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Interactions between pain and psychopathology in pediatric and adult patient populations

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CHAPTER 3

IMPLICATIONS OF INFLAMMATORY PROCESSES ON A DEVELOPING CENTRAL
NERVOUS SYSTEM IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

IMPLICATIONS OF INFLAMMATORY PROCESSES ON A DEVELOPING CENTRAL NERVOUS SYSTEM IN CHILDHOOD -ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, increasingly affecting pediatric and adult populations. Neuropsychiatric manifestations (i.e., cognitive dysfunction and mood disorders) appear to occur with greater severity and poorer prognosis in childhood vs adult-onset SLE, negatively impacting school function, self-management, and psychosocial health, as well as lifelong health-related quality of life. In this review, we describe pathogenic mechanisms active in childhood-onset SLE (cSLE) such as maladaptive inflammatory processes and ischemia, which are hypothesized to underpin central phenotypes in cSLE cases, while the role of alterations in protective central nervous system (CNS) barriers (i.e., the blood-brain barrier) are also discussed. Recent findings derived from novel neuroimaging approaches are highlighted as the methods employed in these studies hold potential for identifying CNS abnormalities that would otherwise remain undetected with conventional MRI studies (e.g., T2-weighted/FLAIR sequences). Furthermore, we propose that a more robust presentation of neuropsychiatric symptoms in childhood-onset SLE (cSLE) is in part due to the harmful impact of a chronic inflammatory insult on a developing central nervous system (CNS). Although the immature status of the CNS may leave cSLE patients more vulnerable to harboring neuropsychiatric manifestations, the same property may represent greater urgency to reverse the maladaptive effects associated with a pro-neuroinflammatory state, provided that effective diagnostic tools and treatment strategies are available. Finally, considering the crosstalk between the CNS and other organ systems affected in cSLE, we postulate that a finer understanding of this interconnectivity and its role in the clinical presentation in cSLE is warranted.

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a complex autoimmune disease with an estimated prevalence of 1.89-25.7 per 100,000 children¹. A challenging aspect of cSLE is the occurrence of neuropsychiatric or neurological features such as cognitive dysfunction, mood disorders, encephalopathy, or seizures². Alongside renal and hematological involvement, as well as medication toxicity, neuropsychiatric features appear to be more prevalent and severe in childhood compared to adulthood SLE cases^{3,4}. Cognitive dysfunction and other neuropsychiatric symptoms of cSLE can negatively impact self-management, psychosocial health and overall health-related quality of life (HrQoL) during development and adulthood, and relate to more SLE disease damage⁵⁻⁸. Moreover, challenges for patients and clinicians alike may arise when neuropsychiatric symptoms of SLE (i.e., cognitive dysfunction, depression) exacerbate medication non-adherence. In a cyclical manner, difficulties with medication adherence may worsen disease activity or neuropsychiatric symptom severity.

Early diagnosis and implementation of effective treatment of central nervous system (CNS) involvement in cSLE patients is critical^{2-4,9}. However, such an objective is hindered by heterogeneity in neuropsychiatric symptom presentation (type and severity), a clinical focus on more understood cardinal features of cSLE (e.g., systemic inflammation, arthritis, cutaneous manifestations, or renal complications), and the unavailability of sensitive clinical tools that facilitate accurate detection and monitoring of neuropsychiatric or neurological symptoms in cSLE. With respect to the latter, while some cSLE patients with central nervous system (CNS) involvement demonstrate abnormalities on standard-of-care neuroimaging, in other individuals with neuropsychiatric symptoms no remarkable findings are observed (**Supplemental Material Box 1**).

Outside of cSLE, prior work has revealed that inflammatory states are associated with cognitive dysfunction and depressed mood¹⁰. Therefore, bidirectional interactions between disease activity or inflammatory status with neurocognitive deficits or potent emotional states should be expected in cSLE. While a greater genetic susceptibility may independently yield an overall more progressive disease status in childhood- vs. adult-onset SLE patient populations, what remains largely unclear are the neuropathological mechanisms associated with more severe presentation of neuropsychiatric symptoms and the poorer long-term prognosis in cSLE cases¹¹. We hypothesize that the neurodevelopmental status of the CNS represents a point of vulnerability in cSLE patients such that systemic immunological disruptions (i.e. inflammatory insults and autoantibody-mediated injury) may relate to more pronounced neuropsychiatric phenotypes in patients with cSLE relative to their adult counterparts. Here, the variable trajectory for individual CNS structures, from the prefrontal cortex to cerebellar lobules are considered. We further discuss how this variability may integrate with CNS involvement in cSLE. Our review of cSLE patient cases with neuropsychiatric presentations suggests involvement of specific brain systems, i.e. basal ganglia or cerebellar regions, which may play a role in cognitive dysfunction and altered emotional status in cSLE. The potential inflammatory pathways and interactions between the brain and non-CNS systems that may be affected in cSLE are reviewed. Finally, novel clinical research tools and approaches that may enable a more in-depth analysis of neuropathological features in cSLE patients are discussed.

Selection Criteria for this Review

The literature review was conducted using published literature, cohort studies, case reports and systematic reviews, collected through a search of PubMed and Google Scholar publications in English. Search terms included combinations of the following keywords: “systemic lupus erythematosus”, “childhood”, “lupus”, “neuropsychiatric symptoms”, “CNS”, “mood disorder”, “psychosis”, “acute confusional state”, “cognitive dysfunction”, “seizures”, “cerebrovascular disease”, “movement disorder”,

“headache”, “inflammation”, “pathogenesis”, “inflammatory subtype”, “ischemic subtype”, “immune system”, “autoantibodies”, “cytokines”, “brain barrier”, “barrier dysfunction”, “blood-brain barrier”, “blood CSF barrier”, “meningeal barrier”, “glymphatic system”, “choroid plexus”, “neuroimaging”, “microstructure”, “gray matter”, “white matter”, “cortical”, “subcortical”, “neurodevelopment”, “development”, “early life stress”, “renal system”, “kidney”, “lupus nephritis”, “skin”, “gastrointestinal”, “microbiome”, “cardiovascular”, “PRES”.

Overview of CNS Symptoms in cSLE

While children and adolescents with cSLE frequently report neuropsychiatric-type symptoms such as mood changes and cognitive problems, symptom severity can vary and objective signs of neuropsychiatric involvement can go undetected during routine clinical workup without implementation of specific neurocognitive testing. A subset of patients with cSLE will meet clinical criteria for neuropsychiatric cSLE (cNPSLE). The classification of cNPSLE is based on the nomenclature defined by the American College of Rheumatology (ACR). This classification system, albeit defined in adult cohorts, has been extrapolated to the pediatric population. Based on a limited number of pediatric studies, specific syndromes of cNPSLE are briefly described below in terms of estimated prevalence, approximate age of onset, and behavioral phenotypes. These neuropsychiatric presentations are usually not limited to a single symptom as they may occur simultaneously, and recurrence of neuropsychiatric symptoms is often observed in cNPSLE.

Mood Disorder

Mood disorders have an estimated pooled prevalence of 28.3% in patients diagnosed with cNPSLE, with an average onset at the age of 16.5 ± 2.9 years^{2,3,12,13}. Increased symptoms of depression and anxiety in cNPSLE populations may also be reflective of the inherent challenges relating to living with a chronic illness.

Psychosis

Approximately 22.7% of cNPSLE patients develop psychosis, typically in the form of visual hallucinations, and less frequently auditory hallucinations, with an estimated mean age of onset of 15.4 ± 3.2 years^{2,12,13}.

Paranoid delusions may also present as a form of psychosis.

Acute Confusional State

The pooled prevalence of individuals with cNPSLE that experience acute confusional state during the course of their disease is 15.7%, with an average age of symptom onset at 16.2 ± 6.1 years^{2,12}. Acute confusional state, or 'delirium', is defined as an observable state of impaired consciousness, perception, attention, or cognition lasting for hours or days.

Cognitive Dysfunction

Prior reports indicate a high prevalence of cognitive dysfunction in cNPSLE (32.9%), with a mean age of onset at 15.8 ± 5.1 years^{2,3,12,13}. In addition to standard neuropsychological testing, the validation of the computerized neurocognitive battery Pediatric PedANAM has the potential to facilitate early and accurate diagnosis of cognitive dysfunction in cSLE, although it has not yet been implemented in standard clinical practice to date¹⁴.

Seizures

Seizures occur in an estimated 48.6% of cNPSLE cases with an average onset at the age of 16.4 ± 2.9 years and rarely occur as the sole neuropsychiatric manifestation^{2-4,12,13}. They are often concomitant with cerebrovascular disease, cognitive dysfunction, and elevated levels of antiphospholipid antibodies (aPL)¹⁵. Posterior reversible encephalopathy syndrome (PRES), a multisystemic complication presumably

caused by vasogenic subcortical brain edema in the posterior lobes of the CNS, commonly presents with seizures¹⁶.

Cerebrovascular Disease

The average onset of cerebrovascular symptoms in cNPSLE is reported at the age of 15.0 ± 5.9 years(1–3)^{3,4,12}. Younger patients with SLE, in particular, have a much higher relative risk of cerebrovascular manifestations when compared to the general population, including up to a 10-fold increase in the risk of stroke and other cerebrovascular events¹⁷.

Movement Disorder

Movement disorders, such as chorea, affect up to 9.4% of patients with cSLE with a mean age of onset at 15.2 ± 3.6 years^{2,12,13}. Movement disorders often precede the appearance of other neuropsychiatric manifestations and usually occur in tandem with seizures, acute confusional state, and/or cerebrovascular disease, specifically brain ischemia. Unilateral chorea is seen more frequently than bilateral chorea. Ataxia, otherwise known as impaired coordination, and parkinsonism can also occur in cNPSLE¹⁸.

Headache

Headache is the most common neuropsychiatric symptom in children, affecting an estimated 52.5% of cNPSLE patients, at an average age of 12 ± 3.9 years^{2,5,12,13}. However, differentiating lupus headache from other common causes of headache is challenging, as there are no available biomarkers, and the prevalence of headache in the general population is also high¹⁹. A possible association between CNS pathology and headache in cNPSLE has been suggested, as lupus headache is specifically factored into the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scoring system.

Nonetheless, the concept of a lupus headache is questionable given the high prevalence of headache in other diseases or healthy populations⁵. Moreover, diagnosis of lupus headache requires unresponsiveness to narcotics, which cannot be ascertained as these are rarely prescribed to children with SLE.

Other CNS Manifestations

Other less prevalent neuropsychiatric manifestations affecting the CNS are aseptic meningitis and demyelinating syndrome. Aseptic meningitis, reported 5.1% of patients is defined as a syndrome of fever, headache and meningeal irritation and can be detected through cerebrospinal fluid (CSF) analysis^{2,13}. Demyelinating syndromes in cNPSLE patients are a very rare occurrence in this disease, with a pooled prevalence of 3.2%^{2,13}.

Pathogenic Mechanisms in NPSLE

Two main pathophysiologic mechanisms have been proposed in NPSLE, the inflammatory and ischemic subtype, although these distinct phenotypes are much contested and most likely complementary. The ischemic subtype associates with microvascular and thrombotic processes with altered blood flow to specific brain regions, whilst the inflammatory phenotype relates to pathogenic autoantibodies and disruption of the blood- cerebrospinal fluid (CSF) barrier or blood-brain barrier (BBB). Blood vessel injury and thrombosis in the ischemic phenotype is mediated mainly by antiphospholipid (aPL) antibodies and associated pathways²⁰. aPL has not only been linked to focal events such as stroke, but also to neuropsychiatric manifestations such as cognitive dysfunction, psychosis and seizures, via mechanisms independent of thrombosis²¹. Moreover, higher serum levels of aPL antibodies have been reported in patients with NPSLE compared to those with SLE only²².

In the inflammatory phenotype, CNS lesions appear to follow from autoimmune related processes in association with autoantibodies, including anti-N-methyl-D-aspartate receptor (anti-NMDAR), anti-ribosomal P protein (anti-Rib-P), and anti-aquaporin 4 (anti-AQP4)²³. In the pathogenesis of SLE, some of the known key factors driving inflammation that have also been linked to CNS involvement involve elevation of pro-inflammatory cytokines, including interferon alpha and gamma (IFN- α and IFN- γ), interleukins-1 and 6 (IL-1 and IL-6), interleukin 17, tumor necrosis factor alpha (TNF- α), and B-cell-activating factor (BAFF), increased expression of toll-like receptors (TLR) 7 and 9, as well as activation of pathogenic T helper cell subsets²⁴. A subset of antibodies that bind to DNA and NMDA receptors, DNRAbs, are observed in brain tissue and CSF of patients with SLE. In a mouse model where the BBB is disrupted, these autoantibodies are found to cause excitotoxic neuronal death in the hippocampus²⁵, suggesting that they are likely pathogenic in NPSLE. Moreover, elevated levels of CSF albumin, haptoglobin, β -2 macroglobulin and α -2 macroglobulin are found in NPSLE, correlating with development of diffuse NPSLE²⁶. Increased levels of pro-inflammatory cytokines including IL-6, TNF- α , CXCL8/ IL-8, monocyte chemoattractant protein-1 (CCL2), macrophage Inflammatory protein-1 alpha (MIP-1 α) and IL-12p70 were observed in new-onset status epilepticus patients, highlighting the importance of innate immunity-related inflammation in pathogenesis of neuropsychiatric syndromes, although causality has not been established, and seizure activity itself may also contribute to this inflammatory response²⁷. Complement pathway activation is implicated in subsequent tissue damage in various organs via complement-mediated cytotoxicity as well as neutrophil chemotaxis. There is evidence that complement split products such as C5a increase BBB permeability²⁸. Moreover, complement activation has been linked to microglia-mediated synaptic loss and increased anxiety-like behaviour in a murine NPSLE model²⁹. Post-mortem histopathological lesions such as microthrombi and vasculopathy as well as complement deposition have been related to clinical syndromes defining adult NPSLE³⁰. The inflammatory

subtype of NPSLE has also been linked to distinct structural and microstructural neuroimaging abnormalities which were more pronounced than in the ischemic subtype, suggestive of heterogeneous pathological mechanisms of NPSLE phenotypes^{31,32}. However, the overlap between inflammatory and thrombotic mechanisms is highlighted by the dual roles of various inflammatory mediators, such as neutrophil extracellular traps, in SLE disease activity as well as endothelial activation and thrombosis. As a result, there are close interrelationships between inflammation, microvascular dysfunction and thrombosis.

Protective Brain Barriers

The brain is immune privileged in normal circumstances due to the protective properties at several interfaces, including the BBB, the blood- CSF barrier, the meningeal barrier and the glymphatic system, although existence of the latter is debatable. The BBB prevents neurotoxic compounds and pathogenic autoantibodies circulating in the blood from entering the brain. Simultaneously, there is a closely regulated transport of molecules into and out of the CNS to maintain the chemical composition of the brain, which is essential for normal neurobiological functioning. Perturbations within one of the barriers can allow for the infiltration of autoantibodies and immune cells into the CNS, initiating neuroinflammatory processes and potentially resulting in neuronal atrophy (**Figure 1**). Several inflammatory mediators, including pro-inflammatory cytokines, complement breakdown products, and more recently, activation of the sphingosine-1-phosphate pathway, have been implicated in brain barrier disruptions in SLE and other neuroinflammatory conditions^{33,34}. There are indications that barrier dysfunction plays a central role in the pathogenesis of NPSLE. For one, although uncommon, aseptic meningitis can occur in cNPSLE and implies a disruption of the meningeal barrier, which separates the brain from surrounding tissue²³. Secondly, the glymphatic system provides controlled interaction between interstitial fluid, CSF, and the

lymphatic network, and has the potential to transport leukocytes in and out of the CSF in NPSLE³⁵. However, these pathways have not been thoroughly investigated in the context of SLE. Integrity of the BBB can be measured by several biomarkers, although a single marker without significant limitations has yet to be identified. Recently, the common view on barrier disruption in NPSLE has shifted with more solid evidence for disruption of the blood-CSF barrier rather than the BBB³⁶. Permeability studies have included albumin concentration gradient and IgG gradient between CSF and plasma, which both appear elevated in patients with NPSLE and corresponding animal models. Moreover, passive transfer of anti-P ribosomal antibodies purified from serum of patients with NPSLE directly to mice brains has been shown to induce depressive behaviors. Recently, the importance of the choroid plexus in the CSF barrier has been indicated, as it has an active role for inflammatory responses during CNS infection, and is posited as an entry point of lymphocytes into the CNS in NPSLE³⁷.

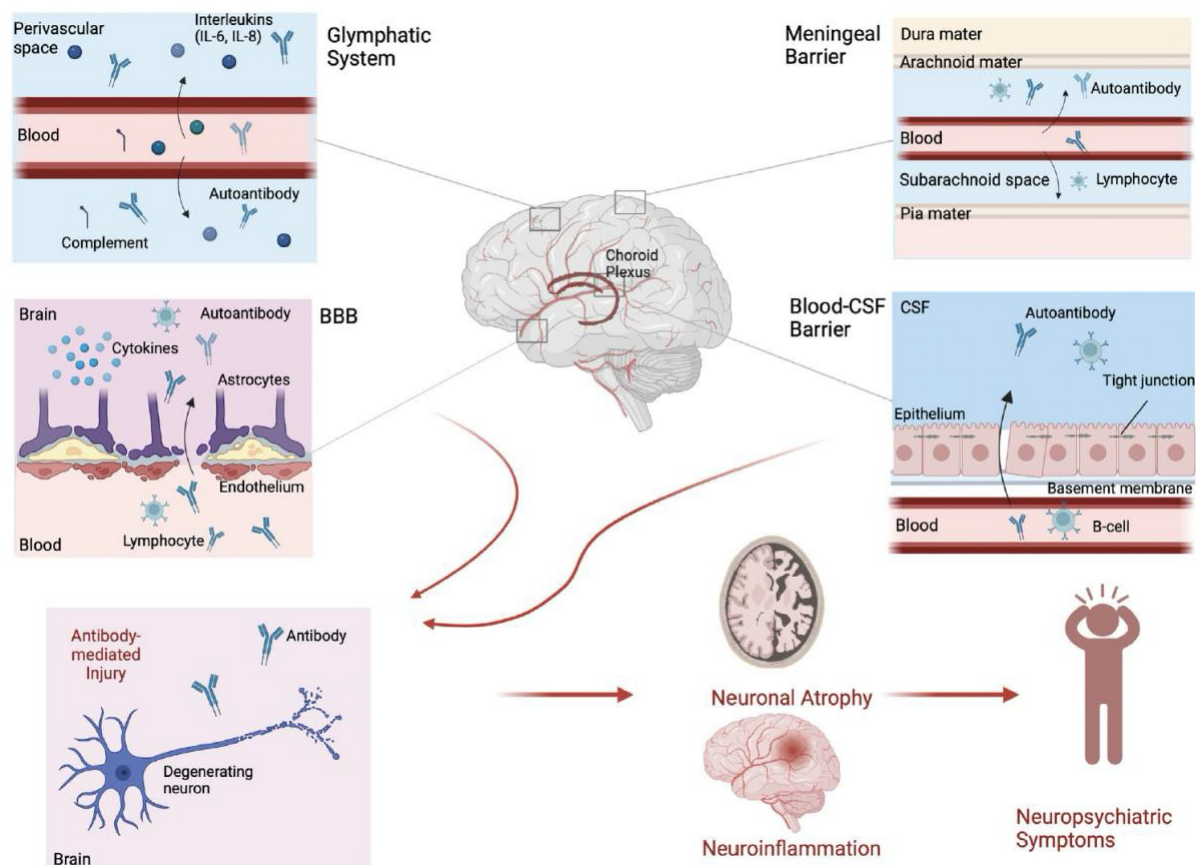


Figure 1. Brain barriers and potential pathways for neuroinflammation that may lead to neuropsychiatric symptoms in NPSLE. The glymphatic system, BBB, meningeal barrier, and blood–CSF barrier are displayed schematically with potential mediators for inflammatory responses, and a breach of one of these barriers may enable antibody-mediated injury by means of immune complex deposition or antibody-dependent cytotoxicity and excitotoxicity. BBB, blood–brain barrier; CSF, cerebrospinal fluid; NPSLE, neuropsychiatric systemic lupus erythematosus.

Imaging Abnormalities

There is a very limited number of studies that have examined structural and functional neurobiological aberrancies in patients with cNPSLE. Nonetheless, an amalgam of cNPSLE case reports and small cohort studies employing neuroimaging approaches indicate involvement of specific CNS structures or networks (**Table 1**). Though an evaluation of cSLE neuroimaging studies is outside the scope of the current review, some insights might be garnered from this body of work. For instance, associations between cognitive dysfunction and imaging findings have been observed in non-NP cSLE studies, such as reduced white/gray

matter volume and reduced global structural connectivity in white matter pathways^{38,39}. Similarly, acute confusional state has been linked to atrophy of the corpus callosum⁴⁰. Moreover, imaging methods such as fMRI and dynamic contrast-enhanced MRI (DCE-MRI) have provided important insights in linking functional aberrancies, BBB permeability and neuropsychiatric symptoms primarily in adults with NPSLE⁴¹. For instance, resting-state functional hypoconnectivity has been associated with memory impairments, while altered task-based functional connectivity was linked to cognitive dysfunction in NPSLE^{42,43}. Altered cerebral blood flow within gray and white matter distinguished between SLE patient with or without neuropsychiatric symptoms as well as control subjects. Morphological or microstructural changes also correlated with disease activity and disease damage scores in these patients⁴⁴. Furthermore, increased BBB permeability as determined by DCE-MRI particularly in the insular regions has been associated with altered mood (e.g., depression or anxiety), while voxel-based morphometry, magnetization transfer ratio, and DCE-MRI have been employed to predict neurocognitive performance in SLE patients using a machine learning-based multimodal imaging model^{45,46}.

White matter

White matter lesions (e.g., focal hyperintensity on T2-weighted MRI) are a frequent finding in cNPSLE. The presence of one or more T2/FLAIR white matter hyperintensities (WMH) represented approximately 72% of MRI abnormalities and were observed in 33% of children with active NPSLE⁴⁷. These MWH lesions occurred within supratentorial white matter and brainstem regions. Similarly, supratentorial white matter lesions and atrophy were observed in another cohort of cNPSLE patients, and case studies showed focal lesions in the periventricular as well as deep and superficial subcortical white matter, specifically in the frontal and temporal lobes⁴⁸ (**Table 1**). Diffusion Tensor Imaging (DTI) studies specifically investigating cNPSLE patients have not been performed, but a global loss of streamline axonal density was observed in

a group of cSLE patients with neurocognitive dysfunction, which included one patient with cSLE and clear neuropsychiatric diagnosis³⁹.

Cortical Gray Matter

Very few studies have examined structural brain alterations in cNPSLE patients, but several case studies have described the occurrence of gray matter abnormalities. One imaging study that focused on children with active NPSLE demonstrated global brain atrophy (18,5%), cortical gray matter lesions (3%) and basilar artery territory infarctions (3%), although no abnormalities on standard of care MRI were observed in 59% of the patients⁴⁷. Moreover, imaging findings in a cohort of 28 children with cNPSLE included cortical gray matter lesions, as evidenced by T2/FLAIR hyperintensities⁴⁹, and a study of cSLE patients with neurocognitive deficit revealed global atrophy and regional decline in gray matter³⁸.

Deep Gray Matter

The previously mentioned study of 28 patients with childhood NPSLE has also revealed hyperintensities in the brainstem and basal ganglia⁴⁹. In the work by Al-Obaidi et al., one cNPSLE patient had evidence of infarctions within the thalamus and the brainstem, but to our knowledge, no other large cohort studies have reported on subcortical gray matter abnormalities⁴⁷. However, several case reports of cNPSLE patients have implicated alterations within subcortical structures including the basal ganglia, thalamus, lentiform and caudate nuclei, and brainstem (**Table 1**).

Cerebellum

The presence of lesions in the cerebellum and brainstem in cNPSLE has been described in previously mentioned cohort studies, as well as in case reports (**Table 1**)^{49,50}. See also **Box 1**. However, the evidence

of cerebellar abnormalities in cNPSLE is sparse, and further investigation to pinpoint specific affected regions is warranted.

Vulnerability of a Developing CNS during Childhood

During childhood and adolescence, gray and white matter structures undergo a variable and region-specific maturation process, whereby peak development from a cytoarchitectural or myeloarchitectural standpoint of some neuronal substrates occurs earlier than others. We postulate that for CNS regions that have not fully developed, exposure to (neuro-)inflammatory insults may yield more robust structural and functional perturbations relative to a fully matured CNS. Internal or external disturbances, mainly, a chronic inflammatory state, on the CNS may not only impact childhood and adolescence but extend into adulthood. Furthermore, in cSLE, some neuropsychiatric manifestations seem to present or become recognized at an earlier age than others. We postulate a link between the developmental status of CNS regions and specific neuropsychiatric symptoms.

Neurodevelopmental Trajectory in Healthy Individuals

Regional developmental patterns of white matter integrity as well as cortical and cerebellar gray matter volume have been characterized using MRI(66–68)^{51–53} (**Figure 2**). The process of brain maturation pertains to distinct patterns of cortical thinning paired with microstructural changes in white matter⁵⁴. The neonatal years encompass a critical stage for brain development, and the complex processes have previously been described⁵⁵. The development of the brain has been shown to follow a general pattern from inferior to superior, and from posterior to anterior regions. There is also variability between cortical and subcortical regions that mediate a range of CNS processes implicated in cNPSLE (e.g., mood regulation or cognitive functioning). For example, the PFC (complex cognitive functioning) displays peak vulnerability between the ages of 14-16, which overlaps with the peak age of onset of cSLE. This is in

contrast to the amygdala (fear and emotion), which is most susceptible to alterations in the first year of life, and then again between the ages of 9 to 11, and the hippocampus (learning and memory), which is most vulnerable between the ages of 3 to 5, when monogenic causes of cSLE presentations predominate.

The total cerebral cortex volume decreases following an inverted U-shape trajectory, peaking around age 7 for both males and females, whilst cerebral white matter continues to increase into mid to late adolescence⁵². Concerning cerebellar volumes, peak volumes appear dependent on biological sex, with the inferior posterior lobe reaching its peak development first, followed by the anterior lobe and the superior posterior lobe⁵³. Importantly, these regional changes in cortical and cerebellar properties during maturation contribute to the evolving cognitive, emotional, and sensorimotor functioning over the course of childhood, adolescence and into adulthood.

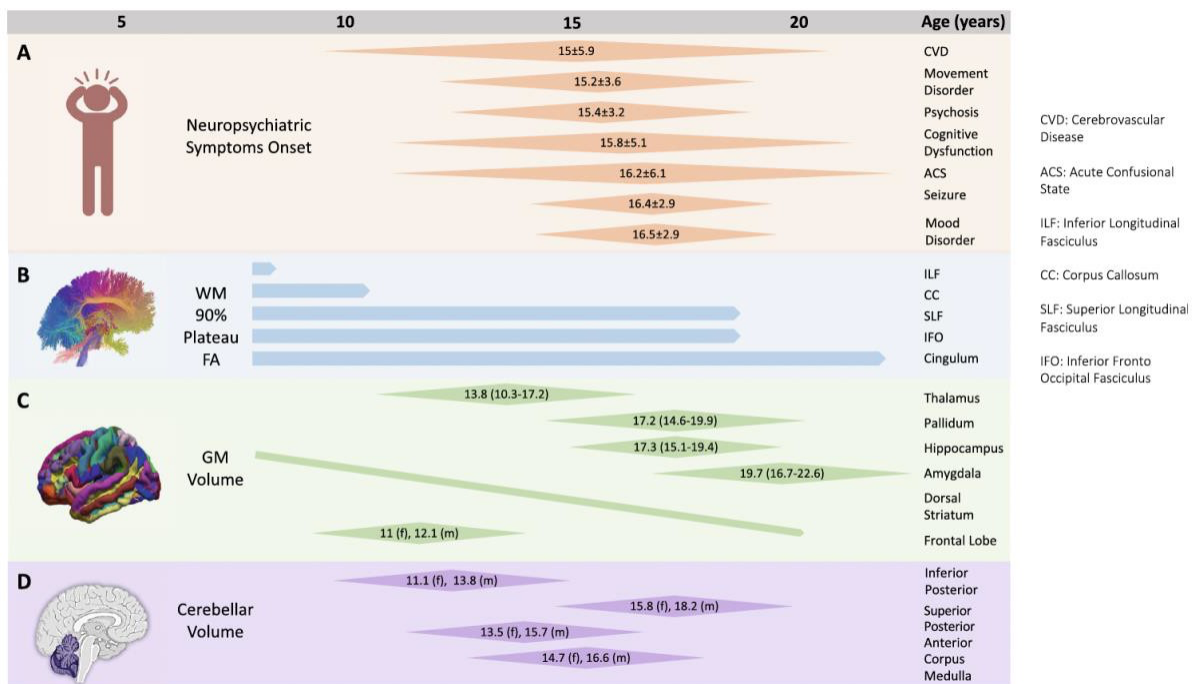


Figure 2. Timeline displaying average age of onset of neuropsychiatric symptoms in childhood NPSLE and developmental peak ages or trajectories of relevant brain regions and structures, indicating vulnerability periods. CVD: Cerebrovascular Disease. ACS: Acute Confusional State. (A) Average age of onset of cNPSLE symptoms; mood disorder (16.5), cognitive disorder (15.8), seizure disorder (16.4), psychosis (15.4), cerebrovascular disease (15), acute confusional state (16.2) and movement disorder (15.2), not

including headache considering the ambivalence of this symptom in cNPSLE¹². (B) White matter tracts fractional anisotropy (FA) 90% plateau value in normal development of Inferior Longitudinal Fasciculus (ILF), Corpus Callosum (CC), Superior Longitudinal Fasciculus (SLF) and Inferior Fronto Occipital Fasciculus (IFO)⁵¹. (C) Gray matter volume peaks in normal development of thalamus (13.8), palladium (17.2), hippocampus (17.3) and amygdala (19.7) and volumetric change trajectory of the dorsal striatum (caudate and putamen) and frontal lobe (11 females, 12.1 males)⁵². (D) Volumetric peaks of cerebellar inferior posterior lobe (11.1 females, 13.8 males), superior posterior lobe (15.8 females, 18.2 males), anterior lobe (13.5 females, 15.7 males) and corpus medulla (14.7 females, 16.6 males)⁵³.

Neurobiological Impact of Early life Stress

Although providing a complete overview of the neurodevelopmental ages and vulnerabilities of specific brain regions is beyond the scope of this review, there is evidence suggesting that early life social-environmental context results in structural alterations. The term early life stress can refer to childhood adversity or trauma, but also encompasses cumulative stress related to built environment, socioeconomic status, and social and community context. For example, exposure to toxins, inadequate nutrition, or emotional neglect have been linked to a range of cognitive and behavioral maladaptations⁵⁶. The CNS circuitry regulating emotions is hypothesized to mature more rapidly following adversity during sensitive periods of development, such as accelerated changes of cortical thickness and volume in, for example, prefrontal cortex, amygdala and other subcortical regions, with more mature functional connectivity of these networks observed in individuals exposed to early life stress⁵⁷. Moreover, decreased integrity of various WM tracts within the mesocorticolimbic systems has been observed in response to early life stress, and such alterations in WM properties persist into adolescence⁵⁸. Increases in perceived stress have also been linked to heightened disease activity and burden in individuals with SLE, albeit this has yet to be studied in children⁵⁹.

Inflammation and Neurodevelopmental Vulnerability in Childhood

Children differ from adults in their levels of cytokines, chemokines and in their ability to produce cytokines, which could result in suboptimal immune response and increased susceptibility to infections. In the brain,

there appear to be regional differences in susceptibility to cytokines, with the hippocampus found to be the most vulnerable region to apoptosis-promoting factors, microglial activation and oxidative stress during experimental sepsis. The striatum (i.e. caudate and putamen) is considered more vulnerable to oxidative damage compared to other brain areas and anterior insula volume appears to be highly sensitive to inflammation⁶⁰. Moreover, patients with sepsis-induced brain dysfunction exhibited volumetric reduction in cerebral and cerebellar white matter, cerebral cortex, hippocampus, and amygdala. In these patients, a loss of volume in the caudate nuclei, putamen and thalamus associated with worse disease outcome including coma and death. The previously presented case studies of cNPSLE patients showed imaging abnormalities in similar regions (e.g. basal ganglia, thalamus, cerebral and cerebellar white matter). Furthermore, in inflammatory NPSLE patients, white matter integrity as measured using magnetization transfer ratio has been linked to cognitive dysfunction, psychosis and mood disorder³². The susceptibility to inflammatory insults in these regions may lead to increased structural injury, resulting in neuropsychiatric manifestations.

Systemic Involvement & Inflammatory Interplay between the Brain and non-CNS Systems

In addition to the CNS, other systems are also commonly affected by cSLE⁶¹. Pulmonary, renal, gastrointestinal, musculoskeletal, hematological, and ocular system injury has been observed and may interact with neurobiological processes in SLE in general. The level of dysfunction of non-CNS systems in SLE also appears to differ between childhood and adult populations.

Renal involvement occurs in up to 70% of children with SLE, typically early in the disease course, and appears to be more common and severe in children with SLE compared to adults^{4,61}. More specifically, proliferative nephritis and urinary red blood cell casts, indicative of more severe kidney inflammation, were more often present in children with SLE than in adults. Moreover, increased

prevalence of cardiac manifestations in juvenile-onset lupus was recently described, and higher rates of acute cardiac manifestations including pericarditis and myocarditis have been observed within childhood-onset SLE, whilst valvular insufficiency was less common in children^{62,63}. In one study, the incidence of cardiovascular injury has been reported lower in pediatric compared to adult SLE and to increase with age. A recent meta-analysis demonstrated greater heterogeneity among publications on adverse cardiovascular events (myocardial infarction and stroke) and a non-significant overall difference comparing childhood and adult-onset SLE was found⁴. Among various cutaneous presentations, malar rash and cutaneous vasculitis seem to occur more commonly in cSLE^{4,9}, and although there are inconsistent reports on gastrointestinal involvement, an increased incidence of such manifestations in cSLE is observed, and oral ulcers appear to have a higher incidence in childhood-onset compared to adult-onset SLE^{9,62}. cSLE has also been associated with higher rates of ocular manifestations compared to adult-onset SLE, whilst general hematological involvement is found similar between these populations. In contrast with general hematologic involvement, the incidence of specific hematological symptoms including hemolytic anemia, thrombocytopenia, leukocytopenia and lymphopenia, as well as the incidences of vasculitis and lymphadenopathy are significantly higher in cSLE patients, whilst articular and pulmonary manifestations may be more common in adults^{4,9,61}. Thrombotic microangiopathy is a rare, life-threatening complication of both SLE and antiphospholipid antibody syndrome that is mediated by terminal complement activation and presents with severe renal injury and neurologic manifestations, including encephalopathy, stroke and seizures⁶⁴.

Inflammatory Interplay between the Brain and non-CNS Systems

There are a number of potential routes by which inflammatory mediators such as cytokines may interact with the central nervous system, and active immune responses within non-CNS systems have been

suggested to impact neurodegenerative processes and contribute to age-related cognitive decline. Inflammatory communication between organs and the brain can take place through various mechanisms, including autoantibodies, cytokines, interferon pathways and cellular mediated injury involving activated T-cell response. For instance, brain damage in SLE patients with CNS involvement has been linked to upregulation of matrix metalloproteinases, a group of tissue degrading enzymes, through increased intrathecal levels of IL-6 and IL-8. We propose an inflammatory interplay among the developing cerebellar and cortical structures and e.g. the renal, gastrointestinal or cardiovascular system with their respective susceptibility to insult resulting in exacerbated disease expression in childhood-onset SLE.

Renal system. Inflammatory molecules such as interleukins, C-reactive protein and tumor necrosis factor in the kidney have been postulated to play a role in the pathophysiology of neuropsychiatric abnormalities that are observed in patients with chronic kidney disease (CKD) as well as oxidative stress and renin-angiotensin communication⁶⁵. Moreover, kidney injury in the form of albuminuria is found to be associated with reduced regional brain cortical thickness, pointing to the presence of a kidney-brain axis⁶⁶. The interaction between the kidney and the brain is not straight forward, as cognitive functioning in children with lupus nephritis was deemed comparable or better compared to other forms of glomerular CKD, whilst a more common history of seizures in lupus nephritis was observed⁶⁷. Various inflammatory mechanisms for cognitive impairment in CKD have been postulated and the kidney-brain interaction in SLE may involve similar pathways. Proposed kidney-brain pathways include microvascular injury in the form of brain microhemorrhages, uremic toxicity leading to endothelial dysfunction, oxidative stress affecting synaptic activity and neurotransmission by means of increased reactive oxygen species (ROS) production and reduced antioxidant function, and the peripheral and tissue-specific cytokine milieu, including overexpression of IL-1 β , IL-6, TNF and transforming growth

factor- β ⁶⁸. Lupus nephritis has similarly been associated with elevated IL-6 and TNF α , oxidative injury and increased ROS, and microvascular injury⁶⁹.

Skin. Another inflammatory factor often implicated in SLE, especially in the skin, is type I interferon⁷⁰. Type I interferon induces expression of chemokines that recruit inflammatory cells to involved tissues. It has been demonstrated that immune cells (neutrophils) can migrate from the inflamed skin to the kidney, and it was hypothesized that they may also move to other organs such as the brain⁷¹.

Gastrointestinal tract. Additional interactions between involved organ systems and the brain in SLE may be mediated by alterations in gut microbiota. Waste product from the kidney can infiltrate the gut lumen and induce changes to the microbiome, thereby impacting inflammatory signaling. Dysbiosis of the gut microbiome has been established in SLE compared to healthy individuals and fecal microbiota transplantation before onset of the disease in lupus mice models is found to alleviate disease severity⁷². The microbiota-gut-brain axis and the influence of gut microbiota on functional and structural brain development is widely acknowledged, and the involvement of microbiota in neurological diseases such as SLE is a topic of great interest⁷³. Although many questions remain to be answered regarding the precise mechanisms by which the microbiome affects the pathophysiology, disease severity and clinical presentations of CNS lupus, it may hold potential for future treatments of SLE.

Cardiovascular system. High systolic blood-pressure, elevated serum total-cholesterol and smoking in childhood, identified cardiovascular risk factors, have been associated with worse midlife cognitive performance⁷⁴. Moreover, the previously described multisystemic complication PRES is characterized by seizures, altered mental status, headache and visual disturbances. Vasogenic causes relating to BBB disruption, cytotoxic mechanisms, neuropeptide pathway dysregulations and

immunogenic interactions have all been hypothesized, potentially overlapping and integrating with each other in the pathogenesis of PRES⁷⁵.

Altogether, the common interacting feature between each of the systems and the brain in SLE pathophysiology seems of an inflammatory nature, and the cross-over of inflammatory factors between these systems and the brain through BBB or blood-CSF barrier disruption may be contributing to increased disease severity as observed in cNPSLE.

Systemic Vulnerability during Childhood

Development-related changes occur not only in the brain but also in non-CNS systems. These may be similarly more severely affected by external insults (systemic inflammation) occurring in childhood, which in turn may lead to more pronounced neuropsychiatric symptoms. Adverse childhood experiences, for example physical, sexual or emotional abuse, have been shown to increase risks of many chronic health conditions, including poor physical and mental health, kidney disease, cardiovascular disease and arthritis⁷⁶. For one, the kidney starts functioning only after birth with maturation of this organ continuing over the first years of life, and an increased vulnerability to environmental insults at an early age has been attributed to the developing kidney undergoing morphological and functional alterations. Childhood adverse events are considered to dramatically increase the risk of developing cardiovascular disease in adulthood. Moreover, during puberty there is an apparent shift in the skin microbiome, associated with progressive sexual maturation. Regarding gastrointestinal development, a critical window in the first years of life for the gut microbiome has been well established, as there is ample evidence implicating that stressful experiences in children and adults can trigger gastrointestinal disorders, and a priming through early life adverse events might sensitize this system⁷⁷.

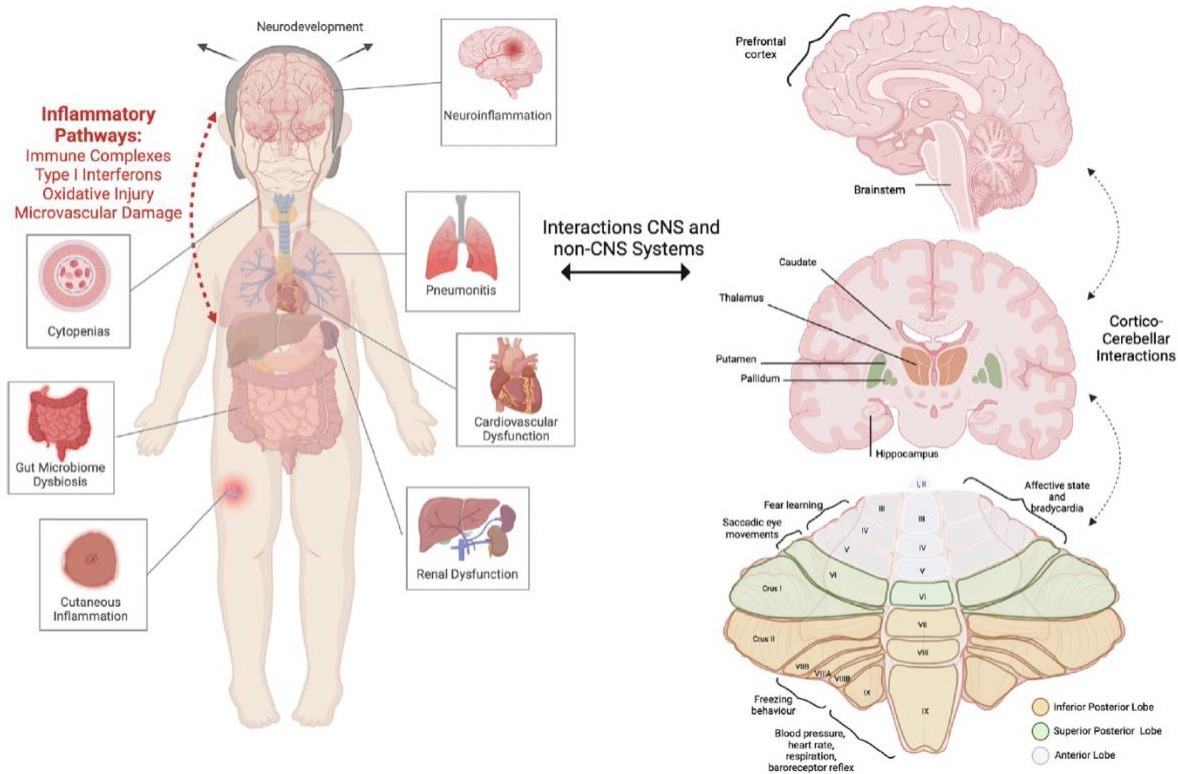


Figure 3. Proposed network of dysfunctional interactions in cSLE. The crosstalk among cortical and subcortical structures including prefrontal cortex and brainstem, thalamus, caudate, putamen, pallidum and hippocampus and cerebellar subdivisions is displayed. An interaction of these brain regions and structures with non-CNS systems through inflammatory and immune related factors is indicated, with vulnerabilities of the developing nervous system potentially leading to exasperated symptoms in childhood-onset SLE compared to adult SLE.

Conclusion

We here reviewed factors that may contribute to robust neuropsychiatric phenotypes in patients with cNPSLE, discussed the impact of inflammation on a developing central nervous system (CNS), and postulated how this might lead to exasperated central nervous system signs and symptoms. Neuropsychiatric symptoms and dysfunction of several non-CNS systems that interact with the brain are common among children with cSLE, which may contribute to more severe symptoms and worse long-term outcomes compared to their adult counterparts. Distinct neurobiological abnormalities in cSLE may contribute to neuropsychiatric symptoms, and the interplay between CNS and non-CNS systems may be of an inflammatory nature. Maturation and development of the brain and other non-CNS systems during

childhood and adolescence may increase susceptibility to inflammatory insults with negative consequences into adulthood. Recent advances in the fields of neuroimaging and a greater focus on inflammatory mechanisms within cNPSLE will allow for a greater understanding of the CNS and non-CNS influences on disease severity and progression. Multimodal imaging could capture pathogenic mechanisms in cSLE more robustly, and further exploration of immunopathologic characteristics such as complement levels, autoantibodies and markers of BBB disruptions may facilitate risk stratification and targeted therapeutics. The large heterogeneity in clinical phenotypes as well as disease trajectories warrants a personalized approach, requiring better tools for early diagnosis, including advanced imaging methods, blood biomarkers and accessible neuropsychiatric assessment with computerized neurocognitive batteries ^{78,79}. This would in turn likely enhance timely and individualized therapies such as targeted immunosuppressive treatments and cognitive performance training. Our review therefore underscores the need to focus future research and clinical efforts on improving early recognition and personalized treatment of cNPSLE, to optimize neurodevelopment, neuropsychiatric and overall outcomes for patients with cSLE.

Table 1. cNPSLE Brain Imaging Cases and Cohort Studies. MRI: Magnetic Resonance Imaging. FLAIR: fluid-attenuated inversion recovery. DWI: Diffusion Weighted Imaging. ADC: Apparent diffusion coefficient.

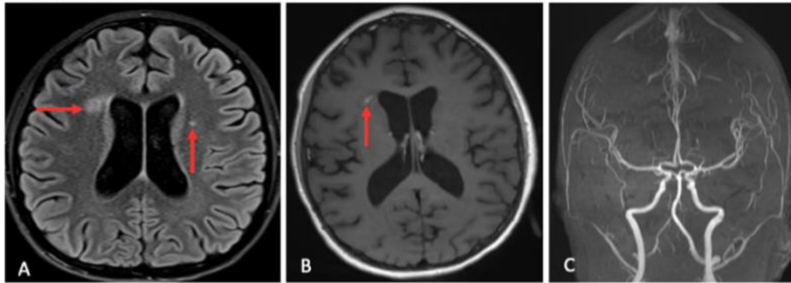
Patient Characteristics	Clinical Presentations	Brain MRI Findings	Source
Female, 7 years old	History of severe headache, recurrent vomiting, cognitive dysfunction, and psychiatric symptoms, including auditory hallucination, irritable mood, and aggressive behavior. 4-days prior to admission presenting with ataxia, diplopia and morning vomiting. Presented with broad-based unsteady gait, bilateral dysmetria, horizontal nystagmus and hyperreflexia of the lower members.	Multiple lesions both cerebral hemispheres, with irregular borders and intermediate intensity on T2-weighted images, located at the gray matter-white matter junction, in both temporal lobes (with hippocampal involvement), right insula, right anterior superior frontal lobe and left frontal lobe; marked cerebellar atrophy. Results are highly suggestive of encephalitis	Ferraria et al. 2013 ⁵⁰
Female, 11 years old	Admitted with fever, headache, arthralgia, tremors and mood disorder and diagnosed with	Increased signal intensity in the anterior basal ganglia on both sides of the T2-weighted	Sato et al. 2014 ⁸⁰

	NPSLE, one year after initial SLE presentations of malar rash, arthralgia, photosensitivity, oral ulcers and Raynaud's phenomenon.	images, FLAIR), DWI and ADC maps. Improvement seen after 5 months of treatment with steroids, Intravenous immunoglobulin, plasma exchange and cyclophosphamide	
Female, 14 years old	Admitted with fever, headache, tremors, memory dysfunction, and mild cognitive dysfunction and diagnosed with NPSLE. Initial SLE symptoms at age 13 included fever, polyarthritis, headache, oral ulcers, purpura, pancytopenia and hypocomplementemia.	Increased signal intensity in the right caudate nuclei and paralateral ventricle. MRI performed 5 months after treatment with steroids and cyclophosphamide showed improvement, and headache, tremors and cognitive impairment was reduced.	Sato et al. 2014 ⁸⁰
Female, 15 years old	Admitted at age of 15 with fever, headache and rash and diagnosed with NPSLE. Initial presentations of SLE at age 14 included prolonged fever, oral ulcers and malar rash and mesangial nephritis.	Increased signal intensity in the anterior lentiform nuclei on the left side. MRI performed 5 months after treatment (with steroids mycophenolate mofetil and methylprednisolone) there was improvement, and headache, fevers, oral ulcers and malar rash and MRI 3 weeks later no longer showed high-intensity lesions.	Sato et al. 2014 ⁸⁰
Male, 13 years old	Diagnosis of cerebral SLE, Acute onset generalized dystonic (choreic) movements. Recurrent episodes of erythematous maculopapular rash. Upon review of past: several episodes of polyarthralgia with occasional joint stiffness, a history of photosensitivity, occasional oral ulcers and Raynaud's phenomenon, along with mild intermittent fatigue for the last 2 years.	Numerous discrete focal lesions located in deep and subcortical white matter, bilaterally and almost symmetrical in the frontal and temporal lobes and centrum semiovale.	Athanasopoulos et al. 2018 ⁴⁸
Unspecified, 14 years old	Unspecified NPSLE diagnosis	Infarction of the cerebellum, brainstem, posterior thalamus on the right and mild hydrocephalus with restricted diffusion	Al-Obaidi et al. 2016 ⁴⁷

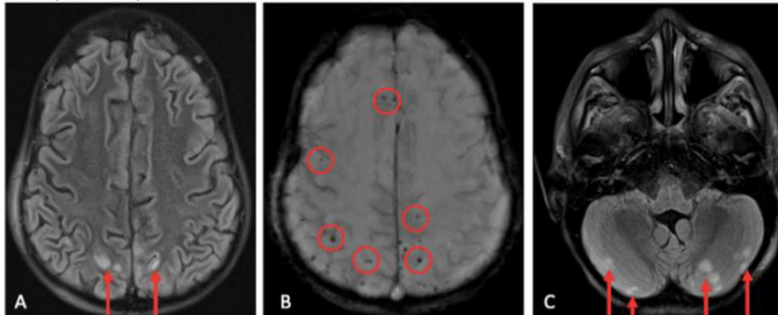
Unspecified, 16 years old	Delirium, psychosis, seizure or abnormal behavior, NPSLE diagnosis	Hyperintense foci in supratentorial white matter and bilateral basal ganglia with cerebral atrophy.	Lim et al. 2021 ⁴⁹
27 patients, female: male ratio 4.4:1, median age of 11 (range 4-15)	Subgroup with abnormal MRI's (n=11) presented with seizures, aseptic meningitis, cerebrovascular disease, demyelination ,headache, movement disorder, transverse myelopathy, cognitive disorders, psychiatric disorders, autonomic disorder, peripheral neuropathy and myasthenia-like syndrome.	Hyperintensities in supratentorial white matter, brainstem, gray matter and cerebellum. Parenchymal defect in cerebellum, and atrophy in supratentorial white matter and cortical gray matter.	Al-Obaidi et al. 2016 ⁴⁷
28 patients, female: male ratio 3.7:1, median age of presentation 10 years old (IQR 9-12),	Symptoms included seizures, cerebrovascular disease, psychosis, acute confusional state, mononeuropathy, headache, cranial neuropathy, aseptic meningitis, mood disorders, movement disorders and acute inflammatory demyelinating polyradiculopathy.	Supratentorial WMHs, hyperintensities in the brainstem, cortical gray matter, basal ganglia and cerebellum. Supratentorial white matter atrophy and parenchymal defect.	Lim et al. 2021 ⁴⁹

Box 1. Neuropsychiatric Symptoms in cSLE Cases with and Without Neuroimaging Abnormalities. Three cSLE patients at Boston Children’s Hospital with neuropsychiatric symptoms are described. All three cases had a historical clinician diagnosis of lupus cerebritis. While Cases 1 and 2 demonstrated abnormalities on standard-of-care MRI, Case 3 was absent of any gray or white matter lesions. Such heterogeneity points to the need for identifying and validating additional clinical approaches that can aid accurate and early detection of central nervous system manifestations of cSLE as well as mechanically inform neurobiological factors that underly neuropsychiatric symptoms in cSLE.

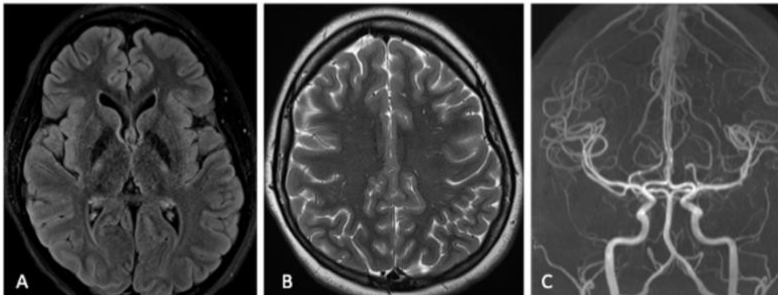
cSLE Case 1. An 11-year-old female presenting at initial diagnosis with depressed mood, lupus nephritis, arthritis, and diffuse alveolar hemorrhage, followed by subacute left-sided weakness. Prior to neuroimaging, the patient had been treated with cyclophosphamide, hydroxychloroquine, pulse-dose methylprednisolone, mycophenolate mofetil, sulfamethoxazole-trimethoprim and multiple antihypertensive medications. Multisequence MRI consisting of (A) fluid attenuated inversion recovery (FLAIR) MRI, (B) T1-weighted MRI (post-contrast), and (C) time-of-flight magnetic resonance angiography (TOF-MRA) was performed. Multifocal periventricular white matter lesions were identified (red arrows) and lateral ventricles appear mildly dilated, while TOF-MRA was normal.



cSLE Case 2. A 9-year-old female presenting with recurrent and focal right hemiconic seizure. SLE was diagnosed two months prior in the setting of fever, lymphadenopathy, cytopenias, serositis (pericardial effusion), acute kidney injury and hypertension. Prior immunosuppressive treatments received included pulse-dose methylprednisolone and intravenous immunoglobulin. For treatment of seizure due to suspected lupus cerebritis, she received rituximab, plasmapheresis, and cyclophosphamide. (A) FLAIR MRI demonstrated patchy juxtacortical hyperintensities within the precuneus and cuneal cortices as well as the temporal/occipital convexities (not shown), (B) accompanied by over 50 punctate foci demonstrating microbleeds (e.g. red circle) observed on susceptibility weighted imaging (SWI), and (C) FLAIR fat-suppressed showed hyperintensities bilaterally in cerebellar hemispheres. T1-weighted MRI (not shown) demonstrated no contrast enhancement.



cSLE Case 3. A 15-year-old female presenting with acute on chronic worsening of severe depression and suicidal gesture at initial diagnosis of SLE. Other presenting features of SLE included antiphospholipid antibody syndrome, cytopenias and lupus nephritis. The patient has also suffered from migraine, headaches, nausea/ vomiting, photophobia, sonophobia, dizziness, spinning and tinnitus and occasional blurred or double vision. She was subsequently treated with pulse dose methylprednisolone, cyclophosphamide, rituximab and hydroxychloroquine. No abnormalities were observed on (A) FLAIR MRI, (B) T2-weighted MRI, or (C) TOF-MRA.



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