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Review Article

Neuropsychiatric involvement in Juvenile Systemic Lupus

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Abstract

Juvenile systemic lupus erythematosus (jSLE) is a chronic inflammatory disease affecting multiple systems, which occurs in individuals under 16 years old and presents in a pattern of remission and relapse. Clinical symptoms in children are varied and may include cutaneous, renal, hematological, constitutional, and neuropsychiatric problems. About 14–95% of people with jSLE experience a wide spectrum of neuropsychiatric symptoms. These manifestations can lead to significant morbidity and mortality, especially in younger individuals. The most common neuropsychiatric symptoms include headaches, seizures, cognitive impairments, and mood disorders. The underlying pathophysiological processes are intricate and not yet completely understood, with a significant emphasis on autoantibodies in ongoing research. Diagnosing neuropsychiatric jSLE is still a difficult task that often relies on exclusionary criteria. This article examines the neuropsychiatric symptoms linked to jSLE, focusing on the goal of ensuring early diagnosis and timely treatment for affected children and adolescents.

Keywords:- Juvenile Systemic Lupus erythematosus, Neuropsychiatric manifestations, Headaches, Cognitive dysfunction, Seizures, Psychiatric manifestations, Autoantibodies.

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SMJ,2025 Vol. 29 No (2) 2025 71 - 74

Introduction

People under the age of sixteen are affected with juvenile systemic lupus erythematosus (jSLE), a chronic autoimmune illness with multifactorial involvement.[1,2]

jSLE is an uncommon illness that causes severe morbidity and death, with an estimated frequency of 3.3 to 24 instances per 100,000 pediatric patients. [3]

The female-to-male ratio varies from 4:3 in early infants to 5:1 in teenagers, indicating a significant female preponderance in Jsle.[4]

It is extremely uncommon for jSLE to appear in children under the age of five. The typical age at which it first appears is between eleven and twelve. A more severe course of the disease is linked to a younger age at diagnosis.[5]

Between 14%.[6] and 95%.[7] of individuals with jSLE have juvenile neuropsychiatric systemic lupus erythematosus (jNPSLE). A potentially serious and occasionally fatal side effect of systemic lupus erythematosus (SLE) is neuropsychiatric lupus erythematosus (NP-SLE).[3-5]

In addition to affecting the prognosis and consequences of the disease, it can significantly impact the patient's quality of life. Crucially, compared to SLE patients without NP signs, the inclusion of neuropsychiatric symptoms is linked to a roughly threefold increase in mortality. [5]

The neuropsychiatric symptoms observed in juvenile systemic lupus erythematosus (jSLE) encompass a wide range of manifestations. Based on the 19 criteria established by the American College of Rheumatology (ACR), these symptoms involve components affecting both the central nervous system (CNS) and the peripheral nervous system (PNS).[8]

Therefore, qualified teams from medical specialties should be included in the diagnosis and treatment of neuropsychiatric jSLE. Even with such a long number of symptoms, it is crucial to remember that not all potential manifestations may be included in the ACR's categorization.[9–10]

Additionally, this classification does not explicitly include conditions such as neuromyelitis optica spectrum disorders, leukoencephalopathy, posterior reversible encephalopathy syndrome, or chronic inflammatory demyelinating polyneuropathy. [11]

Fatigue is a common concern among SLE patients across all age groups, significantly affecting their overall well-being and quality of life. Distinguishing whether this fatigue results from neuropsychiatric involvement, a general inflammatory "constitutional" symptom, or is linked to a "low mood" can often be challenging. [12]

Identifying and diagnosing neuropsychiatric (NP) features in individuals with juvenile systemic lupus erythematosus (jSLE) can be challenging due to the broad spectrum of clinical presentations and the prevalence of non-specific symptoms such as headaches, mood disturbances, anxiety, and catatonia. Equally complex is determining whether NP symptoms are directly related to SLE. Current diagnostic guidance relies on experience-based criteria, including the timing of NP events relative to jSLE diagnosis, the occurrence of NP symptoms in non-SLE populations, and the presence of other risk factors for NP involvement, such as persistent infections or metabolic abnormalities unrelated to jSLE. Evidence suggests that NP-SLE is more prevalent and severe in jSLE (15–95%) compared to adult-onset SLE (14–80%). Prompt diagnosis, accurate outcome prediction, and personalized treatment are essential for managing NP-SLE, alongside addressing the associated psychosocial challenges, morbidity, and mortality.

Methods

The review included studies published in English between January 1988 and December 2023 that focused on neuropsychiatric symptoms in individuals with juvenile systemic lupus erythematosus (jSLE). These encompassed original research and review articles, including prospective, cross-sectional, retrospective studies, and case reports. Additionally, research exploring the pathophysiological mechanisms and diagnostic approaches related to juvenile neuropsychiatric SLE (jNPSLE) was considered.

The electronic database MEDLINE, accessed through PubMed, was searched using terms such as neuropsychiatric lupus, pediatric, juvenile, childhood, neurological, and psychiatric symptoms. Articles addressing neurological, psychiatric, and neuropsychiatric features of lupus in children, adolescents, or young adults were targeted. Reference lists of relevant articles were also reviewed to identify additional studies.

Studies that did not particularly look at the neurological and/or mental symptoms of juvenile Systemic Lupus Erythematosus (jSLE) or that replicated data from another research were not taken into consideration. To ascertain if the remaining papers qualified for inclusion, full text analysis was performed on each. The data extraction procedure was carried out by three separate investigators. Disagreements were settled by consensus.

Seventy of the 210 items that were found in the first search were eventually included in the literature review. We separated the resulting symptoms that were reported in the literature into three primary groups: unusual neurological symptoms, psychiatric symptoms, and typical neurological symptoms. Table 1 lists the variety of neuropsychiatric symptoms that have been documented in the literature. The pathogenesis and diagnostic techniques of neuropsychiatric issues were also our main topics.

Results

Table 1: The frequency range, pathophysiology-related causes, and reported spectrum of neuropsychiatric juvenile systemic lupus erythematosus presentations.

Neuro-psychiatric manifestations in juvenile SLE	Clinical symptoms	Pathogenesis and Autoantibodies correlation	Reported frequency and citation references	Type of Evidence
Headache	Headache (Tension) Migraine Headache (Cluster) Intractable headache Increased intracranial hypertension	AGA ACA	12.2 [5]- 75 % [13]	Review
Cognitive dysfunction	Loss of memory Executive functions defect Deficit in visual processing Loss of concentration	AnAb aPL	16.9–70.8 % [5], 14.8–100 %[6]	Review & *meta*-analysis
Seizures	Seizures (Generalized) Tonic, clonic Atonic Myoclonic Absence Seizures (Focal)	AnAb aPL ACA IL 1 and 6, TNF-a	11.4–52.2 %[5]	Review
Cerebrovascular Disease	Cerebral venous thrombosis	aPL LA Microthrombi vasculopathy	11.3–30 %[5], 20 %[13]	Review
Movement Disorders	Rigidity Chorea Tremors Akinesia Parkinsonism	aPL	5–20 %[14]52–91 %[14]	Case report
Mood Disorders	Depression Suicidal ideas	AGA Anti-SSA(Ro) antibodies Anti-rib-P ACA Treatment with corticosteroid	62 % [15] 33 % [15]	Cohort study
Psychosis	Anxiety Hallucinations Visual disturbance	Anti-rib-P ACA	5–37.1 %[5] 32 % [15] 34–37 %[16]	Review, systematic review and *meta*-analysis,
Peripheral neuropathy	Poly-neuropathy Mono-neuritis Guillain Barrè Syndrome Myasthenia Gravis disease	AGA AECAs	5–15 %[13]	Review
Transverse myelitis	Paresthesia Paraplegia Paraparesis Urinary retention	ACA	1–2 %[17]	Case series
Retinal manifestations	Vision loss (Blindness)	aPL Thrombocytopenia Active vasculitis	0.8 % [18]	Case report

Notes: Anti ganglioside antibodies (AGA), Anti cardiolipin antibodies (ACA), Anti neuronal antibodies (AnAb), Antiphospholipid antibodies (aPL), Interleukins (ILs), Tumor Necrosis Factor-a (TNF-a), Lupus anticoagulant antibodies (LA), Anti-ribosomal-P antibodies (anti-rib-P), Anti-endothelial cell antibodies (AECAs).

Discussion

Because jSLE is a complicated condition, diagnosis and treatment remain challenging. The absence of current child-specific categorization criteria is a significant barrier to diagnosing neuropsychiatric disorders. Although the recently published EULAR/ACR-2019 criteria may help close this gap, children still have a poorer specificity than adults. **(10)**

Since they provide a more definitive diagnosis and early management, future research should concentrate on cognition testing, novel autoantibodies, and improved imaging methods.**(19)**

Neuropsychiatric symptoms are not rare enough to be ignored because research suggests that up to 46% of children and adolescents with jSLE may have them. **(20)**

In a recent jSLE cohort research conducted in the UK, neuropsychiatric features were present in half of the 428 patients at the first visit.

According to Appenzeller et al.**(21)** most jSLE patients experience neuropsychiatric events within the first two years of their illness, and between 30 and 70 percent of patients present with many neuropsychiatric events over the course of their illness. These events are associated with death and impairment.

The most frequent neurological manifestations are headaches, cognitive impairment, seizures, cerebrovascular illness, and mobility issues, whereas mood disorders, psychosis, and anxiety are prominent in psychiatric presentations. Peripheral neuropathy, ocular involvement, and the occurrence of posterior reversible encephalopathy syndrome (PRES) can complicate the early detection of juvenile neuropsychiatric systemic lupus erythematosus (jNPSLE), as its clinical spectrum is broad and often complex.

Nonetheless, considerable advancements have been achieved in elucidating the pathophysiology of jNPSLE. These include insights into its immunological and inflammatory mechanisms, as well as the role of autoantibodies in driving specific clinical manifestations. By developing promising biomarkers, an understanding of pathomechanisms will speed up diagnosis. To improve patient care and treatment outcomes, pediatric-specific research is also required.

Conclusion

Rheumatologists and pediatricians should be on the lookout for any neurological or mental symptoms that may appear subtly alongside other uncommon symptoms of juvenile lupus or on their own as the first sign. Early detection and successful treatment of neurological and mental symptoms may depend on heightened suspicion of hidden rheumatic illness.

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