Juvenile Systemic Lupus Erythematosus: neuropsychiatric manifestations

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ABSTRACT

Juvenile Systemic Lupus Erythematosus (jSLE) is a chronic and multisystemmic autoimmune disease, which appears before 16 years old with an incidence of 10 to 20 cases per 100000 children. The clinical spectrum of jSLE can be quite variable. The most common symptoms are constitutional, followed by the cutaneous, musculoskeletal, renal, and neuropsychiatric involvement.

Neuropsychiatric involvement in jSLE has a prevalence ranging from 20 to 50.9% and results in significant morbidity and mortality.

The most common clinical manifestations of juvenile neuropsychiatric SLE (NPSLE) are headache, cognitive dysfunction, mood disturbances and seizures.

The pathophysiology of juvenile NPSLE is not yet fully known, but immunological and inflammatory factors, such as autoantibodies, cytokines and prothrombotic states are widely described. The role of autoantibodies in the onset of specific clinical manifestations has also been recognized.

Juvenile NPSLE manifestations are often difficult to diagnose. In addition to semiological aspects, the study and validation of neuropsychological testing and neurocognitive assessment for the juvenile SLE population are essential. The role of advanced imaging techniques should be explored.

The treatment of juvenile NPSLE must be individualized according to the type and severity of clinical manifestations, relying on symptomatic therapy, anticoagulants or steroids. New therapeutic approaches, including biotherapies need controlled randomized trials for further validation.

This article aims to review the pathogenesis, clinical manifestations, diagnosis and treatment of juvenile NPSLE.

Keywords: Juvenile Systemic Lupus Erythematosus; Neuropsychiatric Manifestations; Autoantibodies; Treatment.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune, chronic and multisystemmic autoimmune disease[1-3], characterized by a broad clinical spectrum, an array of immunological abnormalities and a variable course and prognosis. In its pathogenesis are involved environmental, hormonal, immunologic and genetic factors, although its etiology is still unknown[4,5].

The American College of Rheumatology classification criteria are used to diagnose juvenile SLE (jSLE)[3], considering its appearance before sixteen years old a very important criterium[6]. The median age of onset of disease is 10-12 years[7], being rare in children under five years old. The age of onset may influence the course of disease in terms of clinical presentation, organ involvement, and serological findings[8,9]. jSLE represents 15-20% of all SLE cases. The estimated incidence of jSLE ranges from 10 to 20 per 100000 children, depending on the ethnic population[3,10].

The clinical spectrum of jSLE can be quite variable[3]. As it can assume characteristics of other pathologies, its diagnosis in pediatric age is very difficult. Systemic constitutional symptoms such as fatigue, weight loss and fever[3] are considered to be the most common presentation symptoms, followed by skin involvement, including malar rash and fotossensibility, musculoskeletal disease including arthralgia/arthritis[11], renal and neuropsychiatric disease[7].

Neuropsychiatric involvement in SLE (NPSLE) includes the neurological syndromes of the central nervous system (CNS), of the peripheral nervous system

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(PNS) and of the autonomic nervous system (ANP) and psychiatric disorders[12], in the absence of secondary causes[6,13,14].

NPSLE can precede the onset of lupus[15] or occur at any time during its course, mainly within the first year from the time of diagnosis[4,11,16].

Juvenile NPSLE is a major cause of morbidity and less so of mortality in jSLE patients[16], and its prevalence ranges from 22 to 50, 9% among several studies[6,11,13,15-20]. Some studies suggest that jSLE has a more serious course and a more frequent neuropsychiatric involvement than adult SLE[7,9].

There are no guidelines for the treatment of NPSLE, thus, it should be individualized, according to the type and severity of clinical manifestations and other system or organs involvement[21].

Based on up-to-date references, this article aims to review the main clinical manifestations, pathogenesis, diagnosis and treatment of juvenile NPSLE.

MATERIAL AND METHODS

Forty-four scientific articles published between 1999 and 2010 in journals with an impact factor of 3 were researched. Those articles were obtained in the PubMed database.

The keywords used were "systemic lupus erythematosus", "juvenile systemic lupus erythematosus", "neuropsychiatric", "autoantibodies", "pathogenesis" and "treatment".

NEUROPSYCHIATRIC MANIFESTATIONS OF JUVENILE SLE

The prevalence of neuropsychiatric manifestations of jSLE ranges from 22 to 50,9%[6,11,13,15-20]. A major source of variance in the rates of occurrence has to be attributed to the lack of standard definitions for the pediatric lupus population and for the NPSLE [15,16]. In order to develop a standardized nomenclature system for the NPSLE in 1999 "The American College Rheumatology nomenclature and case definitions for Neuropsychiatric Manifestations in Systemic Lupus Erythematosus" has been published[22], which describes twelve syndromes concerning CNS and seven syndromes concerning PNS (Table I).

Neuropsychiatric manifestations can be classified according to their etiology and severity (Table II). The majority of thrombotic mechanisms cause focal manifestations and diffuse manifestations are described as being due to non-thrombotic mechanisms. However, some studies mention that diffuse manifestations can also be consequent to thrombotic mechanisms[21].

Headache is the most common neuropsychiatric manifestation, and its prevalence ranges from 39.6 to 75% among several studies[6,11,13,15-20]. Headache is subdivided into five categories: migraine, tension headache, cluster headache, headache from intracranial hypertension and non-specific intractable headache[16]. Headache is frequently seen in association with more severe CNS involvement, including psychosis, acute confusional state[11,16] and seizures[6].

Cognitive dysfunction is one of the most common neuropsychiatric manifestations, which prevalence ranges from 16.9 to 70.8%[6,11,13,15-20]. There is no specific clinical spectrum, and the degree of impairment can range from mild or subclinical findings to severe dementia[11]. The most common reported areas of impairment include verbal and nonverbal learning and memory, verbal fluency, complex problem solving, psychomotor speed and executive functioning[23]. Available data do not suggest that demographic factors such as race and ethnicity are predictive of cognitive impairment in SLE[19].

Cognitive development, which critical cognitive maturation period from late childhood through adolescence and into young adulthood coincides with the pediatric age spike for SLE onset, is a complex process. Thus, patients who develop juvenile SLE are at a period of exceptional vulnerability of the CNS, which may result in a particular risk for delays and impairments in cognitive development[19].

Mood disorders, with a prevalence which ranges from 11.4 to 57%[6,11,13,15-20], include **depression**, the most common of the mood disorders and **mania** and **bipolar disorder** that are rare. A reactive depression secondary to chronic disease and a depression secondary to corticosteroid use must be excluded[16,25].

Seizures have a prevalence that ranges from 11.4 to 51%[6,11,13,15-20] and are associated with other CNS involvement in most cases, such as headaches, cerebrovascular disease and cognitive dysfunction, with isolated seizures occurring in less than 25% of cases. Generalized seizures are more common than focal seizures[11].

Psychosis, which prevalence ranges from 5 to 37.1%[6,11,13,15-20], has visual hallucinations as its main characteristic, which in turn is not present in idiopatic schizophrenia of childhood, what helps to exclude this diagnosis[16]. Tactile and auditory hallucinations

TABLE I. NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS SYNDROMES

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder	Neuropathy, cranial
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

TABLE II. CLASSIFICATION OF NEUROPSYCHIATRIC MANIFESTATIONS ACCORDING TO THEIR SEVERITY AND ETIOLOGY – A FEW EXAMPLES

	Severe clinical manifestations	
Mild clinical manifestations	Diffuse/Nonthrombotic	Focal/ Thrombotic
Anxiety disorder	Refractory Anxiety	Ischemic Stroke
Depression	Refractory Psychosis	Transient ischemic attak
Seizure	Generalized seizures	Cerebral vein thrombosis
Psychosis	Acute confusional state	
Headache	Aseptic meningitis	

and suicidal ideation might be present. Steroid-induced psychosis may be differentiated from NPSLE by the presence of uncommon features of NPSLE, such as mania and excessive crying[11].

Cerebrovascular disease occurs in 11.3 to 30% of cases[6,11,13,15-20] and includes a spectrum of SLE-associated cerebral blood vessel abnormalities, ranging from small arteries to large arteries, such as cerebral vein thrombosis, which is seen in about 25% of juvenile NPSLE patients[16]. Microthrombotic and microembolic events in the form of ischemic stroke and transient ischemic attack are common, while cerebral bleeding is rare.

Headaches and seizures are the most common clinical signs and symptoms of cerebrovascular disease[11] but hemiparesis, quadriparesis, spastic diplegia or spastic quadriplegia should also be considered[6].

Anxiety disorders occur in 1.8 to 14% cases[6,11,13,15-20] and possible psychological reactions related to the possibility of having a major chronic systemic illness might be excluded[22].

Movement disorders have a prevalence which ranges from 5.6 to 20%[6,11,13,15-20]. Chorea is the most common movement disorder and it is more common in juvenile SLE than in adult-onset SLE[11]. Most patients only have one episode of chorea, and unilateral chorea, which is seen more commonly than bilateral chorea[16]. Chorea also affects more frequently the upper limbs[6].

PNS involvement occurs in 5.6 to 15%[6,11,13, 15-20] of all patients with juvenile SLE. It may occur with or without concomitant CNS involvement. Optic neuropathy and oculomotor palsy are the most common cranial neuropathies and facial palsy and trigeminal neuropathy are less frequent. Unlike in adults with SLE, autonomic dysfunction has been only rarely reported in juvenile patients[16].

Less common CNS symptoms include: Transverse myelitis, which may present with acute paraplegia or quadriplegia and may be the presenting sign of SLE[6,11,16], diabetes insipidus, Parkinson`s syndrome, leukoencephalopathy, as well as retinal vascular disease, consisting of arterial or venous occlusion, cotton-

wool spots, optic disc edema, retinal hemorrhages or ischemic optic neuropathy, which can be found in up to 10% of patients[16].

PATHOGENESIS OF JUVENILE NPSLE

The exact mechanisms underlying the pathogenesis of NPSLE remain unknown[19]. However, it is acknowledged that NPSLE pathogenesis is a complex process incorporating immunologic factors such as the production of autoantibodies against brain structures and the deposition of immune complexes in the central nervous system.

A mechanism proposed by some studies[27,28], but not yet confirmed, suggests that the binding of certain autoantibodies, such as the Anti-endothelial cell antibodies (AECA) and the Anti-phospholipid autoantibodies (aPL) or the immune complexes to the endothelium of blood-brain barrier (BBB) leads to stimulation of signaling pathways, with activation of transcription factors such as nuclear factor *kappa B*[27]. Thus, there will be an induction of synthesis of cytokines and chemokines and expression of adhesion molecules, which leads to an increased permeability of the BBB. Access of antibodies to the central nervous system may occur through a disrupted blood brain barrier or again through synthesis in the nervous system. Autoantibodies, binding molecules exposed on the surface of neurons, lead to a neurotoxic effect[28].

Some cytokines and chemokines were shown to be elevated intrathecally, such as interleukin-6 (IL-6), IL-1, IL-8, IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, monocyte chemotactic protein 1 (MCP-1)/CCL2, Interferon-gamma inducible protein-10 (IP-10)/CXCL10 and Fractalkine/CX3CL1[19].

During the systemic inflammation inherent to SLE, homeostatic balance shifts toward coagulation that favors pro-thrombotic states, which might play a role in the pathogenesis of NPSLE[26].

Autoantibodies are potential immunological markers for the diagnosis and prognosis of NPSLE. According to their specificity (neurons, endothelium, ubiquitous cellular components) these autoantibodies are divided into three groups (Tables III, IV)[21].

AUTOANTIBODIES

A significant number of reports confirmed the association between neuropsychiatric manifestations in SLE and the presence of autoantibodies (Table V)[4,19,28-30]. The studies included patients with jSLE and adult SLE. However, only a few studies have focused in children

so the conclusions in SLE adult patients were extrapolated to jSLE. There is a high variability among different studies because of the differences in the populations of patients studied and the laboratory tests used to detect serum antibodies[28].

Some studies show an association between **Anti-ganglioside antibodies (AGA)** and migraine, dementia and peripheral neuropathy, depression[27,28] and cognitive disfunction, suggesting that the detection of AGA has a predictive value for the onset of a neuropsychiatric flare[29].

In comparison to SLE patients without neuropsychiatric symptoms, an increased incidence of **Anti-neurofilament antibodies (ANFA)** has been reported in patients with NPSLE. **Anti-microtubule-associated protein 2 antibodies (AMAP2)** have been detected in sera from patients with NPSLE, but, like the **Anti-glial fibrillary acidic protein antibodies (AGFPA)**, there is no conclusive evidence about its role in NPSLE pathogenesis[28].

Anti-DNA antibodies cross-reactive with NMDA receptor (ARNMDA) are found in 25 to 50% of patients with SLE and brain dysfunctions seem clearly to be correlated with the presence of antibodies in CSF, and symptom severity correlates with antibody titles. In a murine model, these antibodies induce non-inflammatory, excitatory and apoptotic[19] neuronal damage in the hippocampus and amygdala, when a breakdown of the BBB is caused by a bacterial lipopolysaccharide and epinephrine, respectively[28]. The neuronal damage in the hippocampus results in cognitive dysfunction and the damage in the amygdala leads to behavioral disorders.

Anti-endothelial cell antibodies (AECA) have a clinical association with disease activity and neuropsychiatric manifestations in SLE[31,32]. **Anti-Nedd5 antibodies (ANedd5)** titles are higher on the group of patients with neuropsychiatric manifestations than in patients without these disorders. However, there is no conclusive evidence concerning their pathogenic role.

The serum **Anti-triosephosphate isomerase antibodies IgG** index is higher in the NPSLE than in other autoimmune diseases, demonstrating a high specificity for the diagnosis of NPSLE. The **anti-histone antibodies** are prevalent in approximately 50% of NPSLE patients[28].

Anti-ribosomal P antibodies (ARP) are highly specific for SLE, since they do not occur in healthy individuals or in patients with other diseases[4]. Several studies show a strong association between elevated plas-

TABLE III. ANTI-NEURONAL AUTOANTIBODIES ASSOCIATED TO NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Autoantibodies	Target	
Anti-neuronal Autoantibodies	AGA	Component of the cell plasma membrane which modulates cell signal transduction events ; predominantly in the nervous system
	ANFA	Intermediate filament occurring with neurotubules in the neurons and having cytoskeletal and transport functions
	AMAP2	Restricted to neurons; important in the control of cytoskeletal integrity and other neuronal functions
	AGFAP	Involved in cell structure and movement, in cell communication and in the functioning of the blood brain barrier.
	ARNMDA	NR2 receptors bind the neurotransmitter glutamate; play a role in learning and memory
Anti-endothelial cell antibodies	ANedd5	Cytoskeletal GTPase that play an essential role in cytokinesis

AGA – Anti-ganglioside antibodies; ANFA- Anti-neurofilament antibodies; AMAP2 – Anti-microtubule-associated protein 2 antibodies; AGFAP – Anti-glial fibrillary acidic protein antibodies; ARNMDA – Anti-DNA antibodies cross-reactive with NMDA receptor; ANedd5 – Anti-Nedd5 antibodies

TABLE IV. AUTOANTIBODIES SPECIFIC TO UBIQUITOUS CELLULAR COMPONENTS ASSOCIATED TO NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Autoantibodies	Target	
Autoantibodies specific to ubiquitous cellular components	ATPI	Plays an important role in glycolysis and energy production.
	ASSA/Ro	Nuclear and cytoplasmic polypeptid
	ASm	Ribonucleoproteins that plays a central role in the processing of pre-mRNA in the nucleus
	AHT	Chief proteic components of chromatin
	ARP	Makes up the ribosomal subunits in conjunction with rRNA; ARP recognizes a new integral membrane protein of the neuronal cell surface preferentially distributed in areas involved in memory, cognition, and emotion
	APL	Anionic phospholipids or protein-phospholipid complexes; includes **ACLA** and **LAC**

ATPI – Anti-triosephosphate isomerase antibodies; ASSA/Ro – Anti-SSA/Ro antibodies; ASm – Anti-Smith antibodies; AHT – Anti-histone antibodies; ARP – Anti-ribosomal P antibodies; APL – Anti-phospholipid antibodies; ACLA – Anti-cardiolipin antibodies; LAC – Lupus anti-coagulant antibodies.

ma ARP titles and neuropsychiatric manifestations, specially psychosis and severe depression[19,28]. Other studies report a possible relationship between changes in ARP titles and clinical changes in psychosis, suggesting its periodic monitoring[16]. However, 15 to 25% of patients without NPSLE have these autoantibodies present in their serum and less than one third of NPSLE patients have positive ARP[33,34].

Anti-phospholipid antibodies (APL) lead to microthrombotic events, which are responsible for focal manifestations, such as ischemic stroke, transient ischemic attacks and cerebral vein thrombosis[35,21].

The association between aPL and etiopathogenesis is not yet known, such as headache, seizures, cognitive dysfunction, psychosis and depression is suggested in some studies, but not yet fully established[25]. Chorea is universally associated with aPL in several pediatric studies[7,11] and in most patients with chorea and transverse myelitis these antibodies are present[16]. A recent study concerns an association between aPL and mul-

TABLE V. AUTOANTIBODIES ASSOCIATED WITH CLINICAL MANIFESTATIONS

Autoantibodies	Clinical Manifestation
AGA	Cognitive dysfunction; Depression; Migraine; Peripheral neuropathy
ARNMDA	Cognitive dysfunction; Behavioral disorders
ARP	Psychosis; Severe depression
APL	Ischemic stroke; Transient ischemic attacks; Cerebral vein thrombosis; Headache, Seizures, Cognitive dysfunction, Psychosis and Depression; Chorea; Transverse myelitis

tiple small high-density lesions on the brain Magnetic resonance imaging (MRI), which in turn are compatible with subclinical cognitive manifestations, that are only detected through formal neuropsychometric assessment[36].

Anti-cardiolipin antibodies (ACLA) are reported in a study as the only type of aPL with statistically significant association with ischemic stroke[18]. Several studies show an association between ACLA and seizure, chorea[6] and PNS involvement[16].

Lupus anti-coagulant antibodies (LAC) are universally associated with the risk of cerebral thrombosis[13,16]. One study refers a positive association between LAC and cerebrovascular disease at diagnosis and an association between persistently high LAC titles and chorea[37].

DIAGNOSIS OF JUVENILE NPSLE

Making the diagnosis of juvenile NPSLE is not an easy task[29], and it should include a comprehensive clinical history and a physical examination[19].

Secondary causes of NP manifestations such as infection, hypertensive encephalopaty, metabolic abnormalities[13], drug side effects, including corticosteroids[14] and congenital or acquired CNS disease not related to SLE[6], should be excluded. Complete blood cell count, inflammatory markers, serum autoantibodies, lumbar puncture and cerebrospinal fluid (CSF) analysis, electroencephalography (EEG) and CNS imaging[6,11,19,25,38] must be performed in order to exclude secondary causes and to confirm the diagnosis of NPSLE.

Inflammatory markers such as erythrocyte sedimentation rate and C-protein rate may be normal in one third of patients with psychosis and cognitive dysfunction and they are often elevated in patients with cerebrovascular disease and seizures[11,19,25]. One study did not detect any association between serum complement and neuropsychiatric manifestations[6].

Some authors argue that a child with SLE should do an APL test at the time of diagnosis and then another at least once a year as part of routine screening[38].

EEG is reported in a study as a valuable mean of diagnosis of cognitive dysfunction[39], however, another study found that EEG findings are usually abnormal only when seizures are present[16].

One study showed that microembolic signals on transcranial Doppler were more frequent in the cases with NPSLE when compared with the cases without NPSLE and were higher for all SLE patients than for healthy controls[40].

Ideally, computorized tomographic (CT) or MRI should be performed in all patients with NPSLE[15] to assess for structural and functional abnormalities[19]. However they rarely play a role in the assessment of non-thrombotic manifestations.

CT imaging of the brain can be useful in emergency settings to exclude cerebral haemorrhage, large infarct, intracranial hypertension and cerebral vein thrombosis, when MRI is unavailable[19]. In contrast MRI scans are more effective in detecting early lesions and lesions secondary to small vessel involvement. Lesions seen on MRI are frequently small, multifocal, and bilateral with high signal intensity affecting more commonly the white matter[16], suggestive of cerebral vasculopathy or thought to be due to multiple small infarcts[36].

According to one study, MRI with *fluid attenuated inversion recovery* seems to be more sensitive in NPSLE than conventional MRI, especially for lesions that are close to CSF-tissue interfaces[40].

Vasculopathy, if present, involves small vessels not detectable by MR angiography. If a vasculopathy is strongly suspected, conventional arteriography may be the best option. However, arteriography may also fail to detect changes in the smallest vessels[19].

Positron emission tomography (PET) and Single photon emission computerized tomography (SPECT)

have been shown to be highly sensitive for the diagnosis of diffuse manifestations in NPSLE. PET frequently identifies areas of hypometabolism, most often in the parietal or frontal lobes[19] and SPECT reveals, more commonly, multiple brain areas with hypoperfusion, most often in the frontal lobe.

SPECT may be used to monitor disease severity and guide therapy[41], although it has little or no value in monitoring CNS disease activity[16].

Despite their high sensitivity, PET and SPECT do not have a clear specificity. These modalities require further study and results should be interpreted cautiously[19].

Promising imaging modalities, including Proton magnetic resonance spectroscopy (MRS), Magnetization transfer imaging (MTI) and Diffusion weighted imaging (DWI), may reveal important information in the future, assessing biochemical aspects, quantification of brain activity and differentiation inflammatory lesions from ischemic damage, respectively. Further studies are necessary to provide a true understanding of the clinical usefulness of these techniques[14,19,40,42].

A multidisciplinary assessment is needed and it may include self, teacher and parent reports of cognitive difficulties or recent behaviour disorders[19].

A psychiatric consultation may be required for diagnosis of depression and for the exclusion of reactive depression secondary to chronic disease, psychosis and anxiety disorder[22].

Formal neuropsychological assessment is recommended whenever cognitive decline is suspected, and some authors argue that all children with SLE should undergo formal neurocognitive assessment at diagnosis to establish a baseline level of cognitive function, given the challenge in detecting cognitive abnormalities[19].

A wide array of instruments that can provide comprehensive and useful information is available for formal neurocognitive testing, such as *Mini Mental Status Exam*[22], a standardized core set of neuropsychological tests for assessment of pediatric cognitive function proposed by *Childhood Arthritis and Research Alliance* and the computer-administered neurocognitive assessment *Pediatric-Automated Neuropsychological Assesssment Metrics*[19]. However, no standardized battery has already been validated for the pediatric SLE population. Changes inherent to age and development, and the limited information about premorbid functioning difficult the effectiveness and interpretation of neurocognitive tests in pediatric population. Moreover,

they take several hours to be performed and the language and cultural factors and the potential for score inflation via "learning effects" after repetitive testing are limitations of all neurocognitive tests[19].

TREATMENT OF JUVENILE NPSLE

The clinical diversity of NPSLE, the difficulty in defining outcome measures and the lack of diagnostic criteria have been considered the biggest obstacles to the performance of controlled clinical trials related to study treatment options which difficult the comparison between different therapeutic regimens. Once there are no guidelines for the treatment of juvenile NPSLE, it should be individualized and based upon clinical experience[6].

The management of patients with juvenile NPSLE has to overcome these challenges: trying to control the disease and preventing the damages induced by medications[7].

It is important to differentiate between mild and severe manifestations and between thrombotic and non-thrombotic disease.

Patients with mild neuropsychiatric disease such as anxiety, depression, seizures, psychosis and headache or migraine may be treated conservatively with anxiolytics, antidepressants, anticonvulsants, antipsychotics, analgesics / anti-inflammatory drugs / calcium antagonists and ergotamine, respectively. Long-term antiepileptic treatment is indicated in the presence of concomitant cerebrovascular disease and / or persistent EEG abnormalities. Anticoagulation may be considered in a selected group of patients with seizures and persistent aPL positivity. Avoiding corticosteroids in these particular cases has also helped in the reduction of complications such as secondary infection, osteoporosis or aseptic necrosis[21]. Patients with cognitive disfunction should receive psychological support and educational interventions to maximize memory and function[19].

The recognition of the role of APL in the appearance of severe thrombotic/focal events on NPSLE contributed to a more assertive therapeutic approach. Due to the high risk of recurrence, in the case of previous thrombosis or high titers of APL, including ACLA, long-term anticoagulation with warfarin is mandatory, with an International Normalized Ratio values between 2.5 to 3.5. For patients with low or moderate levels of ACL, without any clinical symptom, and no previous episode of thrombosis, a prophylaxis with low-dose aspirin may be sufficient, even though its application

is controversial[7].

There is no evidence whether patients with subclinical cognitive manifestations and small lesions with high signal intensity in the MRI, which in turn are associated with the presence of APL, would benefit from antiagreggrant therapy based on aspirin. Patients who fail to respond to antiaggregant therapy, show progression on the brain MRI lesions or develop cognitive dysfunction and should receive anticoagulant therapy with warfarin[28].

Acute severe diffuse CNS manifestations generally require high doses of intravenous corticosteroids and chronic severe diffuse CNS manifestations generally require oral corticosteroids, preferably for short periods[21].

The use of intrathecal corticosteroids[43] or cyclophosphamide may be used in refractory cases to corticosteroids. There are no randomized controlled trials comparing the effectiveness and safety of cyclophosphamide and corticosteroids[21]. A combination between cyclophosphamide and corticosteroids has been described in some pediatric studies as useful for the treatment of severe NPSLE[6,11,16].

Combination therapy with syncronized plasmapheresis and subsequent cyclophosphamide in severe NPSLE has been proposed by some authors and it seems that patients who respond better to plasmapheresis are those with more severe illness[44].

In selected patients with APL positivity and whose neuropsychiatric manifestations are difficult to be differentiated between thrombotic and non-thrombotic ones, such as chorea and transverse myelitis, can be treated with a combination and monitored closely therapy with corticosteroids, cyclophosphamide and anticoagulation. Chorea may also respond to an additional anticonvulsant therapy[21].

Intrathecal methotrexate or corticosteroids, hyperbaric oxygen, azathioprine, mycophenolate mofetil, memantine, plasmapheresis and biotherapies as rituximab[16,19] require further controlled clinical trials to confirm their usefulness in the NPSLE.

CONCLUSIONS

Neuropsychiatric manifestations in jSLE represent an important diagnostic challenge because of its diversity and complexity. The most common neuropyschiatric manifestations are headache, cognitive dysfunction, mood disturbances and seizures.

Although its true pathogenesis is still unknown, it seems that some autoantibodies have a positive predictive value concerning to some manifestations, such as Anti-ganglioside antibodies, Anti-DNA antibodies cross-reactive with NMDA receptor, Anti-ribosomal P antibodies and Anti-phospholipid antibodies.

However, many areas remain unclear. Formal neuropsychological tests should be validated for the pediatric population with SLE and new imaging techniques should be explored. In order to improve the prognosis of children with NPSLE and to clarify pathophysiology, diagnosis and treatment aspects, further controlled clinical trials are needed.

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