vasculitis with great endothelial proliferation and appearance of fibrin thrombi. A distinctive feature in which it is associated with NPSL is that in this case the involvement is more diffuse than focal, however it is rare. On the other hand, emboli can be generated that cause macroscopic infarctions, including hemorrhagic ones, secondary to Libman-Sacks endocarditis, which is associated with the presence of antiphospholipid antibodies [10].

In general terms, it could be concluded that focal manifestations could be related to a process of vascular occlusion, while in diffuse involvement (for example, psychiatric ones) the pathophysiological basis is associated with anti-neuronal antibodies, although in principle the antibodies can target the endothelium and trigger heart attacks. Other theories have to do with deficiencies in the recycling of nucleosomes from apoptotic cells due to C1q deficiencies, and this eventually triggers the production of autoantibodies in states in which there is an increase in this form of cell death such as infections. viral or exposure to sunlight among others.

Headache

57% of patients with SLE report some type of headache (migraine 31.7% and tension headache 23.5%), it has been documented that chronic tension headache is the most prevalent in SLE, which may be associated with a greater burden of anxiety and depression in patients; However, no mechanism has been identified to explain this symptom, nor an association between headache and the state of the disease, which is why; Its inclusion as a manifestation of SLE is a matter of debate [11]. Therefore, when performing the headache approach, it is recommended to rule out other causes, taking into account anamnesis, physical examination and complementary examinations, thus things in the algorithm proposed by Bortoluzzi, et al. This manifestation is not considered to establish the probability of suffering from NPSL [12].

Cerebrovascular disease

Strokes and TIAs occur in 5%-25% of patients with SLE, with a mean age of 37 years [10], with a higher incidence of ischemic stroke, TIA (>80%), intracranial hemorrhage (3%-5%) and venous sinus thrombosis (2%) [13], it has been described that strokes are related to a higher mortality rate in patients with SLE [14], who have between 1.5 and 3 times greater risk of suffering from a stroke compared to the rest of the population [15].

Cerebrovascular disease in SLE is explained by different mechanisms such as small vessel angiopathy, the production of inflammatory mediators, the formation of antibodies against phospholipid and ribosomal neuronal antigens, early atherosclerosis, thrombosis, embolism, dissection and vasculitis, in addition to factors that they do not depend on SLE such as age and comorbidities such as hypertension and diabetes mellitus [14]. Regarding secondary prevention in patients with SLE, it is indicated to reduce thrombotic events, although there is no clear evidence, hydroxychloroquine or chloroquine may be indicated in this scenario [16].

Seizures

Seizures occur in 14%-25% of SLE patients compared to 0.5%-1% in the general population, with generalized seizures being more common [10], it has been described that up to two-thirds of patients will present a seizure during the first year of diagnosis [17,18]. Furthermore, in patients with antiphospholipid antibodies, it has been documented that positivity against beta 2 glycoprotein antibodies confers 11 times more probability of presenting seizures, while the presence of lupus anticoagulant is associated with a lower incidence [19]; pro-inflammatory cytokines such as IL1, IL6, and TNF alpha have also been described, which activate the hypothalamic-pituitary-adrenal axis and generate a reduction in the seizure threshold [20]; some studies suggest a direct effect of antibodies on neurons, while others propose that it is due to ischemia or infarctions caused by thrombosis, embolism, hemorrhage or vasculopathy mediated by antiphospholipid antibodies that generate vascular occlusion. The paraclinics that can guide the diagnosis are: MRI, Electroencephalogram (EEG), and Cerebrospinal Fluid (CSF) analysis; MRI is the gold standard to detect reversible focal lesions, infarction, atrophy, intracranial hemorrhage and other CNS lesions that occur in SLE; Up to 42%of SLE patients have some EEG abnormality; regarding CSF analysis, it is useful to exclude CNS infection [17].

In relation to treatment The European league against rheumatism recommends that anti-epileptics not be started in patients with single or infrequent episodes. Patients with SLE mainly present seizures of focal onset, and if one of the risk factors for recurrence is corroborated (>2 unprovoked seizures in a 24 hours interval, evidence of brain lesions on imaging or epileptiform discharge on EEG, it can be initiate management with valproate and lamotrigine as second line therapy.

Aseptic meningitis

Less than 2% of patients with SLE develop aseptic meningitis, the clinical picture consists of fever, headache, meningeal signs; an increase in cellularity can be seen in the CSF, with mononuclear cells being predominant, and proteins are also elevated; however, there are several entities that produce similar findings. In addition, an association has been found between non-steroidal anti-inflammatory drugs, withdrawal of the drug leads to recovery [10]. The use of corticosteroids and supportive measures is indicated as treatment.

Depression, psychosis and delirium

Mood disorders should be considered as a primary disorder, as an event secondary to the clinical picture of SLE, or due to steroid therapy in the course of SLE. Depression has been documented as the most common mood disorder in SLE (10.8%-39.6%), with a prevalence 6 times higher than in the healthy population, where several factors influence such as iatrogenic effects of corticosteroids, diagnosis, disease activity, and concomitant neuropsychiatric disorders; Different biological changes have been proposed that can explain depression in SLE, among them is the dysfunction of the hypothalamic-pituitary-adrenal axis. In addition, autoantibodies such as anti-p Ribosomal Abs and anti-NMDA antibodies have been involved, which can cause lesions in the neurons of the limbic system and generate deterioration at the level of behavioral and emotional functions.

Psychosis in SLE can occur in up to 1%-2% and generally occurs within the first 3 years of the disease. It has been reported that more than 50% of cases occur in the first year after diagnosis of SLE manifesting with visual and auditory hallucinations that generate

deterioration in social, work or other areas of functioning. It can be explained by damage mediated by autoimmune deregulation where anti-phospholipid antibodies are involved, by metabolic alterations or secondary to medications.

As delirium appears as one of the rare psychiatric manifestations of SLE, it is a challenge to determine whether it is due to an exacerbation of the primary disease or a secondary cause such as CNS infection, metabolic disorder or adverse effect of corticosteroids; In addition, other manifestations of NPSL (aseptic meningitis, cerebrovascular accidents) may be associated with delirium. In the presence of changes in mental status, imaging should be considered, in addition to evaluating the possibility of infection in patients treated with immunosuppressive therapy.

Movement disorders

Movement disorders in patients with SLE have a low incidence, however it has been described that disorders such as parkinsonism, dystonia, tics, tremors may occur as one of the early signs of CNS involvement. The most frequent manifestation is chorea, which is characterized by involuntary, hyperkinetic movements with dance characteristics where any part of the body is involved; in SLE it has been associated with the presence of antiphospholipid syndrome where persistently elevated antiphospholipid antibodies, lupus anticoagulant, anticardiolipin antibodies and anti-beta 2 glycoprotein antibodies are evident. Two pathogenic mechanisms have been proposed, the first through ischemic-vascular pathway mediated by immune complexes and the second mediated by inflammation and neurotoxicity, orchestrated by complement activation, increased permeability of the blood-brain barrier, migration of autoantibodies, and the production of immune complexes and pro-inflammatory cytokines. Most patients present an episode of chorea that subsides over days to months and does not usually require specific treatment, although symptomatic management can be given with dopamine receptor antagonists.

Others (Myelopathy, peripheral nervous system disorders, cranial neuropathies)

Myelopathy has been described in 40%-50% of patients with SLE between 2 to 4 years after diagnosis, being associated with the positivity of anticardiolipin antibodies; the demyelinating disease is characterized by the appearance of focal inflammatory lesions in the cerebral white matter, which causes an alteration in the functioning of the nerve fibers in the neuronal pathways and produces neurological deficit and clinical disability depending on the location of the lesion.

Neuro-ophthalmological manifestation is optic neuritis, which occurs in up to 1% of patients with SLE. The condition is characterized by a sudden loss of vision, generally with a central scotoma, and pain when making eye movements. The physical examination revealed a relative afferent pupillary defect and papillitis.

Mononeuritis multiplex, Guillain Barre syndrome, chronic inflammatory polyneuropathy, and myasthenia gravis have been described among them [10]. Electrophysiological evaluation of the peripheral nerves of patients with SLE suggests that peripheral neuropathy occurs in approximately 10% of patients, where axonal neuropathy is evident in 70% and signs of demyelination in 20% of patients, presenting mainly in lower limbs asymmetrically, having a negative impact on the patient's quality of life.

Diagnosis

Due to the wide spectrum of manifestations in NSPLE, diagnosis is challenging. With this review we intend to emphasize the most important aspects of this process; thus, the anamnesis and physical examination focused on the neurological system are always the fundamental mechanisms [10]. Then it is necessary to rule out infectious metabolic causes and primary (psychiatric) causes. Therefore, the following paraclinical tests are recommended in the initial evaluation (**Table 4**).

Table 4: Initial evaluation.

Rule out secondary causes	HIV serology, VDRL, B Hepatitis
Immunological tests	C3, C4, ANA, anti-DNA anti-ENA
Related autoantibodies	Anti-ribosomal antibodies
	Anti N-Methyl-D-Aspartate (NMDA) antibodies
	Antineuronal antibodies
	Antiganglioside antibodies
Cerebrospinal fluid study	Rule out infections
Others	Neuroimaging (Brain MRI), EEG, neuropsychological tests, echocardiogram, carotid Doppler

Note: HIV: Human Immunodeficiency Virus; ANA: Antinuclear Antibodies; ENA: Extractables from the Nucleus, MRI: Magnetic Resonance Imaging, EEG: Electroencephalogram

Serology

An important pillar for diagnosis is serology, the initial studies are shown in the aforementioned **Table 4**, these are intended to rule out secondary causes, on the other hand the complement and anti-DNA levels are useful to evaluate lupus activity [7], it has been described that autoantibodies in the nervous system, both systemic and cerebral, have poor specificity, are also polyclonal and directed at multiple targets [10]. Within these autoantibodies, the anti-p Ribosomal Abs, the anti-NMDA antibodies, stand out; however, others such as anti-endothelial and anti-neuronal have also been associated. It should be remembered that these Abs are related to inflammation, and it is also accepted that they are generally produced peripherally and cross the blood-brain barrier. It has also been established that they explain the diffuse involvement of the disease.

Anti-P-ribosomal Abs are associated with psychosis in many series of cases. They are usually detected by ELISA and are found in cerebrospinal fluid and serum. Regarding anti-NMDA antibodies, it must be said that their target is the NR2 subunit of the NMDA receptor, the latter being mainly found in the amygdala, anterior hypothalamus and hippocampus, has been associated with cognitive and mood disorders. Other Abs, such as anti-endothelial antibodies, have less clear evidence but in some studies they have been associated with psychotic episodes, anti-endothelial antibodies have been associated with psychosis and depression, and anti-aquaporin 4, which is found in astrocytes and the glia and are associated with neuromyelitis optica, but there are studies that show their presence in patients with SLE and in demyelinating disorders of the neuromyelitis optica spectrum.

Discussion

New biomarkers

neuroinflammation have been documented, such as Lipocalin 2 (LCN2), which is an iron transporter with an important role in innate immunity, Osteopontin (OPN), a glycoprotein that is believed to be involved in B lymphocyte apoptosis decreases after treatment.

Due to an increase in the permeability of the Blood-Brain Barrier (BBB), the CSF levels of some molecules may be related to its dysfunction, including albumin, haptoglobin and β-2 microglobulin, as well as also the CSF/serum ratio of α−2 macroglobulin. In serum, a calcium binding protein called S100B that is produced in astrocytes is a reflection of dysfunction in the BBB; also some brain neurotrophic factors involved in cognitive processes could play a similar role.

Images

Magnetic Resonance Imaging (MRI) can show some finding in 50% of patients with NPSLE, some advanced techniques such as morphometry, diffusion-tensor imaging, and white matter hypersensitivity volumetry in MRI, may have an important role. Findings that can be found more precisely using these techniques with brain atrophy or expansion, cortical thinning, and identifying hypersensitive lesions in the white matter.

New diagnostic models

New models to classify the probability of presenting with NPSL have been designed and validated for research and for use in the clinician's work. Among these, we highlight that of Bortoluzzi, et al., in which it is based on the premise that SLENP is a diagnosis of exclusion, using an algorithm that provides a probability score, ranging from 0 to 10. This algorithm considers four items, three of which were similar to those used by the ACR. The items include the temporal relationship of neuropsychiatric events with the diagnosis of SLE, the recognition of confounding factors, the presence of minor or common neuropsychiatric events and the presence of SLE risk factors suggested by the EULAR (active SLE and the presence of anti-phospholipid antibodies). Based on the probability score generated, patients are considered to experience non-neuropsychiatric events (score <3), undefined events (score between 3-6), or neuropsychiatric events attributable to SLE (score >6) (**Table 5**) [12].

Table 5: Diagnostic model.

	Score
Item 1: Time of onset of LESNP with respect to the clinical onset of SLE	
Before (>6 months before the onset of SLE)	0
Concomitant (Within 6 months of SLE onset)	3
After (>6 months after SLE onset)	2
Item 2: Minor or non-specific events of LESNP according to the definition of Ainiala, et al*.	

Present (minor or common events as proposed by Ainiala, et al.)	0
Absent (LESNP events other than those proposed by Ainiala, et al.)	3
Item 3: Confounding factors or associations not related to SLE as defined by the ACR glossary**	
None or not applicable	2
Present (a confounding factor)	1
Present (more than one confounder)	0
Item 4: Additional or favorable factors	
None or not applicable	0
Present (an additional or favorable factor)	1
Present (more than one additional or favorable factor)	2
Interpretation: score <3: no NPLES, 3-6: undefined, >6 NPLES events	
Note: *Minor or common events (events that occur frequently in the non-SLE population): Headache, anxiety, minor depressive disorder, mild cognitive impairment, polyneuropathy without electrophysiological confirmation. **ACR 1999 glossary.	

Another contribution in this sense is that of Magro-Checa et al., which involves a battery of neuropsychological, laboratory and radiological examinations performed by a multidisciplinary team of rheumatologists, neurologists, psychiatrists and specialists in vascular medicine. In this model, confirmation of neuropsychiatric events attributed to SLE was dependent on follow-up reevaluation, as 13.8% of neuropsychiatric events were initially misclassified. Both Bortoluzzi et al., and Magro-Checa et al., concluded that diffuse and minor neuropsychiatric events attributed to SLE were difficult to determine in their models, and noted persistent challenges in developing attribution models for NPSLE.

Conclusion

NPSLE is an entity with a pathophysiology that is not entirely clear; it involves various manifestations in the central and peripheral nervous system. Recent models have identified potential screening modalities, including screening tools and biomarkers, and novel therapeutic approaches, that may improve diagnosis and treatment. MRI images and special techniques are powerful tools that show structural differences, however more studies are required that include a large enough sample to validate these changes. Despite the enigmatic nature of the LESNP, these contributions have allowed us to better understand the behavior of this entity and open new perspectives in its study.

Conflict of Interest

There is no conflict of interest on the part of the authors.

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