

NOVEL INFORMATION ON NEUROPSYCHIATRIC LUPUS ERYTHEMATOSUS

Thozama Dubula¹, Lourdes de Fátima Ibañez Valdés², Humberto Foyaca Sibat^{3*}

¹MBChB, FRCP Rheumatology, Ass Professor, HOD, Department of Internal Medicine and Therapeutic and Division of Neurology. Nelson Mandela Academic Hospital. Walter Sisulu University. Mthatha, South Africa.

²MD, MSc, FRCP, Sen Lec, Ag Res Inv., Department of Internal Medicine and Therapeutic and Division of Neurology. Nelson Mandela Academic Hospital. Walter Sisulu University. Mthatha, South Africa.

³MD, MSc, PhD, Full Professor, FCP, FRCP, FResInv, Department of Internal Medicine and Therapeutic and Division of Neurology. Nelson Mandela Academic Hospital. Walter Sisulu University. Mthatha, South Africa.

*Corresponding author: Humberto Foyaca Sibat, humbertofoyacasibat@gmail.com

ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is classified as an immunological condition presenting a wide spectrum of symptoms and signs affecting several system and organs, such as kidneys, blood cells, skin, nervous system, joints, and different membranes

Objectives: To search for novel information on autoantibodies and pathogenesis of SLE.

Methods:

A large search of the articles published in SCOPUS, and MEDLINE to identify manuscripts related to NPSLE. From 01st, January 1990 to 30th, January 2026, we comprehensively review the medical literature and selected the following issues: "systemic lupus erythematosus" OR "neurolupus" OR "neuropsychiatric SLE" OR "lupus cerebritis" OR "autoantibody", OR "CNS lupus" OR "neurological manifestations of SLE".

Results: After searching the medical literature, 297 articles were retrieved. We removed 189 duplicated titles and abstracts; 108 articles were selected. Based on applied inclusion/exclusion criteria 53 manuscripts were removed; therefore, 35 studies investigated the role of autoantibodies on the pathogenesis of NPSLE

Conclusions: We hypothesised that those cerebellar features are a consequence of combined vascular dysfunction and autonomic damage of the cerebellar neurons locate at the cerebellar cortex mainly stellate, basket, candelabrum and Lugaro cells with an associated partial pyramidal tract lesion to explain the hypertonia. As far as we know, this is the first case presenting NPSLE characterized by an atypical global cerebellar syndrome reported in the Medical Literature.

The most important elements involved in the pathogenesis of NPSLE are apoptotic debris, INF-alpha production, interleukin 21, B cell expression, CD40L, and helper T cell.

KEYWORDS: Systemic lupus erythematosus, neuropsychiatric SLE, autoantibodies, neurological manifestations of SLE, lupus cerebritis.

INTRODUCTION

SLE is classified as an immunological condition characterised by a affecting multiple system and organs, such as nervous system, renal system, blood components, skin, joints, and serous membranes [1]. Other authors reported that SLS is most seen in young females, with a 9:1 women-to-men ratio [2]. Most cases of SLE are observed in people of Hispanic, African, and Asian origin. At the same time, other ethnic and socioeconomic factors show quite different patterns, although many patients arrive from areas with reduced access to healthcare [3].

Many broad-spectrum autoantibodies play a crucial role in the pathophysiology of SLE by targeting cytoplasmic, nuclear, and cell-surface antigens [4], facilitating the formation of immune elements, tissue swelling, and complement expression [5]. Therefore, to confirm the diagnosis of SLE, it is mandatory to detect the specific autoantibodies mentioned in the 2019 EULAR/ACR classification criteria [6]. Other authors have shown that the clinical features of SLE are associated with specific autoantibodies [7]. These autoantibodies are essential to disease pathogenesis, contribute to immune complex formation and organ damage, and serve as essential diagnostic and prognostic markers [8].

SLE damage the brain in around 20–40% of lupus patients [9]. It most often occurs in females between the age of 20 to 50 years olds [10, 11]. Neurological sequela can be due to either focal medical conditions relating to unknown aetiology or cerebrovascular disease [12].

In 2022, Gros *et al.* reported a 42-year-old lady presenting a two associated connective tissue disorder such as SLE/systemic sclerosis (SSc) and acute renal failure presenting Raynaud's phenomenon, arthritis, synovitis, myalgias, telangiectasia, higher cerebral functions (delirium, obnubilation-neurolupus), malignant raised arterial pressure, PRES and esophagitis associated to positive anti-Sm antibodies, anti-RNP (1/5120), antinuclear antibodies, and anti-DNA; treated with Nicardipine, Urapidil, peritoneal dialysis, low-dose corticosteroids, Hydroxychloroquine, Methotrexate and Rituximab which were stopped due to the risk to get COVID-19 infection [13].

On the other hand, many manifestations of SLE (organ and serologic), including lymphocytosis-driven dermatological disorder, kidneys, and CNS, and anti-dsDNA antibodies, can be reproduced in a lupus murine model in which the disease is progressive [14].

Pagkopoulou et al. reported that SLE cases exhibit classical blood markers, like anti-Sm antibodies, ANA (antinuclear antibodies), and anti-dsDNA antibodies. However, a new confirmatory set of antibodies was delivered as a diagnostic cornerstone for SLE, such as antiphospholipid antibody, anti-nucleosome antibodies (ANuA), anti-C1q, anti-cytokine antibodies and anti-ribosomal P because their capacities to be associated to specific phenotypes, specific organ involvement, predict flares and disease activity under the long-lived plasma cell expression and B cell tolerance failure [8].

To confirm the diagnosis of SLE, apart from clinical features, along with specific autoantibody positivity, should be documented, despite the diagnostic challenge, because clinical features are frequently vague, insidious in onset, and not all can be observed simultaneously. We hypothesised that the most used laboratory investigations for screening SLE can be nonspecific and can identify many other conditions, even in healthy people. However, the actual classification criteria used for SLE, might helpfully guide its use in assessing clinical manifestations and investigation findings [15]. Still, it's remarkable relevant to keep in mind that they are not diagnostic criteria up to date.

In 2024, Saffioti *et al.* reported a case presenting an infrequent type of Whipple disease, with cord involvement as isolated transverse myelitis, treated with immunosuppressive therapy for SLE [17].

The 3'–5' DNA exonuclease activity is an important function in DNA replication and repair. It allows DNA polymerases to remove nucleotides from the 3' end to the growing DNA strand, which helps to correct errors made during nucleotide incorporation. However, a meta-analysis of published studies by Rioux and colleagues found no association among SLE and *TREX1* risk variants in their series [18].

2. MATERIALS AND METHODS

A large search of the articles published in SCOPUS, and MEDLINE to identify manuscripts related to NPSLE. From 01st, January 1990 to 30th, January 2026, we comprehensively review the medical literature and selected the following issues: "systemic lupus erythematosus" OR "neurolyupus" OR "neuropsychiatric SLE" OR "lupus cerebritis" OR "autoantibody", OR "CNS lupus" OR "neurological manifestations of SLE".

3. RESULTS

3.1. Literature Search

After searching medical publications, 297 articles were retrieved. We removed 189 duplicated titles and abstracts; 108 manuscripts are chosen. After assessing the inclusion/exclusion criteria 53 publications were removed; finally, 35 articles investigated the role of autoantibodies related to the pathogenesis of NPSLE

CASE REPORT

14-year-old lady presenting with fever, dry cough, loss of energy, photosensitivity and weakness of the proximal muscles for 3 days. She had associated depigmented skin lesions involving the face, scalp, neck, hands and feet. She was diagnosed with systemic lupus erythematosus and dermatomyositis a year ago (03/2025) when she presented with skin rash, proximal muscle weakness, loss of energy and fever. Her current treatment included mycophenolate mofetil 750mg bd, chloroquine 200mg daily 5/week, prednisone 5mg daily, paracetamol 1g bd. Clinical examination revealed a sick looking young lady, pale, not oedematous, no lymphadenopathy. Her vital signs were as follows: BP121/82, P 97/min, Oxygen sats on room air 99%. She had right basal crepitations with mild respiratory distress, with normal cardiovascular and abdominal examination. Neurological examination revealed bilateral intentional tremors with no other neurological fallout or features of cerebellar disorder.

Results of initial investigations were as follows:

U&E: 135/4.3/104/19/3.8/52

WHP: 11.36/ 9.9 (100.6/29.1)/ 176

LFT: 56/25/9/942/175/174/468 (TP/Alb/Bili/AST/ALT/GGT/ALP)

CRP 24/ESR 42/ CK 648/ C3 0.50/C4 0.05/ Urine prot:crea ratio 0.069

Urine microscopy: granular casts, leucocytes 16 000/HPF

Blood culture: gram positive cocci, grew coagulase negative staphylococci

An assessment of sepsis with lung and possible renal involvement leading to flare of SLE in the form of cutaneous vasculitis and lupus nephritis was made.

Initial treatment included:

Solumedrol 500mg IV daily for 3 days followed by prednisone 50mg daily orally – for a possible lupus nephritis

Ceftriaxone 1g IV bd for 5 days for possible pneumonia

Mycophenolate mofetil and chloroquine were continued

Topical steroids were added after dermatology review for cutaneous vasculitis lesions

Fluconazole 200mg orally daily for 5 days for oral thrush

Two days after commencing solumedrol, the patient developed worsening tremors,

drowsiness, cerebellar dysarthria, mild spasticity in the upper limbs with normal reflexes, horizontal vestibular nystagmus, abnormal postural reflexes, positive rebound response, ataxic gait, positive Romberg test falling forward, and bilateral dysidiadokinesia. An assessment of cerebellar dysfunction possible from an infective process or neuropsychiatric lupus was made. A computed tomography of the brain revealed diffuse cerebral oedema with no infarcts. A lumbar puncture which was performed revealed a CSF opening pressure of 30 cm of water, no cells, protein 0.44, glucose 2.2. ADA 0.4.

Antibiotic therapy escalated to meropenem 1g 8 hourly IV, prednisone tapered to 5mg over a week and mycophenolate dose reduced to 500mg bd orally.

Her level of consciousness deteriorated, and she developed worsening respiratory distress with new chest infiltrates on chest Xray. She succumbed to her illness 24 days after admission from sepsis and active disease.

COMMENTS AND FINAL REMARKS.

Our patients present a global cerebellar syndrome with clinical manifestation of Archi-paleo and neo cerebellum with mild spastic hypertonia on both upper limbs no related to the cerebellar dysfunction. We hypothesised that those cerebellar features are a consequence of combined vascular dysfunction and autonomic damage of the cerebellar neurons locate at the cerebellar cortex mainly stellate, basket, candelabrum and lugaro cells with an associated partial pyramidal tract lesion to explain the hypertonia.

After a comprehensive search of the medical literature, we identified thirty-five investigations on the role of autoantibodies related to the pathogenesis of NPSLE. We documented our hypotheses on the role played by autoantibodies on pathogenic mechanism of NPSLE.

In the past, when SLE affected the brain, it's named "neurolupus", "lupus cerebritis", or "CNS lupus" despite none those names certainly encompass the types of neuropsychiatric (NP) syndromes caused by SLE. Now it's universally accepted that when SLE attack the nervous system causing neuropsychiatric (NP) manifestations, it is nominated NPSLE and its clinical features can be focal or diffuse and it can be rather challenging to diagnose [19]. In 1999, other authors reported case definitions and standard nomenclature for NPSLE syndromes which include CNS (12) and PNS (7), syndromes [20]. **See Table 1**

TABLE 1

Focal			
Central Nervous System	Investigations to be performed		
Stroke	Echocardiogram, ECG, MRA, Doppler techniques and CSF studies.		
Demyelinating Disorders	MRI and CSF investigations for multiple sclerosis		
Aseptic Meningitis	LP and MRI		
Headaches			
Myelopathy	CSF analysis and Gad-enhanced MRI		
Seizure Disorder	CSF,	MRI,	EEG
Movement Disorders: Chorea	MRI		
Peripheral NS	Investigations to be performed		
AIDP	EMG, NCV, EMG, CSF studies		
Myasthenia Gravis	CT chest and neck exclude thymoma/thymic hyperplasia, thyroid disease, AChR, MuSK, and LRP4 antibodies.		
Autonomic Disorder			
Plexopathy	NCV, EMG, MRI		
Polyneuropathy	EMG and NCV		
Mononeuropathy (Single or Multiplex)	EMG, NCV		
Cranial Neuropathies	MRI		

NPSLE include many neurologic (epileptic seizures) and psychiatric (psychosis) symptoms typically present within the first year after its diagnosis (early onset) [20]. NPSLE affects more the CNS (93.1%) than the PNS late-onset (6.9%) [21].

The most often NP syndromes seen at the clinical setting are headaches, mood disorders, and mild cognitive dysfunction in an occurrence rate around 10–20% [22]. **See Table 2**

TABLE 2

Diffuse	
Central NS	Investigation to be performed
Acute Confusional state	CSF studies and MRI to ruled out associated infections
Disorders of Mood	Psychiatric assessment
Anxiety	
Psychosis	Psychiatric evaluation
Cognitive dysfunction	Neuropsychiatry testing

Other quite often neuropsychiatric syndromes include cerebrovascular disease, seizures, and anxiety while uncommon presentations include peripheral nerve disease, psychosis, delirium, and cognitive dysfunction and uncommon ones may be mononeuritis multiplex, demyelinating syndrome, involuntary movement, cranial neuropathy, aseptic meningitis, Guillain-Barre syndrome, autonomic disorders, plexopathy, and postsynaptic neuromuscular junction disorders [22].

The focal neuro-syndromes included headaches due to tension-type headache, migraines, lupus headache and idiopathic intracranial hypertension), chorea, aseptic meningitis, seizure disorders, cerebrovascular disease, demyelinating syndrome and non-compressive myelopathy [23]

Acute-onset chorea is an uncommon NP initial manifestation of SLE and its quite often associated with positive antiphospholipid antibodies which frequently respond very well to immunosuppressive therapy. Medeiros *et al.* reported a 20-year-old lady presenting an acute onset hemichorea and fever [24].

Other authors reported a 41-year-old woman complaining of dyspnoea with a generalized myxoedema, alopecia, and an acute polyradiculoneuritis associated to SLE responding to corticosteroid and cyclophosphamide boluses [25].

Ischemic stroke secondary to vasculitis is a quite common neurologic condition seen in SLE cases, typically within the first five years of onset. Ischemic stroke can be associated to acquire thrombophilia cause by hypercoagulable state due to antiphospholipid syndrome but related to Lipman-Sack endocarditis, and accelerated atherosclerosis [26].

As a member of the aetiological group of acquired thrombophilia, antiphospholipid syndrome (APS) is known as autoimmune condition typically associated to specific antibodies such as anti-cardiolipin IgM and IgG, antiphospholipid antibodies (APLAs)— anti-beta2glycoprotein IgM and IgG, and lupus anticoagulant—which are able to create a hypercoagulable state, leading to arterial and venous thrombosis, recurrent abortion and other manifestations. On the other hand, APLS is closely involved in the pathogenesis of ischemic stroke, cerebral venous sinus thrombosis, cognitive disorder, venous thromboembolisms, polyneuropathy, and movement disorders plus other conditions like livedoid vasculopathy and obstetric complications [26, 27].

Non-recurrent epileptic seizures are more common than secondary epilepsy due to SLE expression at the early stage of the process [28].

Around 50% of SLE cases qualify for NMOSD. Therefore, if patients present symptoms or signs such as cytopenias, rashes, or glomerulonephritis, then the first differential diagnosis must be SLE until proven otherwise [29].

In some patients presenting SLE, a comorbidity of posterior reversible encephalopathy syndrome and progressive multifocal leukoencephalopathy have been reported [30]

All NPSLE clinical manifestations are close associated with CNS-reactive autoantibodies, including those directed to glutamatergic NMDA receptor [31].

Lesions in the white matter and cortical atrophy are quite often in cases with NPSLE, [32].

The commonest presentations of focal peripheral nervous system (PNS) syndromes are represented in **FIGURE 1** (which include peripheral nerve disease like polyneuropathy (Pn), single or multiplex mononeuritis, monoradiculopathy (Mr), Guillain-Barré syndrome (AIDP), autonomic disorders (AuDi), MG, cranial neuropathies (CN), and plexopathy (Px) [33, 34].

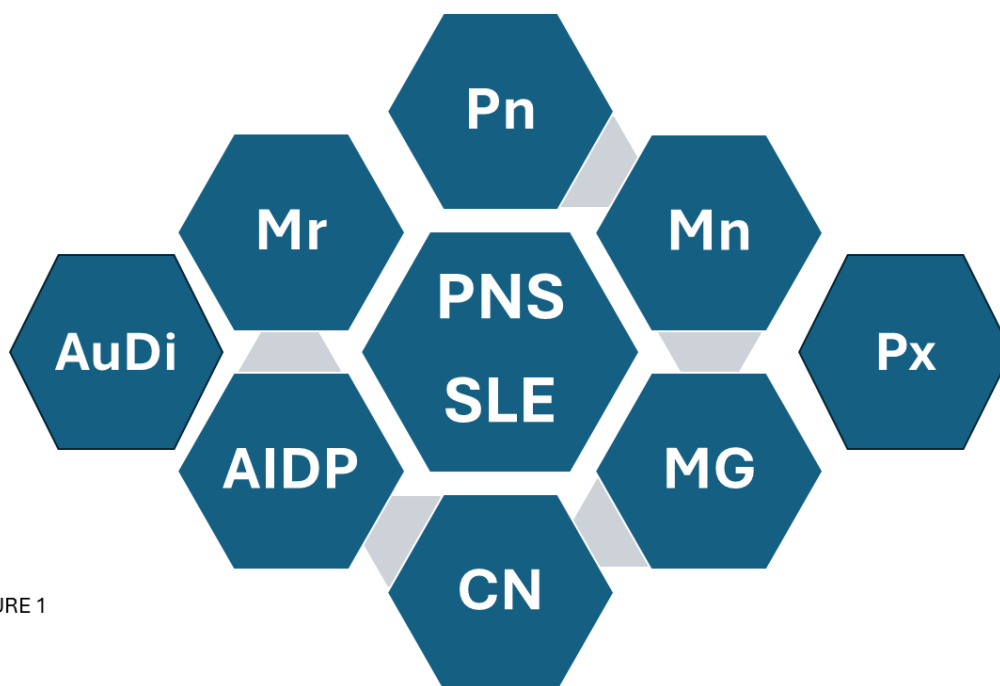


FIGURE 1

FIGURE 1: List of the medical conditions related to SLE affecting the peripheral neuropathy system and neuromuscular junction: CN: cranial neuropathy, AIDP: acute inflammatory demyelination polyneuropathy, MG: myasthenia gravis, AuDi: autonomic disorders, Mr: monoradiculopathy, Mn: mononeuropathy, Pn: polyneuropathy.

Being PN the commonest presentation followed by cranial nerves disorder, single or multiple mononeuritis usually associated to livedo reticularis, arterial hypertension and higher disease expression and occurrence [35].

AIDP is most commonly present as flaccid ascending paralysis and the cranial nerve lesions (III, V, VI, and VII) are quite frequently seen in SLE cases including small fiber peripheral neuropathies [36].

Diffuse CNS syndromes include an anxiety disorder, cognitive impairment, acute confusional state, mood disorders, and psychosis. Around 14-95% of cases present mild-to-moderate cognitive impairment. Notwithstanding, marked cognitive dysfunction is only seen in 3-5% of SLE cases while progressive cognitive decline is extremely uncommon. However, cognitive impairment, psychosis, and depression are closely associated with the presence of many Ab, like anticardiolipin despite none of them have been proven to be certain for confirmation of final diagnosis [37, 38].

The most affected higher cerebral functions in SLE are executive function, memory, visual and verbal disturbances, attention disorder plus decreased psychomotor activities.

Psychosis is usually observed either within three years of SLE onset or in the year prior. Events associated with lupus psychosis are preceded by SLE NP situations mainly in African young male patients [39].

At this point is good to clarify that some common clinical conditions such as depression, anxiety, headaches, and mild cognitive impairment can be present but do not always reflect overt CNS lupus expression.

NPSLE is a great diagnostic challenge due to none of the before-cited clinical manifestations are specific of SLE and due to the scanty of biomarkers for confirmatory diagnosis or lack of pathognomonic MRI findings. Therefore, final diagnosis might be based on expertise of well recognised expert or high skilled professional's criteria.

The most relevant risk factor for NPSLE is graphically represented in **FIGURE 2** and include previous marked NPSLE events, disease activity, male sex, and positive APLAs which have been supported by other authors [40, 41]. See **FIGURE 2**

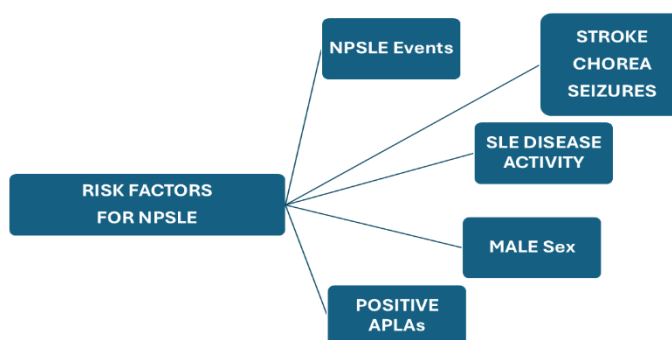


FIGURE 2

FIGURE 2: Here we represented the most relevant risk factor for NPSLE including previous NPSLE events, generalized SLE disease activity, male sex, and positive APLAs.

In 2024, Medina and colleagues performed a descriptive cross-sectional study applying a Montreal Cognitive Assessment (MoCA test) into a group of SLE cases looking for cognitive deficits as manifestations of neurolupus attending a third-level hospital and they found 16% of presence of cognitive deficits as neuropsychiatric syndrome associated to SLE [42].

Elevate IL-6 levels is associated to microglial activation in the hippocampus (memory and emotion) of NZB/W-F1 lupus animal an associated behavioural disturbance [43].

As cited before, interleukin-6 is the most often elevated biomarkers of NPSLE apart of increased CSF levels of autoantibodies [44-46] and nitric oxide [47].

In patients with NPSLE, the microglia and protoplasmic astrocytes are crucial regulators of CNS inflammation and neuronal metabolism [48].

In lupus mice, high rates of microglial phagocytosis of synapses (fundamental signaling connection between neurons) have been confirmed [49].

Other authors reported that in lupus, microglia and distortional genetic signature leads degeneration of the nervous system in cases with NPSLE [50], while in similar patients' increased levels of glial fibrillary acidic protein (CSF) have been confirmed [51]. On the other hand, cognitive deficit (CD) is a neuropsychiatric syndrome associated with SLE [52]

NPSLE is accompanied by a broad range of symptoms which require imaging investigations, laboratory testing, neuropsychological evaluations and multidisciplinary approach with multiple assessments to confirm the final diagnosis. The main therapy for NPSLE cases is based on management of clinical manifestations through anti-thrombotic therapies and immunosuppressive drugs [23].

Other authors have reported that disruption of cerebrospinal fluid-blood barrier and BBB in NPSLE cases present high concentrations of intrathecal albumin in the intrathecal space [53-55].

In 2024, Reynolds and collaborators described some of the higher brain functions like memory, cognition, affective emotional burdens, depression, and anxiety as common manifestations seen in patients presenting NPSLE with increased levels of interleukin-6 (inducing loss of sucrose) related to neuroinflammation [12, 56] and neurotoxic glial cells expression in the brain. Neuropsychiatric features can appear before clinical manifestations and diagnosis of SLE [57].

Sans-Pola and collaborators documented a series of patients with SLE with extrarenal disease activity treated with off-label rituximab and found that cases NPSLE, thrombocytopenia, and dermatological lupus responded better compared with those with joint disease [12, 58]

Brief comments on pathophysiology of autoantibodies in SLE.

The most remarkable elements participating in the pathophysiology of SLE are: dysregulation of interferon (IFN) type I signaling, breakdown of B-cell tolerance, apoptotic clearance, and dysfunctional T-cell help plus epigenetic modifications, neutrophil extracellular trap (NET) creation, genetic susceptibility and complement pathway dysfunction [59-61].

These pathogenic processes include a sustainable autoimmune presence and sustainability of pathogenic autoantibodies. Nevertheless, elaboration of autoantibody is a consequence of complex disruptions in both adaptive and innate immunological response. On top of that is the B-cell tolerance breakdown, both in peripheral tissues and the bone marrow, leading to the expression and survival of reactive B-cells [62].

The before cited, expressed B cells provide affinity maturation and somatic hypermutation in germinal centres, producing high-affinity, class-switched autoantibodies [63]. See **FIGURE 3**

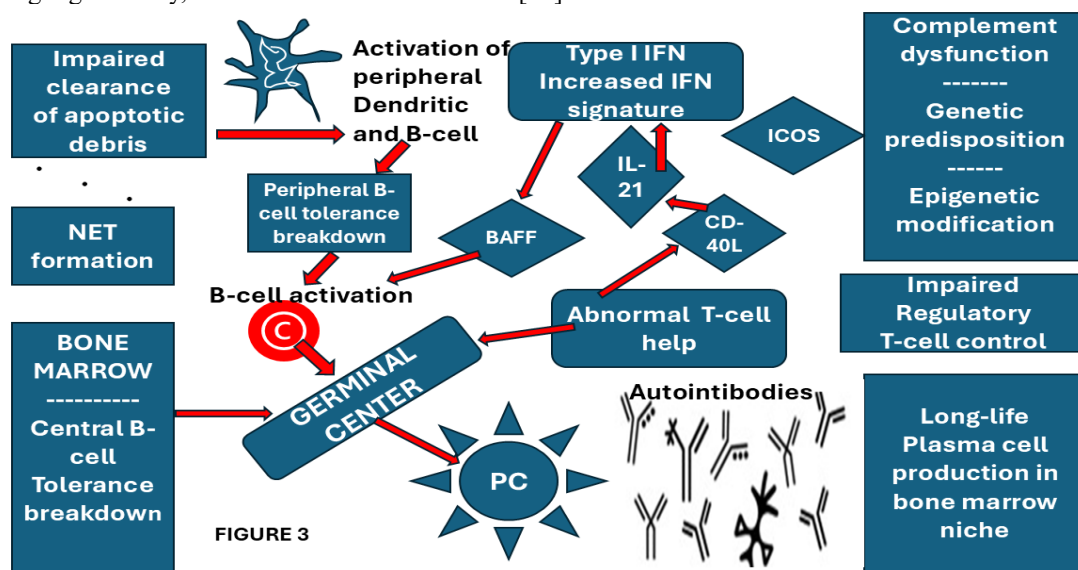


FIGURE 3: Pathophysiologic mechanism of antibody production in SLE. Key events include defective apoptotic debris clearance, neutrophil extracellular trap (NET) formation, and dysregulated type I interferon signaling, which stimulate plasmacytoid dendritic cells and autoreactive B cells via TLRs.

Lack of clearance of the apoptotic debris is an early process in pathogenesis of SLE leading to intracellular autoantigens like histones, nucleosomes, and ribonucleo-proteins, to remain extracellularly and to be identified as immunogens [64].

High expression of the before cited receptors encourages IFN production, mainly IFN- α [65]

In SLE patients, B cells can show several abnormalities such as elevated survival signaling via B cell-activating factor (BAFF), elevated activity of CD40, CD80, and resistance to apoptosis [66]

These elements allow the differentiation into plasma cells and the expansion of autoreactive clones which release pathogenic autoantibodies [67].

Furthermore, T lymphocytes lead abnormal modulation of the B-cells via inducible T-cell costimulatory, enhanced activity of interleukin-21, CD40L, germinal center reactions, generation of plasma cells and memory B cells [68]. Other implicated factor in the pathophysiology of NPSLE is the high production of autoantibodies caused by defective regulatory T cells and dysregulated follicular helper T cells [69].

One of the reasons to explain the higher prevalence of SLE in female compared with male patients is related to the X-chromosome which harbours several immune-related genes, such as CD40L, and TLR7 that can escape from X-inactivation and be over expressed in ladies [70, 71].

We hypothesised that another explanation can be based into estrogenic activity in female which can regulate immune responses through increasing BAFF activity, leading B cell survival, and seeking T cell responses addressee to Th2 phenotype, favouring maintenance and autoantibody production as has been cited during periods of hormonal fluctuation like pregnancy and puberty which were proposed by other investigators [72]. Therefore, after revising all available publication we concluded that most important elements involved in the pathogenesis of NPSLE are apoptotic debris, INF-alpha production, B cell expression, CD40L, interleukin 21 and helper T cell. However, forthcoming well designed investigations must be performed to confirm or modified our hypotheses.

CONCLUSION

As far as we know, this is the first case presenting NPSLE characterize by an atypical global cerebellar syndrome reported in the Medical Literature.

The most important elements involved in the pathogenesis of NPSLE are apoptotic debris, INF-alpha production, interleukin 21, B cell expression, CD40L, and helper T cell.

ACKNOWLEDGMENT

To thanks to Dr Sibi Joshep for his collaboration on the management of our case series

Ethics Statement:

The current review does not qualify for Ethical Approval

Patient Privacy:

All information related to identification of patients were removed to provide complete anonymity.

Conflicts of Interest:

Authors report no conflicts of interest

REFERENCES

1. Tsokos G.C., Lo M.S., Reis P.C., Sullivan K.E. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat. Rev. Rheumatol.* 2016; 12:716–730. doi: 10.1038/nrrheum.2016.186.
2. Rahman A., Isenberg D.A. Systemic lupus erythematosus. *N. Engl. J. Med.* 2008; 358:929–939. doi: 10.1056/NEJMra071297.
3. Barber M.R.W., Drenkard C., Falasinnu T., Hoi A., Mak A., Kow N.Y., Svenungsson E., Peterson J., Clarke A.E., Ramsey-Goldman R. Global epidemiology of systemic lupus erythematosus. *Nat. Rev. Rheumatol.* 2021; 17:515–532. doi: 10.1038/s41584-021-00668-1.
4. Dema B., Charles N. Autoantibodies in SLE: Specificities, Isotypes and Receptors. *Antibodies.* 2016; 5:2. doi: 10.3390/antib5010002.
5. Holers V.M. Systemic lupus erythematosus as the paradigm for understanding the complex immune relationships and therapeutic opportunities for targeting complement in autoimmune diseases. *Immunobiology.* 2025; 230:152915. doi: 10.1016/j.imbio.2025.152915.
6. Aringer M., Costenbader K., Daikh D., Brinks R., Mosca M., Ramsey-Goldman R., Smolen J.S., Wofsy D., Boumpas D.T., Kamen D.L., et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol.* 2019; 71:1400–1412. doi: 10.1002/art.40930.
7. Abraham M., Derk C.T. Anti-ribosomal-P antibodies in lupus nephritis, neuropsychiatric lupus, lupus hepatitis, and Chagas' disease: Promising yet limited in clinical utility. *Rheumatol. Int.* 2015; 35:27–33. doi: 10.1007/s00296-014-3058-3.
8. Eleni Pagkopoulou, Charalampos Loutradis, Maria Papaioannou, Maria Daoudaki, Maria Stangou, Theodoros Dimitroulas. Autoantibodies in Systemic Lupus Erythematosus: Diagnostic and Pathogenic Insights. *J Clin Med.* 2025 Aug 12;14(16):5714. doi: 10.3390/jcm14165714.

9. Kivity S, Agmon-Levin N, Zandman-Goddard G, Chapman J, Shoenfeld Y. Neuropsychiatric lupus: a mosaic of clinical presentations. *BMC Med.* 2015;13(1):43. doi: 10.1186/s12916-015-0269-8.
10. Nusbaum JS, Mirza I, Shum J, Freilich RW, Cohen RE, Pillinger MH, et al. Sex differences in systemic lupus erythematosus: epidemiology, clinical considerations, and disease pathogenesis. *Mayo Clin Proc.* 2020;95(2):384–394. doi: 10.1016/j.mayocp.2019.09.012.
11. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan lupus epidemiology and surveillance program. *Arthritis Rheumatol.* 2014;66(2):369–378. doi: 10.1002/art.38238.
12. Joshua Reynolds, Michelle Huang, Yaxi Li, Myriam Meineck, Tamara Moeckel, Julia Weinmann-Menke, Chandra Mohan, Andreas Schwarting, Chaim Putterman. Constitutive knockout of interleukin-6 ameliorates memory deficits and entorhinal astrocytosis in the MRL/lpr mouse model of neuropsychiatric lupus. *J Neuroinflammation.* 2024 Apr 10;21:89. doi: 10.1186/s12974-024-03085-9.
13. Clothilde Gros, Olivier Fogel, Idris Boudhabhay, Charlotte Debiais, Jean-Paul Duong Van Huyen, Aurélie Hummel, Yannick Allanore, Jérôme Avouac. Challenging diagnosis of renal failure associated with severe neurological symptoms in a patient with mixed connective tissue disease. *J Scleroderma Relat Disord.* 2022 Jun 13;8(1):NP6–NP10. doi: 10.1177/23971983221099847
14. Perry D, Sang A, Yin Y, Zheng YY, Morel L. Murine models of systemic lupus erythematosus. *J Biomed Biotechnol.* 2011; 2011:271694. doi: 10.1155/2011/271694.
15. Petri M., Orbai A.M., Alarcón G.S., Gordon C., Merrill J.T., Fortin P.R., Bruce I.N., Isenberg D., Wallace D.J., Nived O., et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012; 64:2677–2686. doi: 10.1002/art.34473.
16. Aringer M., Costenbader K., Daikh D., Brinks R., Mosca M., Ramsey-Goldman R., Smolen J.S., Wofsy D., Boumpas D.T., Kamen D.L., et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann. Rheum. Dis.* 2019; 78:1151–1159. doi: 10.1136/annrheumdis-2018-214819.
17. Carolina Saffioti, Marta Nebiolo, Roberta Caorsi, Alessio Mesini, Mariasavina Severino, Giacomo Brisca, Elio Castagnola, Marco Gattorno. Whipple Disease Presenting as Isolated Transverse Myelitis with Permanent Neurological Damage in a Patient with Systemic Lupus Erythematosus: A Case Report of a Difficult Diagnosis with a Literature Review. *Infect Dis Rep.* 2024 Mar 19;16(2):269–280. doi: 10.3390/idr16020022.
18. Bastien Rioux, Sarah McGlasson, Deborah Forbes, Katy R Reid, Anna Klingseisen, Joe Berry, Neeraj Dhaun, Wan Fai Ng, William Whiteley, David P J Hunt. Oligoprotein type I interferon signatures, but not *TREX1* variants, increase risk of systemic lupus erythematosus in UK Biobank. *Nat Commun.* 2026 Jan 27; 17:1073. doi: 10.1038/s41467-025-67832-z.
19. Reeves DL, Winter KP, Bleiberg J, et al. ANAM® Genogram: historical perspectives, description, and current endeavors. *Arch Clin Neuropsychol* 2007; 22(SUPPL. 1): 15–37.
20. Yimy F Medina, Manuela Rivera, Liliana K Duarte, Carlos M Rodriguez-Plata. Cognitive impairment in a Colombian cohort of patients with systemic lupus erythematosus: A cross-sectional study. *Lupus.* 2024 Sep 15;33(10):1025–1033. doi: 10.1177/09612033241273082.
21. Zhao Z, Rocha NP, Salem H, et al. The association between systemic lupus erythematosus and dementia: a meta-analysis. *Dement e Neuropsychol* 2018; 12(2): 143–151.
22. Appenzeller S, Lapa AT, De Carvalho JF, et al. Cognitive dysfunction and antiphospholipid antibodies. *Curr Rheumatol Rep* 2012; 14(1): 95–98.
23. Veena Patel. The Challenge of Neuropsychiatric Systemic Lupus Erythematosus: From Symptoms to Therapeutic Strategies. *Diagnostics (Basel).* 2024 Jun 5;14(11):1186. doi: 10.3390/diagnostics14111186.
24. Teresa Medeiros, Andreia Vilas-Boas, Vanessa Carvalho, Teresa Santos, Ana Pinho. Chorea as a Manifestation of Systemic Lupus Erythematosus. *Cureus.* 2023 Mar 7;15(3):e35884. doi: 10.7759/cureus.35884.
25. Assma Boudanga, Mohamed Chraa, Oussama Cherkaoui Rhazouani, Najib Kissani. Severe acute polyradiculoneuritis revealing systemic lupus erythematosus: a case report. *Pan Afr Med J.* 2023 May 4;45:8. doi: 10.11604/pamj.2023.45.8.32236.
26. Isenberg DA, Rahman A, Allen E, et al. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology* 2005;44(7):902–906.
27. Touma Z, Urowitz MB, Gladman DD. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288–291.
28. Rayes HA, Tani C, Kwan A, et al. What is the prevalence of cognitive impairment in lupus and which instruments are used to measure it? A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018; 48(2): 240–255]. Demyelinating conditions are quite uncommon.
29. Adhikari T, Piatti A, Luggen M. Cognitive dysfunction in SLE: development of a screening tool. *Lupus* 2011; 20(11): 1142–1146.
30. Shantanam S. European League against rheumatism/American College of rheumatology classification criteria for systemic lupus erythematosus. *Physiol Behav.* 2018;176(1):139–148.
31. Zandman-Goddard G, Chapman J, Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. *Semin Arthritis Rheum.* 2007;36(5):297–315. doi: 10.1016/j.semarthrit.2006.11.003.

32. Monahan RC, Inglese F, Middelkoop H, van Buchem M, Huizinga TW, Kloppenburg M, et al. White matter hyperintensities associate with cognitive slowing in patients with systemic lupus erythematosus and neuropsychiatric symptoms. *RMD Open*. 2021;7(2):e001650. doi: 10.1136/rmdopen-2021-001650.
33. Piga M., Chessa E., Peltz M.T., Floris A., Mathieu A., Cauli A. Demyelinating syndrome in SLE encompasses different subtypes: Do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis. *Autoimmun. Rev*. 2017; 16:244–252. doi: 10.1016/j.autrev.2017.01.011.
34. Justiz-Vaillant A.A., Gopaul D., Soodeen S., Arozarena-Fundora R., Barbosa O.A., Unakal C., Thompson R., Pandit B., Umakanthan S., Akpaka P.E. Neuropsychiatric Systemic Lupus Erythematosus: Molecules Involved in Its Immunopathogenesis, Clinical Features, and Treatment. *Molecules*. 2024;29:747. doi: 10.3390/molecules29040747.
35. Bortoluzzi A., Piga M., Silvagni E., Chessa E., Mathieu A., Govoni M. Peripheral nervous system involvement in systemic lupus erythematosus: A retrospective study on prevalence, associated factors and outcome. *Lupus*. 2019;28:465–474. doi: 10.1177/0961203319828499.
36. Constantin A, Năstase D, Tulbă D, Bălănescu P, Băicuș C. Immunosuppressive therapy of systemic lupus erythematosus associated peripheral neuropathy: A systematic review. *Lupus*. 2020; 29:1509–1519. doi: 10.1177/0961203320948181.
37. Zandman-Goddard G., Chapman J., Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. *Semin. Arthritis Rheum*. 2007; 36:297–315. doi: 10.1016/j.semarthrit.2006.11.003.
38. Carrión-Barberà I., Salman-Monte T.C., Vélchez-Oya F., Monfort J. Neuropsychiatric involvement in systemic lupus erythematosus: A review. *Autoimmun. Rev*. 2021; 20:102780. doi: 10.1016/j.autrev.2021.102780], [Mizrachi M., Anderson E., Carroll K.R., Tehrani N., Volpe B.T., Diamond B. Cognitive dysfunction in SLE: An understudied clinical manifestation. *J. Autoimmun*. 2022; 132:102911. doi: 10.1016/j.jaut.2022.102911.
39. Hanly J.G., Li Q., Su L., Urowitz M.B., Gordon C., Bae S., Romero-Diaz J., Sanchez-Guerrero J., Bernatsky S., Clarke A.E., et al. Psychosis in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. *Arthritis Rheumatol*. 2019;71:281–289. doi: 10.1002/art.40764.
40. Bertsias G.K., Ioannidis J.P., Aringer M., Bollen E., Bombardieri S., Bruce I.N., Cervera R., Dalakas M., Doria A., Hanly J.G., et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. *Ann. Rheum. Dis*. 2010; 69:2074–2082. doi: 10.1136/ard.2010.130476.
41. Govoni M., Bortoluzzi A., Padovan M., Silvagni E., Borrelli M., Donelli F., Ceruti S., Trotta F. The diagnosis and clinical management of the neuropsychiatric manifestations of lupus. *J. Autoimmun*. 2016; 74:41–72. doi: 10.1016/j.jaut.2016.06.013.
42. Yimy F Medina, Manuela R Rivera, Liliana K Duarte, Carlos M Rodriguez-Plata, Emmanuel R De León, Sonia C Rodríguez Martínez. Cognitive impairment in a Colombian cohort of patients with systemic lupus erythematosus: A cross-sectional study. *Lupus*. 2024 Sep 15;33(10):1025–1033. Doi: 10.1177/09612033241273082.
43. Nikolopoulos D, Manolakou T, Polissidis A, Filia A, Bertsias G, Koutmani Y, 2023. Microglia activation in the presence of intact blood-brain barrier and disruption of hippocampal neurogenesis via IL-6 and IL-18 mediate early diffuse neuropsychiatric lupus. *Ann Rheum Dis*.
44. Hu C, Huang W, Chen H, Song G, Li P, Shan Q, et al. Autoantibody profiling on human proteome microarray for biomarker discovery in cerebrospinal fluid and sera of neuropsychiatric lupus. *PLoS ONE*. 2015;10(5):e0126643. doi: 10.1371/journal.pone.0126643.
45. Chun H-Y, Chung J-W, Kim H-A, Yun J-M, Jeon J-Y, Ye Y-M, et al. Cytokine IL-6 and IL-10 as biomarkers in systemic lupus erythematosus. *J Clin Immunol*. 2007;27(5):461–466. doi: 10.1007/s10875-007-9104-0.
46. Ding J, Su S, You T, Xia T, Lin X, Chen Z, et al. Serum interleukin-6 level is correlated with the disease activity of systemic lupus erythematosus: a meta-analysis. *Clinics*. 2020;75:e1801. doi: 10.6061/clinics/2020/e1801.
47. Svenungsson E, Andersson M, Brundin L, van Vollenhoven R, Khademi M, Tarkowski A, et al. Increased levels of proinflammatory cytokines and nitric oxide metabolites in neuropsychiatric lupus erythematosus. *Ann Rheum Dis*. 2001;60(4):372–379. doi: 10.1136/ard.60.4.372.
48. Liddel SA, Marsh SE, Stevens B. Microglia and astrocytes in disease: dynamic duo or partners in crime? *Trends Immunol*. 2020 doi: 10.1016/j.it.2020.07.006.
49. Han X, Xu T, Ding C, Wang D, Yao G, Chen H, et al. Neuronal NR4A1 deficiency drives complement-coordinated synaptic stripping by microglia in a mouse model of lupus. *Signal Transduct Target Ther*. 2022;7(1):50. doi: 10.1038/s41392-021-00867-y.
50. Han X, Xu T, Ding C, Wang D, Yao G, Chen H, et al. Neuronal NR4A1 deficiency drives complement-coordinated synaptic stripping by microglia in a mouse model of lupus. *Signal Transduct Target Ther*. 2022;7(1):50. doi: 10.1038/s41392-021-00867-y.
51. Trysberg E, Nylen K, Rosengren LE, Tarkowski A. Neuronal and astrocytic damage in systemic lupus erythematosus patients with central nervous system involvement. *Arthritis Rheum*. 2003;48(10):2881–2887. doi: 10.1002/art.11279.

52. Loukkola J, Laine M, Ainiala H, et al. Cognitive impairment in systemic lupus erythematosus and neuropsychiatric systemic lupus erythematosus: a population-based neuropsychological study. *J Clin Exp Neuropsychol* 2003; 25(1): 145–151.
53. Abbott NJ, Mendonça LL, Dolman DE. The blood-brain barrier in systemic lupus erythematosus. *Lupus*. 2003;12(12):908–915. doi: 10.1191/0961203303lu501oa.
54. Hirohata S, Arinuma Y, Yanagida T, Yoshio T. Blood-brain barrier damages and intrathecal synthesis of anti-N-methyl-D-aspartate receptor NR2 antibodies in diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematosus. *Arthritis Res Ther*. 2014;16(2):R77. doi: 10.1186/ar4518.
55. Stock AD, Der E, Gelb S, Huang M, Weidenheim K, Ben-Zvi A, et al. Tertiary lymphoid structures in the choroid plexus in neuropsychiatric lupus. *JCI Insight*. 2019;4(11):e124203. doi: 10.1172/jci.insight.124203.
56. Duarte-Delgado NP, Vásquez G, Ortiz-Reyes BL. Blood-brain barrier disruption and neuroinflammation as pathophysiological mechanisms of the diffuse manifestations of neuropsychiatric systemic lupus erythematosus. *Autoimmun Rev*. 2019;18(4):426–432. doi: 10.1016/j.autrev.2018.12.004.
57. Marian G, Nica EA, Ionescu BE, Carlogea DG. Depression as an initial feature of systemic lupus erythematosus? A case report. *J Med Life*. 2010;3(2):183–185.
58. Carla Sans-Pola, Immaculada Danés, Josep Àngel Bosch, Patricia Marrero-Álvarez, Josefina Cortés, Antònia Agustí. Off-label use of rituximab in patients with systemic lupus erythematosus with extrarenal disease activity: a retrospective study and literature review. *Front Med (Lausanne)*. 2023 May 25;10:1159794. doi: 10.3389/fmed.2023.1159794
59. Williams S, Sakic B, Hoffman SA. Circulating brain-reactive autoantibodies and behavioral deficits in the MRL model of CNS lupus. *J Neuroimmunol*. 2010;218(1–2):73–82. doi: 10.1016/j.jneuroim.2009.10.008.
60. Tsokos GC. Autoimmunity and organ damage in systemic lupus erythematosus. *Nat Immunol*. 2020;21(6):605–614. doi: 10.1038/s41590-020-0677-6.
61. Tsokos G.C., Lo M.S., Reis P.C., Sullivan K.E. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat. Rev. Rheumatol*. 2016; 12:716–730. doi: 10.1038/nrrheum.2016.186.
62. Jacobi A.M., Zhang J., Mackay M., Aranow C., Diamond B. Phenotypic characterization of autoreactive B cells—Checkpoints of B cell tolerance in patients with systemic lupus erythematosus. *PLoS ONE*. 2009;4:e5776. doi: 10.1371/journal.pone.0005776.
63. Ullal A.J., Reich C.F., 3rd, Clowse M., Criscione-Schreiber L.G., Tochacek M., Monestier M., Pisetsky D.S. Microparticles as antigenic targets of antibodies to DNA and nucleosomes in systemic lupus erythematosus. *J. Autoimmun*. 2011;36:173–180. doi: 10.1016/j.jaut.2011.02.001.
64. Koutouzov S., Jeronimo A.L., Campos H., Amoura Z. Nucleosomes in the pathogenesis of systemic lupus erythematosus. *Rheum. Dis. Clin. N. Am*. 2004; 30:529–558. doi: 10.1016/j.rdc.2004.04.001.
65. Mande P., Zirk B., Ko W.C., Taravati K., Bride K.L., Brodeur T.Y., Deng A., Dresser K., Jiang Z., Ettinger R., et al. Fas ligand promotes an inducible TLR-dependent model of cutaneous lupus-like inflammation. *J. Clin. Invest*. 2018; 128:2966–2978. doi: 10.1172/JCI98219.
66. Yap D.Y.H., Chan T.M. B Cell Abnormalities in Systemic Lupus Erythematosus and Lupus Nephritis-Role in Pathogenesis and Effect of Immunosuppressive Treatments. *Int. J. Mol. Sci*. 2019; 20:6231. doi: 10.3390/ijms2024623.
67. Howe H.S., Thong B.Y.H., Kong K.O., Chng H.H., Lian T.Y., Chia F.L., Tay K.S.S., Lau T.C., Law W.G., Koh E.T., et al. Associations of B cell-activating factor (BAFF) and anti-BAFF autoantibodies with disease activity in multi-ethnic Asian systemic lupus erythematosus patients in Singapore. *Clin. Exp. Immunol*. 2017; 189:298–303. doi: 10.1111/cei.12975.
68. Crispín J.C., Kyttaris V.C., Terhorst C., Tsokos G.C. T cells as therapeutic targets in SLE. *Nat. Rev. Rheumatol*. 2010;6:317–325. doi: 10.1038/nrrheum.2010.60.
69. Crotty S. Follicular helper CD4 T cells (TFH) *Annu. Rev. Immunol*. 2011; 29:621–663. doi: 10.1146/annurev-immunol-031210-101400], [Sakaguchi S., Yamaguchi T., Nomura T., Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008; 133:775–787. doi: 10.1016/j.cell.2008. 05.009.
70. Berghöfer B., Frommer T., Haley G., Fink L., Bein G., Hackstein H. TLR7 ligands induce higher IFN- α production in females. *J. Immunol*. 2006;177:2088–2096. doi: 10.4049/jimmunol.177.4.2088.
71. Souyris M., Cenac C., Azar P., Daviaud D., Canivet A., Grunenwald S., Pienkowski C., Chaumeil J., Mejia J.E., Guéry J.C. TLR7 escapes X chromosome inactivation in immune cells. *Sci. Immunol*. 2018;3:eaap8855. doi: 10.1126/sciimmunol.aap8855.
72. Dai X., Fan Y., Zhao X. Systemic lupus erythematosus: Updated insights on the pathogenesis, diagnosis, prevention and therapeutics. *Signal Transduct. Target. Ther*. 2025; 10:102. doi: 10.1038/s41392-025-02168-0.