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SYSTEMATIC REVIEW

Neurological complexity of systemic lupus erythematosus: insights into autoimmune encephalitis

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ABSTRACT

Background: Autoimmune encephalitis (AE) is an inflammatory syndrome characterized by autoantibodies targeting the central nervous system (CNS), leading to a wide range of neurological and psychiatric manifestations. **Objective**: This systematic review aims to investigate the coexistence of AE and systemic lupus erythematosus (SLE) to shed light on potential underlying mechanisms. **Materials and Methods**: Following PRISMA guidelines, a comprehensive search was conducted using Boolean logic in research databases i.e., PubMed, ProQuest, ScienceDirect, and Web of Science to identify relevant studies on AE, SLE, and their potential correlation. After the initial screening, exclusion, and quality assessment using the Joanna Briggs Institute Critical Appraisal Checklist, 14 studies were included for analysis. Among 18 patients, 88.9% were female whose an average age was 31.9 ± 12.7 years. Clinical presentations were varied, including cognitive impairment (66.67%), seizures (61.1%), altered mental status (50%), and movement disorders. Neuroimaging and neurophysiological findings consistently aligned with encephalitis, with MRI abnormalities observed in 94.4% of cases. Various autoantibodies were identified, including anti-NMDAR, anti-AMPA-R2, and anti-GluR antibodies. **Conclusion**: The identification of neuronal antibodies is crucial, particularly in scenarios involving both neuropsychiatric SLE (NPSLE) and encephalitis. This investigation aims to reveal etiological insights. The ongoing debate revolves around whether SLE-related encephalitis is associated with NPSLE through SLE antibodies or involves distinct antibodies. Further clinical research is essential to clarify the pathogenic role of autoantibody in SLE-linked AE.

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Highlights

1. The co-occurrence of AE and SLE has been reported in multiple cases.

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2. Clinical and radiological findings consistently showed encephalitis-related abnormalities in SLE along with the identification of neuronal autoantibodies.
3. The overlapping manifestations of AE and neuropsychiatric SLE (NPSLE) present a similar clinical spectrum, emphasizing the need for further extensive research to understand the immune mechanisms involved.

BACKGROUND

Autoimmune encephalitis (AE) is one of the inflammatory syndromes caused by autoantibodies targeting antigens expressed in the central nervous system (CNS), leading to a diverse spectrum of clinical manifestations encompassing both neurological and psychiatric disorders (Uy et al., 2021). Patients with AE typically exhibit various neurological symptoms such as subacute changes in consciousness, behavior, cognitive impairment, seizures, ataxia, and memory disturbances. Seizures, including refractory status epilepticus, are frequently observed (Newman et al., 2018). The variability in both clinical and radiological presentations is rooted in the localized inflammatory response triggered by antibody attacks on specific neural cell structures. Despite initially being considered a relatively rare condition with an annual prevalence of approximately 0.8 per 100,000 individuals, AE is increasingly recognized as a subset of causes for the emergence of mental status disorders previously considered idiopathic. The complex clinical presentation in cases of mental status changes can also be atypical without clear etiological findings, making AE a diagnosis of exclusion (Dalmau, 2016; Kelley et al., 2017). Encephalitis resulting from immune responses can have various underlying causes, including systemic inflammatory autoimmune disorders like SLE, processes following infections, and autoimmune reactions triggered by the herpes simplex virus, or paraneoplastic autoimmunity. However, it can also manifest as idiopathic, and it may not be able to identify a specific primary immunological trigger in this situation (Patel et al., 2022).

Systemic lupus erythematosus (SLE) is a complex and heterogeneous multisystem autoimmune disease that affects various organ systems. In SLE, the involvement of the CNS, referred to as neuropsychiatric SLE (NPSLE), is a common complication of this condition. SLE itself can affect the CNS, leading to a broad and nonspecific range of neuropsychiatric manifestations (Kampylafka et al., 2013; Sciascia et al., 2013; Valesini et al., 1994). Several autoantibodies associated with specific focal and diffuse NPSLE symptoms in SLE identified include anti-phospholipid antibodies, anti-ribosomal P protein antibodies, and anti-N-methyl-D-aspartate receptor antibodies (anti-NMDA) (Sato et al., 2020). The increasing prevalence of confirmed AE cases has generated interest in the concurrent presence of AE and other systemic autoimmune diseases (ADs), particularly SLE. Previous studies have investigated the coexistence of autoimmune encephalitis with other autoimmune diseases. The complex underpinnings of SLE involve genetic and environmental factors, with shared characteristics including specific autoantibodies and autoreactive T cells between AE and SLE (Tadros et al., 2023; Zhao et al., 2019). Moreover, antibodies targeting glutamate receptors, such as anti-NMDA antibodies, have been found in certain autoimmune conditions such as systemic lupus erythematosus (SLE) and Sjogren's syndrome (Arinuma et al., 2008; Lauvsnes et al., 2013). This might suggest a potential link between SLE and AE.

OBJECTIVE

This systematic review investigates the coexistence of AE and systemic lupus erythematosus (SLE) to shed light on potential underlying mechanisms.

MATERIALS AND METHODS

Study design

This systematic review was conducted under the Preferred Reporting Items of the Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure the quality of the study.

Search strategy

A comprehensive search with language restrictions was performed between July and August 2023. The search encompassed the PubMed, ProQuest, ScienceDirect, and Web of Science databases. Boolean logic was employed to search for Medical Subject Headings (MeSH) terms and relevant keywords associated with autoimmune encephalitis, systemic lupus erythematosus, and their potential correlation to identify and extract relevant studies. Detailed information about the search strategies used in this study can be found in the supplementary file.

Eligibility criteria

According to PICO, which mean that P (for patient, population, problem), I (for intervention, prognostic factor, exposure), C (comparison or intervention) and O (for outcome). Any case report or case series that reported the association of AE with SLE in adults aged 18 years and above, with laboratory-confirmed and/or history of AE and SLE as well as the types and clinical manifestations of autoimmune encephalitis, were included. Meanwhile, any studies that lacked sufficient or reliable data, duplicate studies, studies with only abstract available, studies in languages other than English, and author responses were excluded.

Study selection and data extraction

Two independent authors initially screened the studies based on their titles and abstracts, using the inclusion and exclusion criteria to assess relevance. Studies with relevant titles were then collected and filtered, while studies that were irrelevant to the topic were excluded. Subsequently, the authors screened all relevant studies and assessed full-paper manuscripts to determine their eligibility for inclusion. Retrieved studies that had incomplete data were excluded. Furthermore, the authors carried out data extraction from the relevant studies to minimize the risk of reporting and data collection bias. The extracted data were systematically organized into a table that had been prepared beforehand. Any disagreement between the authors was resolved through consensus. The extracted data contained information, including the first author, year, country, study design, number of patients, age, gender, total number of encephalitis cases, SLE laboratory results, cerebrospinal fluid (CSF) analysis, pathogen investigation, neuroradiology findings (CT scan and MRI), neurophysiology findings (EEG), encephalitis laboratory results, type of autoimmune encephalitis, emerging signs, outcomes, past medical history, encephalitis onset, and therapy.

During the abstract screening process, review articles, opinion pieces, and commentary articles (n = 62), along with irrelevant studies (n = 31), non-English reports (n = 6), and studies that did not meet the specified population criteria of the study (n = 5) were excluded. After the evaluation of 33 reports, four reports could not be retrieved, and 13 studies were excluded as they were found to be ineligible for this study. As a result, 14 reports were ultimately included in this study.

Data synthesis and analysis

A narrative synthesis was conducted to qualitatively summarize the findings from the included studies. Sample distribution was calculated using summary statistics (n range), while quantitative data from the included studies was presented as percentages or as mean values along with their standard deviations (mean ± SD).

Quality assessment

The quality of the included studies was independently assessed by two authors using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist. Studies with low methodological quality will be reported. Upon using the JBI critical appraisal instruments to evaluate the case reports and case series included in this systematic review, it was found that 92.8% of the studies were of high quality, while 7.2% were of moderate quality (**Tables 2** and **3**).

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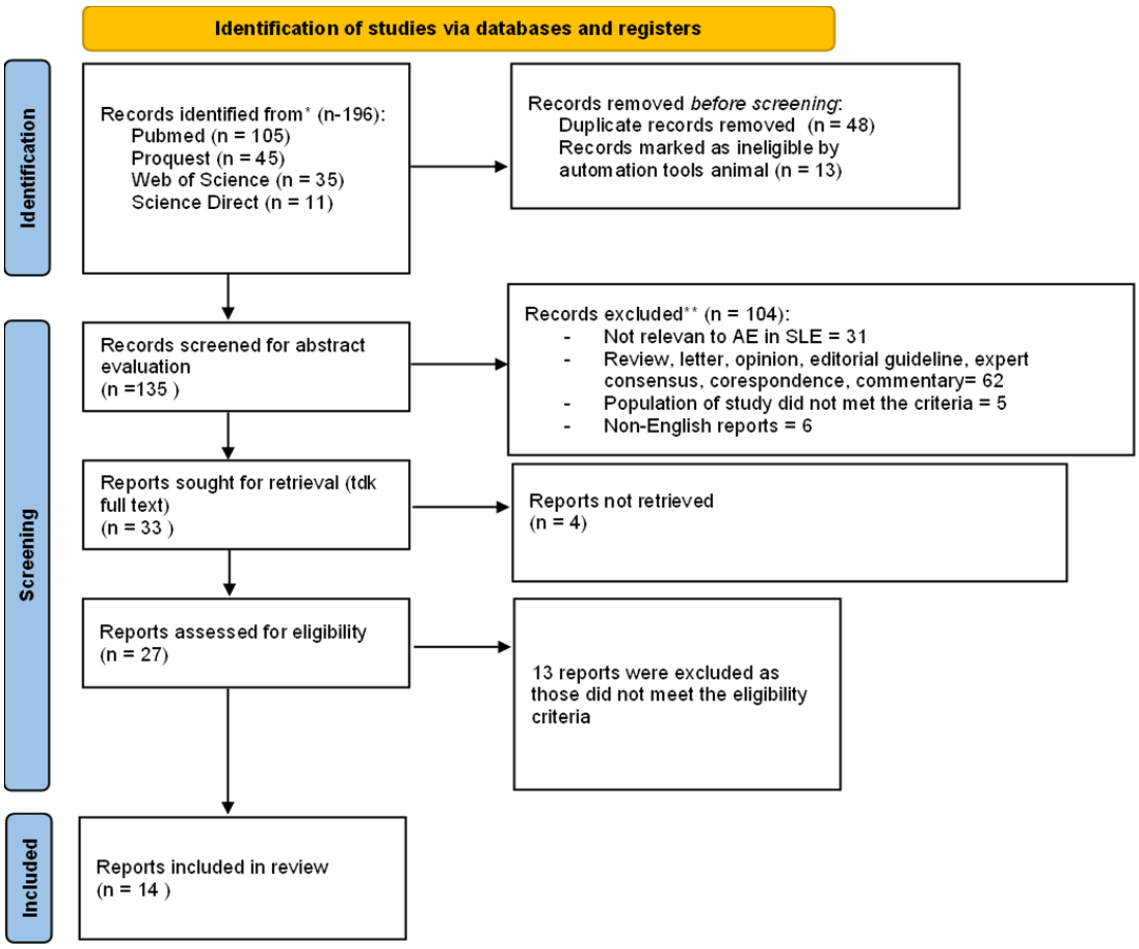

Figure 1. PRISMA flowchart depicting the process of determining eligible research studies.

RESULT

General Characteristics of the Included Studies

Table 1 provides a summary of the main characteristics of the studies included in the analysis. In total, 18 patients were included, of which 88.9% were females and 85.6% were adults with an average age of 31.9 ± 12.7 years. The majority of the patients fell within the age range of 18 to 68 years (**Figure 2**). Most of the patients (77.8%) had a history of SLE before the onset of encephalitis. Among the patients, one patient was reported to have had anti-NMDAR encephalitis previously. The geographic distribution of the studies was predominantly in the USA (28.6%), followed by Japan (21.4%) and China (14.3%). The most common type of AE in this study was limbic encephalitis (n = 11), followed by striatal encephalitis (n = 6). Four studies mentioned the involvement of anti-neural antibodies, such as anti-NMDAR, anti-AMPA-R2, and anti-Glu-R (ε2, δ2, ζ1). Most of the patients exhibited symptoms of encephalitis either recently or years after their SLE diagnosis, with the longest duration being 14 years after the SLE diagnosis. Four cases showed encephalitis as their initial symptom. Clinical manifestations included neurological disturbances such as cognitive impairment (66.67%), seizures (61.1%), headaches (55.6%), and altered mental status (50%), which were the most frequently reported symptoms. Some patients also exhibited systemic symptoms, including fever (44.4%), flu-like symptoms (11.1%), and diarrhea (5.6%). Among the patients, 94.4% were discharged with improvement and 44.4% showed no abnormal findings at the time of discharge. Meanwhile, 50% showed improvement with sequelae during follow-up. One patient died due to an unrelated condition (dilated cardiomyopathy). Abnormal findings were observed in the results of MRI (94.4%), EEG (55.6%), and CSF analysis (55.6%). A comprehensive overview of the diagnostic aspects of SLE patients with encephalitis is presented in **Table 2**.

Table 1. General characteristics of the included studies

No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
1	(Stubgen et al., 1998)	1998	USA	Case report	1	28	21-30	Female	1	SLE	2 years after SLE diagnosis	Improved with sequelae	Limbic encephalitis	CSF: negative anti-Hu, -Yo, -Ri antibodies, positive atypical ANA and anti-ribosomal-P antibodies	Generalized tonic-clonic seizures, headache, mild fever, malaise, dry cough. Lethargic, disoriented for time, decreased attention span and short-term memory deficit.	Prednisone, phenytoin, methylprednisolone, and acyclovir
2	(Kano et al., 2009)	2009	USA	Case Report	1	34	31-40	Female	1	3-year history of photosensitivity	On initial presentation	Improved	Limbic encephalitis	Tumor marker (a-fetoprotein, carcinoembryonic antigen, Ca125, Ca153, Ca199), anti-neuronal antibodies (anti–Hu, anti–Ta, anti–Ma), anti-thyroid antibodies (anti–TPO, anti–TG), voltage-gated potassium channels (VGKC-Ab) antibody were all negative	Headaches, general fatigue, complex partial seizure, and memory impairment. Amnesic syndrome. Low grade fever. Disorientation, severe anterograde and retrograde amnesia.	Acyclovir (30 mg/kg per day) for presumptive diagnosis of HSV encephalitis. Oral methylprednisolone (1 mg/kg per day).
3	(Selcuk et al., 2011)	2011	Turkey	Case report	1	36	31-40	Female	1	SLE	4 weeks after SLE diagnosis	Improved with sequelae	Limbic encephalitis	Normal whole-body PET-CT. Antineuronal antibodies were not tested.	Generalized tonic-clonic seizures, headache, fever, dry cough. Lethargic, disoriented for time, decreased	Phenytoin, methylprednisolone 1gr/day for three days and 1mg/kg for four weeks, and acyclovir

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No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
															attention span and short-term memory deficit.	
4	(Angst et al., 2015)	2015	Brazil	Case report	1	44	41-50	Female	1	SLE	10 years after diagnosis	Improved	Limbic encephalitis	Normal CEA, CA15-3, CA125 and CA19/9	Asthenia, myalgia, anterograde amnesia and temporal disorientation	Methylprednisolone (1 g/d for 4 days) and cyclophosphamide 1g - single dose), oxcarbazepine
5	(Muñoz et al., 2017)	2017	Colombia	Case report	1	27	21-30	Female	1	NM	On initial presentation	Improved with sequelae	Limbic encephalitis	Negative anti-NMDAR antibodies	Flu-like symptoms, seizures, facial dyskinesia, generalized hyperreflexia, ankle clonus reflex, limb jerks responding to tactile stimuli, and opisthotonos posturing	Methylprednisolone 500mg every 24h for 3 days, followed by oral prednisolone 1mg/kg/day and a single dose of cyclophosphamide 750mg, midazolam, fentanyl and dexmedetomidine, rituximab
6	(Sugi et al., 2018)	2018	Japan	Case Report	1	44	41-50	Female	1	SLE	NM	Improved with sequelae	Limbic encephalitis	NMDA receptor antibody negative (none)	Fever, complex partial seizure, and disturbance in consciousness	High-dose steroid therapy
7	(Kelley et al., 2018)	2018	USA	Case series	1	68	61-70	Female	1	SLE, rheumatoid arthritis, type 2 diabetes	NM	Improved with sequelae	Striatal encephalitis	NM	Cognitive decline and generalized weakness	IV methylprednisolone

No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
										mellitus						
					1	20	11-20	Female	1	SLE	NM	Improved with sequelae	Striatal encephalitis	NM	Headaches, anxiety, cognitive impairment	IV steroid and cyclophosphamide, plasmapheresis
					1	24	21-30	Female	1	SLE	Immediately after SLE diagnosis	Improved with sequelae	Striatal encephalitis	NM	Expressive aphasia and headaches	IV steroid
					1	20	11-20	Male	1	SLE, dilated cardiomyopathy	NM	Death	Striatal encephalitis	NM	Altered mental status	NM
					1	37	31-40	Male	1	SLE	NM	Improved with sequelae	Striatal encephalitis	NM	Flulike episode with altered mental status, emesis, headaches, and dystonia	Pulse dose IV steroids with prednisone taper
8	(Manorenj and Shaik, 2021)	2021	India	Case report	1	26	21-30	Female	1	Bipolar disorder	On initial presentation	Improved	Limbic encephalitis	NM	Progressive behavioral disturbances, decreased self-care, inability to communicate and maintain attention, episodes of mood elation and depression, involuntary movements typical of faciobrachial	Olanzapine 7.5 mg and lamotrigine 100 mg daily, antibiotics for ulcers, steroid was not given due to site infection with MRSA

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No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
															dystonic seizures	
9	(Zhang et al., 2021)	2020	China	Case Report	1	23	21-30	Female	1	SLE, anti-NMDAR encephalitis in previous pregnancy	4 years after SLE diagnosis	Improved	Anti-NMDAR encephalitis	Positive anti-NMDAR antibodies in serum and CSF.	Visual hallucinations, persecutory delusion, complex partial seizures	IV pulse methylprednisolone (1 g/day for 5 days) and IV immunoglobulin (20 g/day). Methylprednisolone reduced to 0.5 g for 3 days; 50 mg/day oral prednisone, reduced by 5 mg every 2 weeks; and maintenance dose of 15 mg/day throughout the pregnancy, lamotrigine and levetiracetam, valproic acid.

No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
10	(Asmaa et al., 2022)	2022	Morocco	Case report	1	36	31-40	Female	1	SLE	9 years after SLE diagnosis	Improved with sequelae	Limbic encephalitis	Negative anti-NMDAR antibody	Fever, headache, generalized seizures, memory disorders and altered state of consciousness	Acyclovir, high-dose corticosteroid therapy, polyvalent immunoglobuli, cyclophosphamide, mycophenolate mofetil, antiepileptic therapy, hydroxychloroquine
11	(Li et al., 2022)	2022	China	Case Report	1	21	21-30	Female	1	SLE	2 weeks after SLE diagnosis	Improved	AMPA-R2 limbic encephalitis	CSF and serum: AMPA-R2 antibody detected	Headache, gnathospasmus, gazing eyes, and generalized tonic–clonic seizure, grade II muscle strength of the limbs and decreased muscle tone (weakness)	200 mg/d methylprednisolone and maintained at 40 mg/d, 500 ml/d glycerol fructose, 1.2 g/d of sodium valproate, and 1.0 g/d of levetiracetam
12	(Raventhiranathan et al., 2022)	2022	USA	Case report	1	18	11-20	Female	1	SLE	NM	Improved	Striatal encephalitis	NM	High fever, headache, diarrhea, abdominal pain, deteriorated mental status, auditory and visual hallucinations, gait abnormality	Methylprednisolone, plasmapheresis, 5 sessions, rituximab or cyclophosphamide and covered with acyclovir

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No	Author	Year	Country	Study design	Patients number (N)	Age	Age Group	Sex	Number of encephalitis cases (N)	Past medical history	Onset of encephalitis from SLE presentation	Outcome group	AE type	Other biomarkers	Clinical findings (Signs and symptoms)	Therapy
13	(Tsuchiya et al., 2021)	2021	Japan	Case Report	1	46	41-50	Female	1	SLE	14 years after SLE diagnosis	Improved	Anti NMDAR limbic encephalitis	Serum and CSF Anti-NMDAR type GluRs (anti-GluN2B-NT2 & CT, anti-GluN1-NT) and anti-GluD2-NT & CT elevated	Acute cognitive impairment (difficult to concentrate, sensory aphasia, memory impairment and dyscalculia) and seizures, a low-grade fever, somnolence, pseudobulbar affect and tonic-clonic convulsion, auditory hallucination	Methylprednisolone pulses (1 g/day for three days) followed by a high dose of prednisolone (1 mg/kg; 60 mg/day; IV cyclophosphamide
14	(Yamaguchi et al., 2012)	2012	Japan	Case Report	1	23	21-30	Female	1	NM	On initial presentation	Improved	Anti Glu-R ε2, ζ1 and δ2 Limbic encephalitis	CSF: positive anti-glutamate receptor (ε2, δ2, ζ1) antibodies.	Consciousness disturbance, convulsion, high fever, headache, erythema multiforme	Prednisolone

Table 2. Diagnostic features in patients with SLE-related AE

No	Author	SLE Laboratory Findings (Serum Analysis)	Encephalitis Laboratory Findings (CSF Analysis)			Other Biomarkers	Pathogen Investigation	Neuroradiology Findings		Neurophysiology Findings (EEG)
			Leukocyte	Protein	Glucose			CT Scan	MRI	
1	Stubgen et al.	Antinuclear antigen (ANA) positive, decreased complement levels, negative lupus anticoagulant, normal anticardiolipin antibody	Pleocytosis (lymphocytes predominant)	Elevated (65 mg/dL)	Normal (54 mg/dL)	CSF: anti-Hu, -Yo, -Ri antibodies not detected, atypical ANA and anti-ribosomal-P antibodies positive	Negative HSV antibodies, HIV antibody, CSF VDRL and cryptococcus antigen were not detected	Normal	MRI FLAIR/T2: high signal changes of the medial temporal gray matter and hippocampus bilaterally	Electroclinical and subclinical seizures with generalized onset of left and right temporal lobe, right hemisphere
2	Kano et al.	Antinuclear antibodies (ANA) positive and decreased complement levels. Anti-ribosomal-P, anti–Sm, and anti–RNP antibodies were positive. Negative anti–ds, DNA, anti–SSA and anti–SSB.	Pleocytosis (lymphocytes predominant)	Normal (36 mg/dL)	Normal (71 mg/dL)	Tumor markers (AFP, CEA, Ca125, Ca153, Ca199) were negative, anti-neuronal antibodies (anti–Hu, anti–Ta, anti–Ma) were negative, anti-thyroid antibodies (anti–TPO, anti–TG), VGKC-Ab antibodies were negative	Negative PCR of serum and CSF of CMV, HSV, HHV-6, VZV, and mumps virus	NM	MRI T2/FLAIR sequences: hyperintense signal in the medial temporal lobe bilaterally	EEG: bilateral temporal lobe epileptic activity
3	Selcuk et al.	ANA test positive. Positive dsDNA, anti-Smith (Sm), and anticardiolipin IgG. Decreased C3 level, but normal C4 level.	Lymphocytes predominant pleocytosis	Elevated (75 mg/dl)	Normal (50 mg/dl)	Normal whole-body PET-CT. Antineuronal antibodies were not tested.	Negative HSV type 1, type 2 antibodies	Cranial CT: bilateral calcifications of the globus pallidus.	MRI: increased signal intensity in the bilateral hippocampal and Para hippocampal areas, and symmetrical calcification in the globus pallidus	Electroclinical and subclinical seizures with bitemporal and generalized onset

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No	Author	SLE Laboratory Findings (Serum Analysis)	Encephalitis Laboratory Findings (CSF Analysis)			Other Biomarkers	Pathogen Investigation	Neuroradiology Findings		Neurophysiology Findings (EEG)
			Leukocyte	Protein	Glucose			CT Scan	MRI	
4	Angst et al.	Low C3 and C4, positive anti-P ribosomal, anti SSA and ANA, lymphopenia and thrombocytopenia	Lymphocytic pleocytosis	Normal (36.3 mg/dL)	Normal (56 mg/dL)	Normal CEA, CA15-3, CA125 and CA19/9	NM	NM	MRI T2/FLAIR: hyperintense signal on bilateral hippocampi with restriction in diffusion	A temporal Intermittent rhythmic delta activity (TIRDA) pattern in the left temporal area with an electrographic seizure in the right temporal area
5	Munoz et al.	Positive ANA test, elevated anti-RO and anti-La, positive rheumatoid factor	Normal	Normal (25 mg/dl)	Normal (73 mg/dl)	Negative anti-NMDAR antibodies*	Non-reactive VDRL, bacilloscopies and tuberculin test negative	Normal	MRI T2/FLAIR: hyperintense signals on bilateral uncus, hippocampal formations, amygdala nuclei, striated nuclei and external capsules. Restricted diffusion at the uncus and hippocampal head. 3-month follow-up: atrophy of both hippocampi.	EEG: slow low voltage activity consistent with encephalopathic process, continuous bilateral frontal activity with median voltage spiking
6	Sugi et al.	Positive ANA and anti-DNA antibodies, mild leukocytopenia	Mononuclear pleocytosis	Elevated (62 mg/dL)	Normal	NMDA receptor antibody negative (none)	HHV-6 virus DNA negative	NM	MRI T2/FLAIR: bilateral signal hyperintensity in the hippocampus and amygdala, hippocampus atrophy	NM
7	Kelley et al.	Case 1: NM*	NM	NM	NM	NM	NM	NM	MRI T2/FLAIR: bilateral symmetric hyperintensity of the basal ganglia, thalami, and surrounding white matter	NM

No	Author	SLE Laboratory Findings (Serum Analysis)	Encephalitis Laboratory Findings (CSF Analysis)			Other Biomarkers	Pathogen Investigation	Neuroradiology Findings		Neurophysiology Findings (EEG)
			Leukocyte	Protein	Glucose			CT Scan	MRI	
		Case 2: NM*	NM	NM	NM	NM	NM	NM	MRI T2/FLAIR: hyperintensity of the basal ganglia and surrounding white matter	NM
		Case 3: NM*	NM	NM	NM	NM	NM	NM	MRI T2/FLAIR: bilateral symmetric hyperintensity of the caudate and lentiform nuclei, with patchy hyperintensity of the left and right thalami	NM
		Case 4: NM*	NM	NM	NM	NM	NM		MRI T2/FLAIR: diffuse cortical atrophy, bilateral symmetric hyperintensity of the basal ganglia, and scattered small foci of T2/FLAIR hyperintensity in the bilateral supratentorial white matter	NM
		Case 5: NM*	NM	NM	NM	NM	NM	NM	MRI T2/FLAIR: supratentorial and infratentorial white matter and bilateral caudate, putamen, and thalamus hyperintensity	NM

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No	Author	SLE Laboratory Findings (Serum Analysis)	Encephalitis Laboratory Findings (CSF Analysis)			Other Biomarkers	Pathogen Investigation	Neuroradiology Findings		Neurophysiology Findings (EEG)
			Leukocyte	Protein	Glucose			CT Scan	MRI	
8	Manorenj et al.	Positive ANA test, anti- dsDNA, and anti-Sm	NM	NM	NM	NM	NM	NM	Trident sign in pons, temporal atrophy, and claustrum atrophy	Abnormal, showed diffuse theta wave slowing
9	Zhang et al.	Positive ANA, anti-dsDNA antibodies, and anti-Sm antibodies	Lymphocytic pleocytosis	Elevated (62 mg/dL)	Normal	Positive anti-NMDAR antibodies in serum and CSF.	Negative herpes simplex and varicella-zoster virus PCR, negative fungal and acid-fast bacillus smear and cultures	NM	Brain MRI was normal	EEG: generalized slow theta activity with an extreme delta brush pattern
10	Asmaa, et al	Negative antiphospholipid antibodies	Normal	Normal	Normal	Negative anti-NMDAR antibody	Negative HHV-6 virus DNA	NM	MRI T2-FLAIR: hyper signals in the hippocampus and amygdala. MRI 3-month follow-up: hippocampal atrophy	NM
11	Li et al.	Positive for ANA, Anti-dsDNA, anti-Sm, anti-cardiolipin, anti-ribosomal P protein, anti-nucleosome, and anti-SSA antibodies. Decreased C3 and C4 level.	Pleocytosis	Elevated (354 mg/dL)	Normal	CSF and serum: AMPA-R2 antibody detected	Negative CSF cultures for bacteria and fungi	NM	MRI T1/T2: multiple linear or patchy signal shadows in the bilateral subcortical of the frontal, parietal, temporal, and occipital lobes; the white matter around the lateral ventricle; the basal ganglia thalamus area; the splenium of the corpus callosum; the brainstem; and the cerebellar hemisphere	EEG: paroxysmal or sporadic medium amplitude theta activity and atypical sharp and slow waves

No	Author	SLE Laboratory Findings (Serum Analysis)	Encephalitis Laboratory Findings (CSF Analysis)			Other Biomarkers	Pathogen Investigation	Neuroradiology Findings		Neurophysiology Findings (EEG)
			Leukocyte	Protein	Glucose			CT Scan	MRI	
12	Raventhiranathan, et al	Positive ANA, anti-SSA, anti-Sm, and RNP autoantibodies were elevated, IgG and IgA B2 glycoprotein antibodies were elevated	NM	Elevated (49 mg/dl)	NM	NM	NM	NM	MRI T2/FLAIR: abnormal hyperintensity in the bilateral basal ganglia. VWI: no vessel wall enhancement (vasculitis).	NM
13	Tsuchiya et al.	Negative ANA, anti-dsDNA antibody, anti-RNP antibody, anti-Sm antibodies, anti-Ro/SSA antibody, and anti-ribosomal P	Normal	Slightly elevated IgG index and highly elevated IL-6	Normal	Serum and CSF anti-NMDAR type GluRs (anti-GluN2B-NT2 & CT, anti-GluN1-NT) and anti-GluD2-NT & CT elevated	CSF culture negative, PCR of herpes virus DNA and mycobacterium DNA negative	SPECT: increased blood flow in the left temporal lobe and supramarginal gyrus	MRI: restricted water diffusion around the left thalamus	Generalized slow wave
14	Yamaguchi et al.	Positive ANA, anti-RNP antibodies and lupus anticoagulant	Mild pleocytosis	Elevated (83 mg/dL)	Normal (109 mg/dL)	CSF: positive anti-glutamate receptor (ε2, δ2, ζ1) antibodies	NM	NM	MRI FLAIR: hyperintense lesions in the left medial temporal lobe and the left pulvinar nucleus of the thalamus	Generalized slow wave rhythms

Abbreviation: NM, Not Mentioned; CSF: Cerebrospinal Fluid; VWI, Vessel-Wall Imaging; SPECT, Single-Photon Emission Computerized Tomography; MRI, Magnetic Resonance Imaging; EEG, Electroencephalogram; PET-CT, Positron Emission Tomography Scan; PCR, Polymerase Chain Reaction; VDRL, Venereal Disease Research Laboratory; CEA, Carcinoembryonic Antigen; SLE, Systemic lupus erythematosus; HSV, Herpes Simplex Virus; HIV, Human Immunodeficiency Virus; HHV-6, Human Herpesvirus 6; CMV, Cytomegalovirus; ANA, Antinuclear Antibody; AMPA-R2, α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor 2; Anti–Sm, anti-Smith; anti-NMDAR, N-methyl-d-aspartate antibodies; anti–RNP, Anti-Ribonucleoprotein; anti–dsDNA, Anti-double-stranded deoxyribonucleic acid antibodies; anti–SSA, anti–Sjögren's-syndrome-related antigen A; anti–SSB, anti–Sjögren's-syndrome-related antigen B; anti–TPO, Anti-thyroid peroxidase; anti–TG, Antithyroglobulin antibody; VGKC-Ab, Voltage-gated potassium channel (VGKC) antibodies; AFP, alpha-fetoprotein; VZV, varicella-zoster virus; anti-SSA, anti-Sjögren's syndrome A.

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Evidence-Based Analysis

Initial Encephalitis and SLE-Related Presentation

In most cases, patients had a confirmed history of SLE before experiencing encephalitis symptoms (Angst et al., 2015; Asmaa et al., 2022; Kelley et al., 2018; Li et al., 2022; Raventhiranathan et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Sugi et al., 2018; Tsuchiya et al., 2021; Zhang et al., 2021). The time interval between the initial SLE diagnosis and the onset of neurological complications varied from two weeks to 14 years (Angst et al., 2015; Asmaa et al., 2022; Kelley et al., 2018; Li et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Zhang et al., 2021). However, four cases initially showed neuropsychiatric symptoms. Three cases developed flu-like symptoms and infection before hospitalization and neurological impairment (Kelley et al., 2018; Muñoz et al., 2017; Raventhiranathan et al., 2022). Their clinical presentations included general malaise, rhinorrhea, subjective fever, and dyspnea. For the first case, mycoplasma pneumonia was initially diagnosed (Muñoz et al., 2017), while the other case demonstrated fever, diarrhea, and abdominal and flank pain for three days (Raventhiranathan et al., 2022). Out of ten cases with a history of SLE, six patients developed encephalitis while their SLE was under control with steroid treatment, without significant systemic symptoms. Further examinations revealed abnormalities in serum analysis (positive SLE markers) and MRI findings (Angst et al., 2015; Asmaa et al., 2022; Kelley et al., 2018; Li et al., 2022; Raventhiranathan et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Sugi et al., 2018; Tsuchiya et al., 2021; Zhang et al., 2021). In one case, the patient had a prior history of diagnosed SLE and anti-NMDAR encephalitis, with encephalitis manifestations emerging during pregnancy (Zhang et al., 2021). In another case, the patient was initially diagnosed with bipolar disorder. However, after a thorough investigation, it was confirmed that the patient had SLE with limbic encephalitis and bipolar-like manifestations (Manorenj and Shaik, 2021).

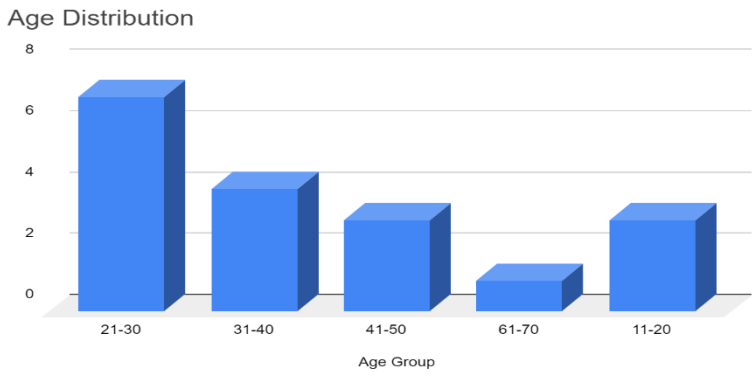

Figure 2. Age distribution of patients diagnosed with SLE and encephalitis

Neurological and Psychiatric Manifestations

The authors observed a spectrum of neurological and psychiatric manifestations such as changes in consciousness, behavioral disturbances, seizures, disorientation, hallucinations, and movement disorders that correspond with the results of EEG and MRI (Angst et al., 2015; Asmaa et al., 2022; Kano et al., 2009; Kelley et al., 2018; Li et al., 2022; Manorenj and Shaik, 2021; Muñoz et al., 2017; Raventhiranathan et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Sugi et al., 2018; Tsuchiya et al., 2021; Yamaguchi et al., 2012; Zhang et al., 2021). These neurological deficits encompass a variety of symptoms, including cognitive impairments such as attention deficits, memory deficits, and aphasia, movement disorders such as dystonia, dyskinesia, gait changes, seizures, pseudobulbar affect,

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delusions, and auditory and visual hallucinations. Mood disturbances were identified in one case (Angst et al., 2015; Asmaa et al., 2022; Kano et al., 2009; Kelley et al., 2018; Li et al., 2022; Manorenj and Shaik, 2021; Muñoz et al., 2017; Raventhiranathan et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Sugi et al., 2018; Tsuchiya et al., 2021; Yamaguchi et al., 2012; Zhang et al., 2021). Several cases exhibited prolonged epileptic seizures during the course of the disease, with a few cases experiencing comorbidities. The first case exhibited prolonged seizures, which were successfully managed on the eighth day of treatment using a combination of five anticonvulsants (Stubgen et al., 1998). The second patient experienced severe seizures and developed non-infectious pneumonitis and renal involvement that required intubation and ICU admission. This complicated case pointed to a diagnosis of SLE with the involvement of CNS. The clinical condition improved with immunosuppressive therapy, but multiple high doses of sedatives were needed to alleviate the neurological complications, including movement abnormalities like peri-oral dyskinesias. Occasionally, the patient would bite the endotracheal tube, resulting in impaired ventilation, which could lead to life-threatening situations (Muñoz et al., 2017).

Another patient showed faciobrachial dystonic seizures and was stuporous. Her condition was complicated by septic shock due to a bed ulcer. The case was considered to involve chronic encephalitis with predominantly psychiatric presentations based on the findings of MRI. Improvement in movement was achieved after antiepileptic and antibiotic administration (Manorenj and Shaik, 2021). While the majority of seizure symptoms improved with the administration of anti-epileptic medications, one case reported a lack of improvement despite undergoing anti-epileptic therapy (Zhang et al., 2021).

The majority of the patients exhibited marked cognitive impairments at the first onset of the disease. One case reported experiencing concurrent cognitive impairments, including sensory aphasia, pseudobulbar affect, auditory hallucinations, memory disturbances, and dyscalculia. These impairments showed improvement within two months following treatment, with memory disturbances being the last to ameliorate. Subsequent findings of the MRI follow-up did not reveal any abnormalities that were present at the onset of encephalitis (Tsuchiya et al., 2021). In contrast, one case showed persistent severe memory impairment and disability three months after hospitalization, with findings of the MRI follow-up showing temporal lobe atrophy (Stubgen et al., 1998). Temporal lobe atrophy and hippocampal atrophy were also noted in other cases, with minimal improvement in memory impairment (Asma et al., 2022; Selcuk et al., 2011). However, some patients reported significant improvement in their cognitive capacities during follow-up, with only minor complaints of delayed thinking and daily routine (Angst et al., 2015; Kano et al., 2009).

Cases with Abnormal Laboratory, Neuroradiology, and Neurophysiology Findings Related to Autoimmune Encephalitis

Several cases reported the identification of specific antineuronal antibodies. Two patients experienced NMDAR encephalitis (Tsuchiya et al., 2021; Zhang et al., 2021), while two others were found to have AMPA-R2 antibodies and antibodies against glutamate receptors (ε2, δ2, ζ1) detected in their cerebrospinal fluid. All these cases exhibited the characteristic neurological impairments of limbic encephalitis, including seizures, cognitive dysfunction, and psychiatric manifestations such as auditory hallucinations. The findings of EEG indicated abnormalities in the form of theta wave activity slowing and generalization. Three out of the four MRI scans demonstrated abnormalities consistent with the clinical presentation, including hyperintensity lesions and multiple signal shadows in the thalamus, basal ganglia, and medial temporal lobe (Li et al., 2022; Tsuchiya et al., 2021; Yamaguchi et al., 201.2; Zhang et al., 2021).

Other cases with negative antineuronal antibodies were diagnosed with encephalitis based on clinical manifestations, abnormal neuroradiological and neurophysiological findings, as well as explorations and exclusion of encephalopathy etiologies. The majority of these cases exhibited typical abnormalities on MRI and/or EEG, including increased signal intensity or atrophy in the medial

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temporal, hippocampal, and parahippocampal areas, amygdala, basal ganglia, and thalamus on MRI, as well as electrographic epileptic activity in the temporal region (Angst et al., 2015; Asmaa et al., 2022; Kano et al., 2009; Kelley et al., 2018; Manorenj and Shaik, 2021; Muñoz et al., 2017; Raventhiranathan et al., 2022; Selcuk et al., 2011; Stubgen et al., 1998; Sugi et al., 2018). One case reported the presence of bilateral calcifications in the basal ganglia, which likely signifies a past pathological process involving the central nervous system (Selcuk et al., 2011).

DISCUSSION

The primary focus of this review was to investigate the co-occurrence of autoimmune encephalitis alongside SLE, a phenomenon that has been observed despite its rarity. Zhao and colleagues also reported a concurrent presence of AE and autoimmune disorders, particularly SLE, in their study (Zhao et al., 2019). Our findings suggested that the most commonly encountered diagnoses in NPSLE patients are limbic encephalitis and striatal encephalitis, both of which present with encephalitis manifestations. It is important to note that NPSLE itself can be further classified into peripheral and central NPSLE, with the latter category subdivided into diffuse and focal NPSLE. The complicated and highly variable clinical presentations within NPSLE have made it difficult to describe an encephalitis syndrome (Bendorius et al., 2018; Haghighi and Haza, 2010; Hanly et al., 2019a; Kowal et al., 2004; Levite, 2014a; Liu et al., 2022; Ota et al., 2022). Some authors have referred to encephalitis manifestations as a representation of NPSLE. Among our findings, the most prevalent neuropsychiatric symptoms include cognitive impairment, seizures, headaches, and altered mental status, which are consistent with previous studies on both focal and diffuse NPSLE (Kampylafka et al., 2013; Vivaldo et al., 2018).

One of the notable aspects of this review is the exploration of the relationship between CNS manifestations of SLE and AE, potentially involving the role of autoantibodies. However, the precise pathogenesis of the connection between SLE and AE remains unclear due to overlapping clinical presentations. Zhao's study sheds light on the fact that anti-LG1 encephalitis exhibits a genetic predisposition linked to the development of other autoimmune diseases (Zhao et al., 2019). More recent research has identified human leukocyte antigen (HLA) alleles in anti-NMDAR encephalitis patients, revealing that although the association is infrequent, the HLA DRB1*16:02 allele is associated with anti-NMDAR encephalitis, specifically targeting the NR1 subunit. HLA DRB1*16:02 was previously linked to an elevated risk of various autoimmune diseases, including Grave's disease, SLE, Sjogren's syndrome, neuromyelitis optica, and relapsing polychondritis. These autoimmune disorders are predominantly mediated by mechanisms of autoantibody formation (Dedhia et al., 2018; Shu et al., 2019). Genetic susceptibility of HLA alleles could potentially contribute to the development of an environment conducive to autoimmune pathology, leading to the coexistence of multiple autoimmune conditions.

The involvement of CNS in NPSLE is often associated with the production of several autoantibodies such as anti-phospholipid antibodies, anti-ribosomal P protein antibodies, and anti-N-methyl-D-aspartate receptor antibodies (anti-NMDA) (Sato et al., 2020). The NMDA receptor, found in neuronal cells within the brain, plays a critical role in memory and learning functions. The functional NMDA receptor is composed of two heterodimeric subunits, specifically the NR1 combined with NR2 subunits (NR2A, 2B, 2C, 2D) or NR3 subunits (NR3A, 3B). NR1/NR2 heterodimers function as NMDA receptors, while NR3 contributes to NR1/NR2 expression or regulates the permeability of Ca2+ via NR1/NR2 receptor channels (Kowal et al., 2004; Ogawa et al., 2016). Elevated levels of anti-NR2 antibodies were identified in the serum and cerebrospinal fluid of patients with diffuse NPSLE, indicating the significant role of anti-NR2 in the onset of diffuse NPSLE and the potential for these antibodies to accumulate in non-neural organs (Liu et al., 2022). Other studies have reported the presence of anti-NR2 NMDAR antibodies in approximately 30% of SLE patients, which play a role in

cognitive dysfunction and psychiatric disorder manifestations (Husebye, 2005; Omdal et al., 2005). However, the concentration of antibodies in the serum does not exhibit a linear relationship with pathology in the CNS (Kowal et al., 2004).

The antibodies that have been generated, specifically the Anti-NMDA-NR2A/B antibodies, exhibit cross-reactivity with ds-DNA antibodies and are associated with neuropsychiatric symptoms, cognitive irregularities, behavioral changes, and mood alterations in SLE patients (Liu et al., 2022). This finding is consistent with the study conducted by Kowal et al., who found that anti-DNA antibodies were shown to bind to both NR2A and 2B subunits (Kowal et al., 2004). These antibodies induced apoptosis of neurons in-vitro in human fetal brain cultures, as well as the loss of neurons in the hippocampus in a murine model after direct in- vivo injection. The loss of neurons in the hippocampus results in impaired memory function and contributes to behavior abnormalities. This occurs because NR2 receptors are distributed in hippocampal neurons, the amygdala, and the basal ganglia, which are integral for cognitive, emotional, and memory functions (Bravo-Zehnder et al., 2015; Ota et al., 2022).

According to Kowal, the antibody alone was sufficient to cause brain pathology, and damage occurred only when the permeability of the blood-brain barrier (BBB) increased (Kowal et al., 2004). When BBB permeability increases, anti-NR2 antibodies gain access to the CNS, where they bind to NMDA receptors, leading to the uncontrolled entry of calcium ions into the cell. These calcium ions are taken up by mitochondria to buffer the incoming calcium, resulting in increased cellular respiration and the production of reactive oxygen species (ROS). The increased calcium ion concentration within the mitochondria causes the collapse of the membrane potential and the opening of mitochondrial permeability transition pores (MPTPs), resulting in the release of proapoptotic molecules and leading to neuronal cell apoptosis. Another cascade involves the activation of cytosolic enzymes such as phospholipases, proteases, and endonucleases that can damage neurons intracellularly, leading to necrosis. This mechanism of neuronal cell death is referred to as excitotoxicity (Bendorius et al., 2018).

The blood-brain barrier (BBB) serves as a protective barrier that separates the brain from systemic blood flow. Its role is to maintain brain homeostasis by preventing harmful elements and inflammatory agents in the bloodstream from entering the brain. At the same time, it selectively transfers essential nutrients to the brain and removes toxic substances and metabolites produced within the brain. An intact BBB can prevent the transport of antibodies from systemic circulation into the brain and plays a crucial role in the pathogenesis of NPSLE (Kowal et al., 2004; Liu et al., 2022; Ogawa et al., 2016). In rodent experiments, anti-NMDA antibodies did not cause neuronal damage until the permeability of the BBB increased (Kowal et al., 2004; Ogawa et al., 2016). The increase in BBB permeability can occur due to autoantibodies and immune complexes binding to the endothelial surface, complement activation, and cytokines such as TWEAK. These changes are often associated with disease activities like cerebral vasculitis, infections, stress, excessive catecholaminergic activity, and nicotine exposure (Hanly et al., 2019b; Kowal et al., 2004). The CSF serum albumin ratio can be used to assess BBB permeability (Liu et al., 2022).

Elevated levels of anti-NMDA-NR1 antibodies are frequently observed in the cerebrospinal fluid (CSF) of patients with anti-NMDA-receptor encephalitis, indicating intrathecal production, and they respond positively to immunotherapy. AE involving anti-NMDAR antibodies is highly specific to the NR1/NR2 heterodimer and causes detrimental effects on the function of NMDA receptors. Conversely, anti-NMDA-NR2A/B antibodies were found in patients with SLE, both with and without neuropsychiatric manifestations, as well as in certain sub-populations of paraneoplastic encephalitis. Anti-NMDA receptor antibodies interact with the NR1/NR2 heterodimer subunit (Levite, 2014b). In a study by Ogawa, higher levels of anti-mNR1 antibodies were detected, along with increased anti-NR1A and anti-NR1C antibodies, in both serum and CSF of patients with NPSLE. The levels of anti-NR1A/NR1C in CSF were significantly higher in diffuse NPSLE compared to focal NPSLE. These

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findings suggested a potential role of NR1-specific autoantibodies in the pathogenesis of NPSLE. It is suggested that anti-NR2 antibodies may cross-react with the NR1 subunit, considering SLE antibodies have been shown to cross-react with NMDA receptor NR2 subunits, leading to neuronal dysfunction (Ogawa et al., 2016). Given the clinical similarities between NPSLE and autoimmune encephalitis, it is plausible that there is a mechanistic link connecting the coexistence of SLE and AE through anti-NR1 antibodies. As previously explained, autoantibodies that can directly target neuronal cells have the potential to cause severe neural damage (Hirohata et al., 2014).

Nevertheless, a recent study conducted by Hirohata et al. evaluated the presence of anti-NR1/NR2 antibodies and analyzed the cross-reactivity of anti-NR2 and anti-NR1/NR2 antibodies. Their study revealed a very low prevalence of anti-NR1/NR2 in NPSLE patients, with only two out of 22 patients detected with anti-NR1/NR2 antibodies in serum, and no anti-NR1/NR2 antibodies were detected in the CSF (Hirohata and Tanaka, 2019). It should be emphasized that the presence of antibodies in the CSF is crucial in the pathology of autoimmune NMDAR encephalitis. Furthermore, the detection of NMDAR antibodies is more sensitive in the CSF compared to serum (Gresa-Arribas et al., 2014). These findings suggested that anti-NR1/NR2 may not be responsible for the encephalitis manifestations in these two patients, making their cases exceptionally rare. Hirohata also indicated that the expression of anti-NR2 in NPSLE may differ from that of anti-NR1/NR2, warranting further exploration (Hirohata and Tanaka, 2019). The conflicting results between studies can be attributed to methodological differences, as Ogawa employed the enzyme-linked immunosorbent assay (ELISA) method, which carries the risk of false positives, while Hirohata's study used cell-based analysis (CBA), known for its higher sensitivity and specificity (Lang and Prüss, 2017; Sechi and Flanagan, 2021).

One case reported an association between anti-NMDAR encephalitis and SLE, with a positive diagnosis of anti-NR1 NMDAR using CBA on NMDAR-HEK293 cells in both serum and the CSF (Wu et al., 2016). This case, along with earlier reports, implies that SLE serves as an indicative factor in the progression of AE. To date, the relationship between SLE and the development of anti-NMDAR encephalitis remains poorly understood. Given the contradictory findings, whether the association between SLE and autoimmune encephalitis is purely coincidental or if other phenotypes are responsible for this connection, further observation on a larger case-cohort is required.

Limitations

This review has several limitations. First, the scarcity of cases has resulted in a limited number of studies available for analysis. Second, the search for studies was restricted to a limited number of databases. Moreover, the potential for publication bias exists because of unreported research and the inclusion of gray literature. Additionally, there may be variations in the methodological quality of the studies included in this review, thereby affecting the reliability of the analytical results. While efforts have been made to screen and evaluate the quality of included studies, the potential for judgment bias remains.

Strengths

This systematic review offers an overarching overview of the available literature, presenting crucial findings that can guide the direction of future research. By mapping the gaps in knowledge and identifying existing challenges, this review has the potential to inspire researchers to engage in a more comprehensive scientific approach toward understanding the correlation between SLE and AE.

CONCLUSION

This systematic review establishes a groundwork for future investigations into the pathophysiology of the immune system underlying the relationship between SLE and autoimmune encephalitis.

Examination of specific neuronal antibodies is essential in this subpopulation, especially when NPSLE patients present with overlapping symptoms and signs that raise suspicion towards autoimmune encephalitis. This exploration aims to elucidate the etiology and provide appropriate therapy to minimize complications. There is still ongoing debate as to whether the encephalitis manifestations in SLE patients are part of the NPSLE spectrum mediated by SLE antibodies or if there exists an alternative pathophysiology involving specific antibodies that contribute to autoimmune encephalitis pathology associated with SLE. Further clinical research is needed to shed light on the pathogenicity of autoantibodies in patients with SLE-associated autoimmune encephalitis.

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Conflict of Interest

The authors declare no conflicts of interest that could potentially bias the findings or interpretations presented in this systematic review. This work has been conducted with complete impartiality and adherence to PRISMA, ensuring the integrity and accuracy of the information provided to the best of our ability.

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Author Contribution

The authors' contribution to the paper is as follows. NNP's role: study conception and design, data analysis and interpretation, writing the draft, and critical revision of the article. FLH's role: data curation, data analysis, and manuscript editing and preparation. All authors reviewed the results and approved the final version of the manuscript.

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