Managing CNS involvement in systemic lupus erythematosus

The occurrence of neuropsychiatric manifestations in systemic lupus erythematosus (NPSLE) represents a diagnostic and therapeutic challenge for patients and clinicians. In this article we briefly discuss new perspectives on the pathogenesis, diagnosis, attribution and outcome of NPSLE. We speculated on the possible role of a rigorous preventive strategy, which takes into account the existence of associated risk factors that are yet to be fully defined, in the management of NPSLE. Finally, we highlight the management options and focus on the established and newly available treatment protocols for the more challenging, in terms of frequency or severity, clinical features of NPSLE.

KEYWORDS: antiphospholipid antibodies ▪ cerebral MRI ▪ cerebral vasculopathy ▪ CNS ▪ epidemiology ▪ neuroimaging ▪ neuropsychiatric manifestations ▪ pathogenesis ▪ SLE serology ▪ systemic lupus erythematosus

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Epidemiology

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease with a broad range of clinical manifestations characterized by inflammatory and immune-mediated pathogenetic mechanisms. Since the first report of stupor and coma in the 19th century, several neuropsychiatric (NP) syndromes have been reported in SLE.

The neurologic syndromes secondary to central, peripheral and autonomic nervous system involvement and the psychiatric syndromes observed in patients with lupus fall under the term NP SLE (NPSLE). In 1999, to define the clinical spectrum of NPSLE, an Ad Hoc Committee on behalf of the American College of Rheumatology (ACR) proposed nomenclature and case definition for 19 syndromes (**Box 1**). For each of these syndromes, diagnostic criteria and an exhaustive list of established exclusions or possible associations were provided in order to help determine the nature of NP event. According to criteria, NPSLE can be attributed to the disease (primary NPSLE) or be a complication of the disease or its treatment (secondary NPSLE), or be completely unrelated to SLE representing an accidentally co-occurring disorder [1]. Since their publication, the ACR classification criteria have been utilized in clinical practice and research. However, high variability in NPSLE prevalence is still recorded varying from 37 to 91% (**Table 1**) [2–6] as a consequence of differences in study populations, misinterpretation and low accuracy of the standardized criteria. In a 6-year prospective study, NPSLE occurred in 95% of childhood-onset SLE patients [7]; 50–60% of NPSLE events occur within the first year after disease onset and 41% of NP events occurring at the time of SLE diagnosis have their onset before [8].

The CNS is more frequently affected than the peripheral nervous system, the latter representing the target of 6–10% of NP events. Therefore, the reported difference in prevalence is mainly due to attribution given to CNS manifestations, especially minor events such as headache, mood disorders and cognitive dysfunction, which represent the most common manifestations of NPSLE.

Ainiala *et al.* performed a population-based study covering an area with 440,000 people and estimated a NPSLE prevalence of 91% among patients suffering from SLE [6]. Assessing the validity of the ACR nomenclature for NPSLE in their cohort of 46 patients and 46 matched controls, the authors found a low specificity (46%) for the proposed criteria. They proposed a revision of the criteria excluding anxiety, headache as well as mild depression, mild cognitive dysfunction (with deficits in less than three domains) and polyneuropathy unconfirmed by electroneurography, which gave rise to a higher degree of specificity (93%) with a 46% detection rate among SLE cases [9].

More recently Hanly *et al.*, in order to determine the prevalence of NPSLE in a multicenter inception cohort of 572 patients at the time of diagnosis (disease duration 5.2 ± 4.2 months), defined a set of decision rules that accounts for the comprehensive list of exclusions and associations in the ACR nomenclature, the revised

Box 1. Neuropsychiatric syndromes in systemic lupus erythematosus as defined by the 1999 American College of Rheumatology nomenclature and their distinction in focal and diffuse neuropsychiatric systemic lupus erythematosus.

- CNS [1]
  - Acute confusional state
  - Anxiety disorder
  - Aseptic meningitis
  - Cerebrovascular disease
  - Cognitive dysfunction
  - Demyelinating syndrome
  - Headache
  - Mood disorders
  - Movement disorder
  - Myelopathy
  - Psychosis
  - Seizures
- Peripheral nervous system [1]
  - Autonomic disorder
  - Cranial neuropathy
  - Guillain–Barré syndrome
  - Mononeuropathy (single/multiplex)
  - Myasthenia gravis
  - Plexopathy
  - Polyneuropathy
- Focal neuropsychiatric systemic lupus erythematosus [8]
  - Autonomic neuropathy
  - Cerebrovascular disease
  - Cranial neuropathy
  - Guillain–Barré syndrome
  - Mononeuropathy
  - Movement disorder
  - Myasthenia gravis
  - Myelopathy
  - Plexopathy
  - Polyneuropathy
  - Seizures
- Diffuse neuropsychiatric systemic lupus erythematosus [8]
  - Acute confusional state
  - Anxiety disorder
  - Aseptic meningitis
  - Cognitive dysfunction
  - Demyelinating syndrome
  - Headache
  - Mood disorder
  - Psychosis

criteria proposed by Ainiala *et al.*, and the temporal relationship between the NP event and the diagnosis of SLE. They found that the proportion of NP events attributable to SLE at the time of diagnosis varied between 19 and 38%, depending upon the decision rules for attribution, and affected 6.1–11.7% of patients [8]. Afterwards they confirmed their results in a cohort of 1206 patients of whom 486 (40.6%) had at least one NP manifestation in a total of 843 events, but only 17.7–30.6% of them were attributable to SLE [10].

New proposals for NPSLE criteria did not consider some of the CNS syndromes traced in the ACR nomenclature as distinctly SLE induced and suggested modification according to other classifications [11,12]. For instance, the current ACR nomenclature of headache disorders covers only five categories, including 'intractable headache, nonspecific' which is not further defined. Comparing the specificity of the International Headache Society (IHS) and ACR criteria in 61 subjects with SLE, Davey *et al.* found that the IHS criteria enabled classification of all headache disorders seen in the cohort whereas the ACR criteria failed to classify 22% of headache disorders [12]. It is conceivable to suppose that although the ACR nomenclature has been a useful tool in research, clinicians need new tools to better diagnose and classify SLE patients suffering from NP events.

Pathogenesis

The most substantiated analysis of NPSLE pathogenetic mechanisms recognizes that antibodies, systemic inflammation and thrombophilic state lead to neuronal dysfunction, intrathecal cytokine production, accelerated atherosclerosis, thrombosis, thromboembolism and vasculopathy (Table 2). Neuropathology findings show that CNS vasculitis occurs in only 7–13% of cases and major infarcts in 10–22%, whereas thrombotic and hemorrhagic microangiopathy (65–83%) as well as microinfarcts (35–71%) are the most frequently observed changes in SLE but they do not always clearly fit with NP symptoms [13–15]. Some clinical expressions of NPSLE, the so-called focal manifestations, such as cerebrovascular disease (CVD) have been mostly associated with the thrombotic effect of antiphospholipid antibodies (aPL) and Libman–Sacks endocarditis [15,16]. On the other hand, the diffuse manifestations such as mood disorders, psychosis and primary cognitive dysfunction are thought to be mainly caused by the immunologic effects of antibodies directed against a variety of CNS structure, thus resulting in different NP dysfunction. [15–17]. This hypothesis is by far the most promising explanation of the protean NPSLE phenotype.

The light subunit of the neurofilament triplet protein and the glial fibrillary acidic protein (GFAP) in the cerebrospinal fluid (CSF) and antibodies against GFAP in the serum of NPSLE patients have been identified [18,19]. Such findings reflect neuronal death and implicate astrocytes in the pathologic process. Although neither neurofilament triplet protein nor GFAP

Table 1. Prevalence of overall neuropsychiatric systemic lupus erythematosus and of each type of syndrome in studies applying the 1999 American College of Rheumatology nomenclature and case definition.

Neuropsychiatric syndrome	Hanly *et al.* n = 111 [2]	Sanna *et al.* n = 323 [3]	Afeltra *et al.* n = 61 [4]	Brey *et al.* n = 128 [5]	Ainiala *et al.* n = 46 [6]
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
NPSLE prevalence	41 (37)	185 (57)	44 (72)	102 (80)	42 (91)
CNS					
Acute confusional state	5 (4.5)	12 (3.7)	0	0	3 (6.5)
Anxiety disorder	1 (0.9)	24 (7.4)	4 (6.5)	27 (21.0)	6 (13.0)
Aseptic meningitis	1 (0.9)	0	0	0	1 (2.1)
Cerebrovascular disease	5 (4.5)	57 (17.6)	15 (24.5)	2 (1.5)	7 (15.2)
– Stroke	2 (1.8)	22 (6.8)	3 (4.9)	2 (1.5)	5 (10.8)
– Transient ischemic attack	3 (2.7)	24 (7.4)	4 (6.5)	0	2 (4.3)
– Chronic multifocal disease	0	6 (1.8)	7 (11.4)	0	1 (2.1)
– Subarachnoid hemorrhage	0	4 (1.2)	1 (1.6)	0	0
– Sinus thrombosis	0	1 (0.3)	0	0	0
Cognitive dysfunction	3/6 (2.7)†	35/57 (10.8)†	32 (52.4)	53/67 (41.4)†	37 (80.4)
– Mild	NR	NR	19 (31.1)	29 (22.6)	26 (56.5)
– Moderate	NR	NR	10 (16.3)	20 (15.6)	7 (15.2)
– Severe	NR	NR	3 (4.9)	4 (3.1)	4 (8.6)
Demyelinating syndrome	3 (2.7)	3 (0.9)	0	0	1 (2.1)
Headache	28 (25.2)	78 (24.1)	13 (21.3)	73 (57.0)	25 (54.3)
– Tension headache	16 (14.4)	36 (11.1)	3 (4.9)	21 (16.4)	7 (15.2)
– Migraine without aura	9 (8.1)¶	33 (10.2)¶	10 (16.3)¶	31 (24.2)	6 (13.0)
– Migraine with aura				20 (15.6)	12 (26.0)
– Intracranial hypertension	0	2 (0.6)	0	1 (0.7)	0
– Aspecific headache	3 (2.7)	4 (1.2)	0	0	0
– Cluster headache	0	3 (0.9)	0	0	0
Mood disorders	16 (14.4)	54 (16.7)	17 (27.8)	62 (48.4)	20 (45.4)
– Major depressive-like episode	9 (8.1)	37 (11.4)	8 (13.1)	37 (28.9)	18 (39.1)
– With depressive features	6 (5.4)	15 (4.6)	9 (14.7)	21 (16.4)	0
– With manic features	0	2 (0.6)	0	3 (2.3)	0
– With mixed features	1 (0.9)	0	0	1 (0.7)	2 (4.3)
Movement disorder	0	4 (1.2)	0	1 (0.7)	1 (2.1)
Myelopathy	1 (0.9)	4 (1.2)	2 (3.2)	0	0
Psychosis	3 (2.7)	25 (7.7)	0	6 (4.6)	0
Seizures	2 (1.8)	27 (8.3)	7 (11.4)	21 (16.4)	4 (8.6)
– Primary generalized	1 (0.9)	10 (3.0)	1 (1.6)	NR	NR
– Partial or focal	1 (0.9)	15 (4.6)	6 (9.8)	NR	NR
Peripheral nervous system					
Autonomic disorder	0	0	2 (3)	0	0
Cranial neuropathy	4 (3.6)	5 (1.5)	3 (4)	2 (1.5)	3 (6.5)
Guillain–Barré syndrome	0	2 (0.6)	0	0	0
Mononeuropathy	0	6 (1.8)	0	9 (7.0)	0
Myasthenia gravis	0	5 (1.5)	0	0	1 (2.1)
Plexopathy	0	0	0	0	0
Polyneuropathy‡	2 (1.8)	9 (2.7)	5 (8.1)	20 (15.6)§	3 (6.5)

†*Cognitive tests were not routinely conducted in all patients but only if indicated (number with cognitive deficit/number underwent cognitive tests suggested by American College of Rheumatology* Ad Hoc *committee).*
‡*Confirmed by electroneurography.*
§*Number of diagnosis confirmed by electroneurography not reported.*
¶*Subcategories are pooled on.*
NPSLE: Neuropsychiatric systemic lupus erythematosus; NR: Not reported.

or GFAP-reactive antibodies are diagnostic for NPSLE these observations demonstrate that some patients sustain persistent CNS injury.

A novel antineurofilament protein, the anti-α-internexin antibody, has been identified as being pathophysiologically relevant to NPSLE cognitive damage and was found in both the serum and CSF of 52% of NPSLE and 19% of SLE patients [20]. Cognitive dysfunction, mood disorders and other diffuse manifestations such as movement disorders and isolated generalized seizures have shown an high prevalence in aPL-positive patients [21] and a nonthrombotic pathogenic effect played by these antibodies has been suggested [22]. Antiribosomal-P antibodies have been detected in patients with psychosis and depression [23,24]. DeGiorgio *et al.* demonstrated that a subset of anti-DNA antibodies recognizes a pentapeptide that is also present in the extracellular domain of the murine and human *N*-methyl-D-aspartate receptor (NMDAR) for glutamate, which are mainly expressed in the hippocampus [25]. Human antibodies against NMDAR lead to neuronal apoptosis and have been detected in the CSF of patients with cognitive dysfunction and depression [26–28].

In vitro and animal models have shown that the presence of antibodies targeting neuronal antigens may result in functional abnormalities and apoptotic cell death. Nevertheless, the role of autoantibodies in NPSLE pathogenesis remains incompletely understood. Recently published data obtained using mouse hippocampal slices are thought to have shed some light on the unknown mechanism of autoantibody-mediated pathogenesis in NPSLE. Faust *et al.* found that NMDAR-reactive antibodies could have a dose-dependent effect [29]. At low concentrations the anti-NMDAR antibodies are positive modulators of receptor function that increase the size of excitatory postsynaptic potentials, whereas at high concentrations they promote excitotoxicity and cause neuronal death. The authors concluded that the effect of different antibody titers or the amount able to enter the brain across the blood–brain barrier (BBB) may mirror the clinical condition of NPSLE patients, in which reversible symptoms may reflect synaptic effects whereas severe episodes with permanent damage may reflect neuronal death [29].

It has been hypothesized that damage of the brain endothelium forming the BBB creates small leaks across it, favoring the access of antibodies and lymphocytes to the CNS and triggering NPSLE development. The barrier breakdown has been attributed to ischemia, caused by aPL or else platelet and fibrin microembolism from Libman–Sacks endocarditis, or to inflammatory endothelium activation caused by local lymphocyte and glial cytokine production (e.g., IL-2, IL-6, IL-10, IFN-α and matrix metalloproteinase) [26–28]. However, co-occurring conditions such as infection, nicotine dependence, hypertensive episode, atherosclerosis and older age might represent risk factors for BBB permeabilization by which antibodies may gain access to their neuronal target triggering NPSLE [30–34]. On the other hand, cytokines and other inflammatory mediators may be neurotoxic *per se* and cause indirect damage by promoting endothelial activation and vascular injury [35,36]. NPSLE syndromes may recognize a single predominant pathogenic mechanism among those mentioned, or more than one. For instance, cognitive dysfunction and seizures may be secondary to stroke and chronic multifocal CVD.

At present, despite their supposed role in the pathogenesis of NPSLE, the detection of the above mentioned antibodies, cytokines or other factors in the sera and CSF of SLE patients does not help to confirm the diagnosis of NPSLE and their use is currently limited to an investigational role.

Risk factors

As very well summarized in a recent review [37], the associated factors that increase a persons risk of developing NPSLE include: high disease activity or damage, especially for seizure disorders and severe cognitive dysfunction [38–43]; previous events or other co-occurring NPSLE manifestations [40,44–46]; Libman–Sacks endocarditis; and persistently positive aPL (moderate-to-high titer of anticardiolipin or anti-β2-glycoprotein IgG/IgM titers or the lupus anticoagulant), especially for CVD, seizure disorder, cognitive dysfunction, myelopathy and movement disorder [3,35,43,45]. Theoretically, tight control over disease activity will help prevent lupus flares with CNS involvement but NPSLE might be unforeseeable and unrelated to systemic flares. Considering that 50–60% of patients with previous NP manifestations experienced a second NP event during the disease course [2–4], especially of the diffuse type, clinicians might consider these kind of patients at high risk for NPSLE recurrence and must subject them to tighter NP control.

Recently, Govoni *et al.* carried out a multicenter retrospective study aiming to analyze, in a large cohort of 959 Italian patients, whether factors and comorbidities associated with NP involvement could be defined and whether a 'risk profile' for NP involvement could be depicted [47].

This study provided some valuable confirmatory data, with the presence of aPL antibodies, high disease activity, high cumulative corticosteroids intake and a young age at disease onset being associated with NP involvement. Other associations remain controversial or unspecific (i.e., psychosis and estrogens intake, psychosis and lower corticosteroids cumulative dose, headache and carotid vasculopathy, seizures and valvular or chronic fibrillation heart disease) and need further confirmation in properly designed prospective studies. A potential role played by some modifiable cardiovascular risk factors such as hypertension and carotid vasculopathy in CVD or hypertension and dyslipidemia in cognitive impairment suggests an aggressive, rigorous and preventive therapeutic approach should be used for these conditions to optimize the management of NPSLE [47]. Future studies investigating the association between the exposure to any risk factor and the time to develop a NP event will help designing prophylactic strategies.

Outcome

Neuropsychiatric SLE has a great impact on patient lives in terms of morbidity, mortality, disability and quality of life. Severe NP manifestations occur early during the course of SLE and contribute to damage accrual [48,49]. Although NP damage does not seem to contribute to mortality, the occurrence of NP infection, cerebrovascular accident and active NPSLE represent a common cause of mortality in lupus patients [50–53]. Quality of life appeared poorer in SLE patients with NP involvement, especially in those of Caucasian origin [53–55]. Moreover, quality of life score reported by patients, calculated using a patient-derived mental component summary (MCS) of the Short Form-36 (SF-36), was lower in patients with NP events that were either SLE related and non-SLE related, and was also lower in patients with CNS involvement and diffuse events [56]. Using the SF-36 summary and subscales, including the MCS, changes in quality of life were strongly associated with the clinical outcome of NP events [57]. A global clinical approach for patients suffering from NPSLE must consider routine assessment of self-reported quality of life, and future NPSLE therapeutic trials must be specifically designed with quality of life among the primary outcomes to develop a treat-to-target therapy.

Diagnosis

From a clinical point of view, NPSLE events can manifest as acute or recurrent, silent or overt and might be unnoticed or catastrophic. As examples, ischemic stroke might be asymptomatic or lead to severe disability or death; on the other hand, seizures might be simple, without impairment of consciousness, or be generalized, with tonic/clonic shakes. Finally, cognitive dysfunction can range from mild impairment to severe dementia. Therefore, clinicians should be warned about the possible occurrence of NPSLE and in particular must be aware of the risks of subtle manifestations.

Preliminary work-up

According to the European League Against Rheumatism (EULAR) recommendations for the management of NPSLE, physicians must give necessary attention to patients' history and physical examination in order to determine the presence, the type and extension of neurological deficit [58]. Recently, Mosca *et al.* developed a physician-administered questionnaire, assisting in the screening of patients with SLE for the presence of nonovert NP involvement, which provide a helpful first-level evaluation before deciding on additional testing [59]. Nevertheless, a multidisciplinary approach including the intervention of dedicated neurologist, psychiatrist and neuropsychologist is recommended in order to challenge the NP involvement as a major factor of the early life-threatening events and a main cause of the late mortality curve and of mental or physical disability in long-term surviving SLE patients.

Clinicians must always look for secondary causes of NP disorders to exclude mimicking conditions (i.e., hypertensive encephalopathy) and to identify causes or aggravating factors, such as dyslipidemia, infections (systemic and CNS infections), concomitant diseases (i.e., thrombotic thrombocytopenic purpura, or hyper- or hypothyroidism) metabolic disturbances (hypoglycemia or uremic syndrome), adverse drug reactions, alcohol or illicit drug use, and withdrawal syndromes, which may be the cause of NP symptoms *per se* or may act as a trigger for NPSLE development. In the presence of CNS involvement clinicians should identify and treat any possible provoking or worsening factors for NP disorder in order to avoid misleading diagnosis and under- or overtreatment. In the absence of CNS involvement the identification of such conditions should lead to clinicians considering such patients to be at a high risk of developing NPSLE. In such patients, performing a tight control and management of disease activity and risk factors, in order to prevent new NP events, should be considered in the treatment for NPSLE (Figure 1).

Table 2. Summary of the relationship between the type of pathogenic event, putative pathogenic mechanism, neuropathologic changes, major neuroimaging findings and associated neuropsychiatric manifestations of CNS involvement in systemic lupus erythematosus patients according to most substantiated analysis.

Type of pathogenic event	Putative pathogenic mechanism(s)	Associated neuropathologic changes	Major neuroimaging findings	Related neuropsychiatric manifestations
Cerebral vasculopathy				
Large cerebral vessel thrombotic occlusion	*Large vessel thrombosis:* • aPL-mediated thrombosis [15]; • Thromboembolism secondary to valvular heart disease (e.g., Libman–Sacks endocarditis) [35,43,45]; • Atherosclerotic thrombosis [35]	*Large vessel thrombosis* [15,70]: • Large focal area of coagulation and necrosis with destruction of neurons and infiltration of inflammatory cells, red blood cells and hemosiderin; • Postischemic macrohemorrhages; • In late stages loss of gliosis (glial hyperplasia replacing neuronal loss) and cortical atrophy	*Acute ischemic stroke:* • DWI restricted diffusivity lesions appear a few minutes after vessel occlusion (ischemic stroke or TIA) [77,78]; • MRI T_1 hypointense, T_2 and FLAIR hyperintense lesions, involving the gray and white matter appear 8–24 h later (stroke). In T_1-contrast-enhanced images, the arterial enhancement usually persists until day 21; the parenchymal enhancement persists for 3–4 months. In late stages, cortical atrophy and ventricular dilation can be seen [68,69,76]	• CVD (e.g., stroke, TIA, sinus thrombosis, CMD) [3,16]
Small CNS vessel occlusion	*Small vessel vasculopathy:* • aPL-mediated ischemia [15]; • Endothelial injury associated with increased SLE disease activity (mechanism not clear: immune complexes (?), cytokine (?), platelet activation (?)) and hypertension [68]	*Small vessel vasculopathy* [15,68]: • Microinfarcts (small foci of coagulation necrosis, infiltration of inflammatory cells, cellular debris) and microhemorrhages; • Arterial intimal fibrous hyperplasia and thrombotic microangiopathy; • Gliosis and cortical atrophy	*Cerebral small vessel disease* [62–72]: • Small focal T_2-weighted hyperintense MRI lesions, without contrast-enhancement (addressed as microinfarcts, microhemorrages, reduced neuronal/axonal density with gliosis); • In late stages, cortical atrophy (generalized thinning of cortex) and dilation of ventricles best seen on T_2 MRI images	• Seizures [15–17,21,22,99]; • Severe cognitive dysfunction (vascular dementia) [14–16,108]; • Myelopathy (?) [15,118]

Ab: Antibody; Anti-rib-P: Anti-ribosomal-P antibodies; aPL: Antiphospholipid antibodies; BBB: Blood–brain barrier; Cho: Choline; CMD: Chronic multifocal disease; Cr: Creatinine; CVD: Cerebrovascular disease; DWI: Diffusion weighted imaging; FLAIR: Fluid attenuated inversion recovery; H-MRS: Proton magnetic resonance spectroscopy; NAA: N-*acetylaspartate; NMDAR:* N-*methyl-*D*-aspartate receptor antibodies; SLE: Systemic lupus erythematosus; SPECT: Single photon emission computed tomography; TIA: Transient ischemic attack.*

Table 2. Summary of the relationship between the type of pathogenic event, putative pathogenic mechanism, neuropathologic changes, major neuroimaging findings and associated neuropsychiatric manifestations of CNS involvement in systemic lupus erythematosus patients according to most substantiated analysis (cont.).

Type of pathogenic event	Putative pathogenic mechanism(s)	Associated neuropathologic changes	Major neuroimaging findings	Related neuropsychiatric manifestations
BBB breakdown				
Permeabilization of the BBB with Abs and lymphocyte access to the CNS and neurotoxic cytokine production [15–36]	*Ischemic* [15,28,29]: • aPL, Libman–Sacks endocarditis; *Inflammatory/immunologic* [28–30]: • BBB endothelium activation/damage in SLE-related systemic inflammatory state: 1) Cytokine mediated 2) Ab mediated *Mixed (?)* [28,31,32]: • BBB endothelium non-SLE-related activation/damage driven by infection, nicotine, hypertension, atherosclerosis (?)	• Microinfarcts and microhemorrhages [70]; • Diffuse edema [70]; • Neuronal (gray matter) and axonal (white matter) loss [70]; • Gliosis and cortical atrophy [70]	*Morphological neuroimaging:* • Features of cerebral small vessels disease (see above) [63–76] *Functional neuroimaging:* • H-MRS neurometabolite abnormalities [79–85] 1) ↓ NAA levels = neuronal/axonal loss 2) ↑ Cho levels = gliosis, vasculopathy, edema 3) ↓ Cr levels = neuronal/axonal loss, gliosis • SPECT hypoperfusion areas which may reflect low neuronal activity [87–89]	• Ab mediated [15–30]: 1) Cognitive dysfunction (anti-NMDAR, aPL) 2) Psychosis, mood disorders (anti-rib-P) 3) Movement disorders, seizures, headache (?), myelopathy (?) (aPL) • Cytokine/inflammation mediated [14,15,35,36]: acute confusional state, psychiatric features, seizures, aseptic meningitis
Vasculitis				
Inflammatory vascular occlusion [13–15]	• Immune complex deposits and inflammation or necrosis involving small vessels in the choroid plexi, leptomeninges, gray matter or white matter, but vessels of any size can be affected [13–15]	• Mononuclear cell infiltrate through the whole vessel wall with fibrinoid necrosis [13–15]	• MRI T_2-weighted and FLAIR hyperintense lesions, variable size, which may involve both gray and white matter. In late stages localized cortical atrophy may be seen. Acute ischemic stroke may occur in large vessel vasculitis [13,68]; • Usually normal cerebral angiogram [13,68]	• Acute confusional state, aseptic meningitis and psychosis, seizures, myelopathy (?) [13–15]; • Stroke may occur depending on size of involved vessel [13–15]

Ab: Antibody; Anti-rib-P: Anti-ribosomal-P antibodies; aPL: Antiphospholipid antibodies; BBB: Blood–brain barrier; Cho: Choline; CMD: Chronic multifocal disease; Cr: Creatinine; CVD: Cerebrovascular disease; DWI: Diffusion weighted imaging; FLAIR: Fluid attenuated inversion recovery; H-MRS: Proton magnetic resonance spectroscopy; NAA: N-acetylaspartate; NMDAR: N-methyl-D-aspartate receptor antibodies; SLE: Systemic lupus erythematosus; SPECT: Single photon emission computed tomography; TIA: Transient ischemic attack.

In this setting, blood tests might be useful to exclude secondary causes, such as metabolic disturbances (hypo- or hyperglycemia, uremia or electrolyte abnormalities), dyslipidemia, vitamin deficiencies, liver or thyroid disease.

A CSF examination is indicated to exclude subarachnoid hemorrhage or CNS infection through Gram strain, microbiological culture and PCR search for viral nucleic acid (e.g., herpes virus or JC virus [JCV]). CSF abnormalities, such as elevated pressure (45%), increased white cell count (22–36%), high protein level (30–75%), low glucose level (4–42%) and oligoclonal bands (25–55%) are common in up to 90% of patients with active NPSLE but are not specific and cannot accurately differentiate SLE from non-SLE-related events [60–62]. However, CSF analyses are quite useful in determining CNS inflammation and BBB breakdown, which in the setting of SLE may indicate severe pathology.

The 'sensitivity versus specificity dilemma' is extremely important when diagnosing NPSLE. Despite high specificity, testing for antibodies in serum and CSF has limited diagnostic value for NPSLE, because of low sensitivity. On the other hand, CSF analysis and the many increasingly sensitive neuroimaging and assay techniques have poor specificity. These are the main reasons why there is no gold standard for diagnosing NPSLE, which is still based on expertise and on the interpretation of a combination of tests.

Neuroimaging

As computed tomography (CT) is an easily accessible technique, it can be used in acutely ill patients to detect brain abnormalities. However, conventional MRI is the test of choice in morphological work-up of NPSLE patients because of its higher sensitivity in detecting infarctions, hemorrhages, reversible leukoencephalopathy, parenchymal mass and abscess [63].

Typical MRI findings are small hyperintense focal lesions in subcortical and periventricular white matter on T_2-weighted and fluid attenuated inversion recovery images, usually with normal T_1-weighted signals and without contrast enhancement. These lesions are detected in 35–60% of patients with long-lasting NPSLE and probably indicate chronic irreversible injury, but they are extremely aspecific as can be found in both patients without CNS involvement (25–50%) [64,65] and without SLE [66]. In a cohort of newly diagnosed patients focal lesions had a prevalence of 8%, suggesting that the brain might be affected very early in disease course [67]. The prevalence of small T_2 hyperintense lesions is higher in focal than diffuse NPSLE (85 vs 55%) and they do not represent acute or active disease but rather old injury [68,69]. The meaning of white matter focal lesions is still controversial but it is conceivable they represent the small vessel vasculopathy, which must not be confused with the rarely occurring vasculitis, characterizing the major histopathological background of brain involvement and their detection define the picture of the so-called cerebral small vessels disease (Table 2) [70]. Their presence correlates with SLE clinical severity, past history of CNS involvement, cognitive dysfunction, aPL, aging, heart valvular disease and hypertension, enhancing the evidence of a risk role played by these factors [39,71–74].

Other MRI findings are large lesions involving the gray and white matter consistent with cerebral ischemic stroke (Table 2). Cortical and basal ganglia gray matter atrophy (2–9%), and subarachnoid and ventricular space dilatation (9–18%) can be detected with conventional and more accurately with volumetric MRI and have been associated with cognitive dysfunction, seizures, CVD and a high cumulative dose of glucocorticoids [68,74,75].

The recommended MRI protocol includes diffusion weighted imaging (DWI) [76]. DWI improves MRI sensitivity in the early detection of acute ischemic stroke lesions and in discriminating between recent (with restricted diffusivity) and old (with normal diffusivity) ischemic lesions, which are hardly distinguishable using conventional tools [77,78]. The use of gadolinium does not increase the sensitivity or specificity of MRI findings in NPSLE but might be useful in detection of acute inflammation and demyelination of the brain and spinal cord.

Proton magnetic resonance spectroscopy (H-MRS) is an MRI application exploring the biochemical profile of CNS and showing different spectra corresponding to different neuronal metabolites such as the *N*-acetyl-aspartate (NAA), choline (Cho) and creatinine (Cr), which has been proven to be more sensitive than MRI in detecting brain abnormalities but is not specific for NPSLE [79,80]. Reduced NAA levels are interpreted as neuronal/axonal loss or dysfunction, an elevated Cho peak is putative of increased cell membrane turnover as seen in demyelination, inflammation or gliosis whilst a diminished Cr peak indicates reduced neuronal axonal density and gliosis [81]. Altered metabolite ratios are observed in SLE even in the absence of MRI lesions [80]. A decreased

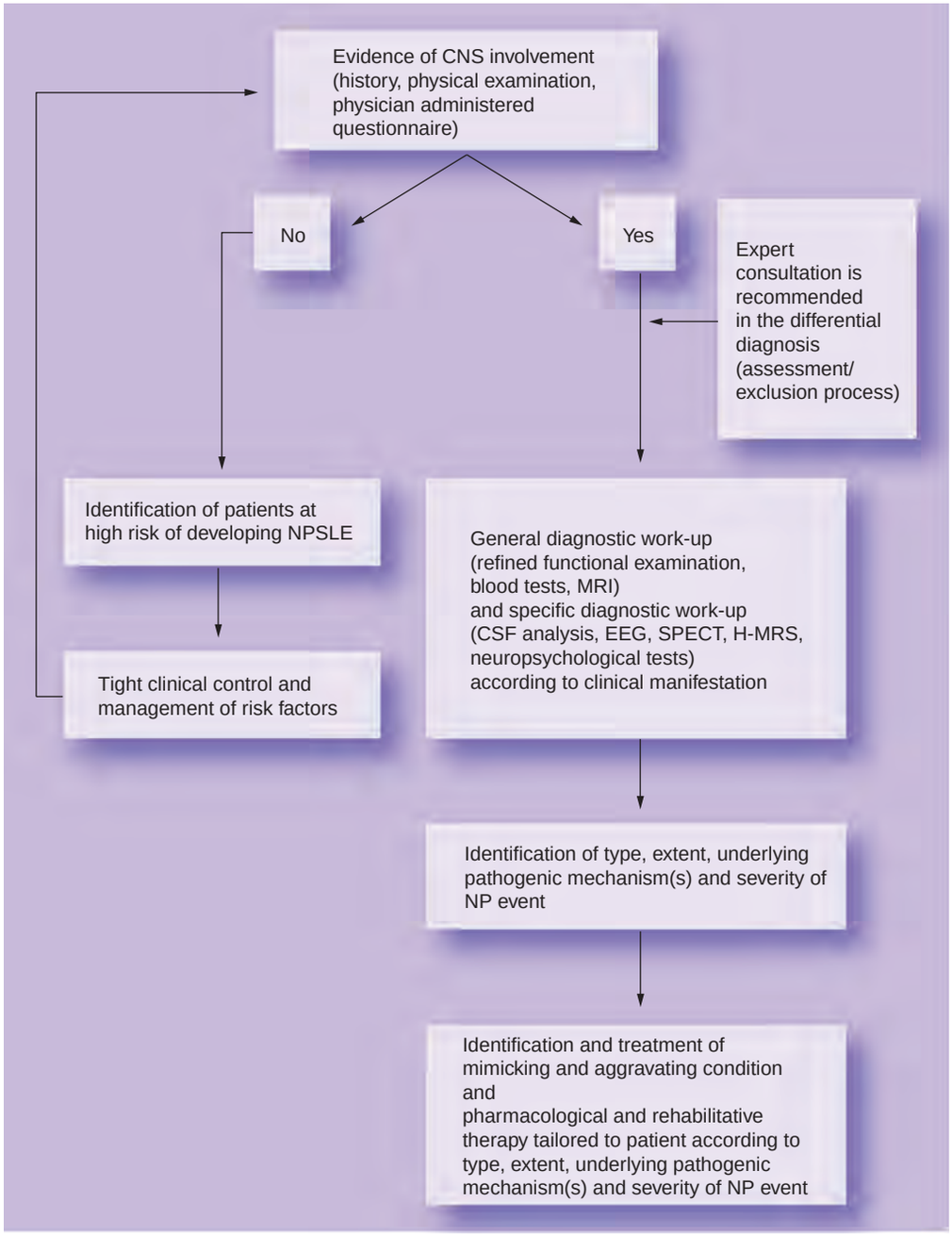

Figure 1. Algorithm for the approach to recognition, monitoring and general management of patients with neuropsychiatric systemic lupus erythematosus.
CSF: Cerebrospinal fluid; EEG: Electroencephalography; H-MRS: Proton magnetic resonance spectroscopy; NP: Neuropsychiatric; NPSLE: NP systemic lupus erythematosus; SPECT: Single photon emission computed tomography.

NAA:Cr ratio correlates with MRI abnormalities, aPL positivity and disease activity but does not correlate with specific NP syndromes, whilst an increased Cho:Cr ratio has been found in active NPSLE [82,83].

Moreover and more interestingly, an increased Cho:Cr ratio as well as hypoperfused areas detected by single photon emission computed tomography (SPECT) have been proven to predict the future appearance of hyperintense T_2-weighted MRI lesions in SLE patients [84,85]. Gasparovic *et al.* recently examined the absolute differences in both regional cerebral blood flow (CBF) and cerebral blood volume (CBV) between patients with SLE and healthy controls through dynamic susceptibility contrast-MRI. The authors found that CBF and CBV within MRI-visible lesions were markedly reduced

relatively to surrounding normal-appearing white matter. On the other hand, CBF and CBV in normal-appearing tissue in patients with SLE were higher than in controls. The authors concluded that brain injury in SLE is characterized by brain hyperperfusion preceding lesion pathology [86]; however, their innovative findings need to be further investigated and confirmed in future studies.

Single photon emission computed tomography is a functional imaging technique that examines brain perfusion and neuronal metabolic activity, and is more sensitive than MRI for diffuse (89 vs 33%) NPSLE but has lower specificity showing abnormalities even in patients with high disease activity without overt NPSLE [19,87–89]. Specificity is improved when moderate-to-severe perfusion deficits at multiple brain regions and involvement of the basal ganglia are detected.

Other techniques such as dynamic susceptibility contrast-MRI, magnetization transfer imaging, diffusion tensor MRI, functional MRI and perfusion weighted imaging have limited use in NPSLE diagnosis because of a nonstandardized role and in the case of PET, because of its high cost.

In every day practice it has been advised to obtain a conventional MRI not only at new NP event occurrence or in presence of modification of a previous NP manifestation, but also at the time of SLE diagnosis, even in patients without NPSLE, to allow baseline staging [90]. It would be particularly advisable in patients with a higher risk of developing future neurological events such as those with persistently positive aPL, dyslipidemia and hypertension. An additional functional imaging technique such as H-MRS or SPECT should be performed, especially in patients with diffuse NP events and who have a negative MRI, in order to detect early brain abnormalities. Castellino *et al.* performed MRI and SPECT simultaneously in 107 SLE patients of whom 66 had CNS involvement. They found both abnormal MRI and SPECT in 37% of patients suffering with diffuse and in 64% with focal NPSLE compared with 27% of patients without CNS involvement ($p=0.441$ and $p=0.028$, respectively). On the other hand, MRI and SPECT were both normal in 15% of patients with diffuse and in 0% of patients with focal NPSLE events versus 41% of SLE patients without NP involvement ($p < 0.01$ in both groups), which led the authors to suggest that coupling morphological and functional diagnostic tools may be more helpful in excluding NP involvement than confirming it [68].

Additional testing in the evaluation of lupus patients with NPSLE includes electroencephalography (EEG), evoked potential, transcranial Doppler ultrasound, MR angiogram and neuropsychological tests. There is good evidence that transthoracic echocardiogram should be obtained, and if normal, then a transesophageal echocardiogram should be obtained to determine the subtle but common lesions of Libman–Sacks endocarditis [91].

However, there has been little consensus on the role of all the mentioned procedures and each one of them has a different value in the diagnosis and follow-up of the CNS syndromes occurring in SLE patients.

Management

Management of CNS involvement in SLE still remains a challenge for clinicians and owing to the lack of randomized controlled trials the current therapeutic approach is still empirical and based on clinical experience.

The general approach to patients with NPSLE is almost the same whilst specific diagnostic work-up is based on the type of NP event (Figure 1). Therapeutic decision depends on accurate diagnosis, identification of underlying pathogenic mechanism, severity of the presenting NP symptoms, and on prompt identification and management of contributing causes of the CNS disease.

Symptomatic therapy, such as anticonvulsants, antidepressants and antipsychotics might be helpful in specific types of NP disease. The use of glucocorticoids is the best available option for the treatment of inflammatory NPSLE manifestations, such as aseptic meningitis, myelitis, demyelinating syndrome, cranial neuropathy, seizures, severe psychosis and acute confusional state [92]. Combination with immunosuppressants as steroid-sparing agents is recommended. Pulse intravenous cyclophosphamide therapy should be reserved to refractory manifestations of active lupus, generally when response is not seen in few days, in severe events or in NPSLE associated with glomerulonephritis [93]. Plasma exchange has been reported to be effective in refractory NPSLE in association with glucocorticosteroids and cyclophosphamide [94,95]. An observational study in ten Japanese patients proved the efficacy of the anti-CD20 monoclonal antibody rituximab in refractory NPSLE [96]. Intravenous immunoglobulin, mycophenolate mofetil, rituximab and intrathecal injections with dexamethasone plus methotrexate deserve further study to confirm their usefulness in the treatment of SLE-related CNS involvement [60,97–99].

Patients with persistently positive aPL at moderate-to-high titers and previous thrombotic events must be managed with anticoagulants to reduce the risk of recurrence and thus prevent of ischemic CVD [100]. Patients with persistently positive aPL at moderate-to-high titers in the absence of previous thrombotic events might be treated with antiplatelet drugs (antithrombotic effect) and/or hydroxychloroquine (antithrombotic effect, prevents lupus flare and reduces lipid levels) [101]. However, no data from controlled randomized trials support the evidence of a primary prophylactic effect of these agents with respect to the occurrence of new NP events in both aPL-positive and -negative lupus patients [101,102]. Conversely, some neuropathologic post-mortem evidence showing a high rate of micro- and macrohemorrhage in the brain of NPSLE patients hypothetically discourage chronic prophylactic antiplatelet use in aPL-negative patients without previous thrombotic episode.

Report on selected NPSLE syndromes

Owing to the wide range of clinical presentations, severity and available therapeutic options, an in-depth analysis of every single NPSLE manifestation is needed. Therefore, in this section we discuss some challenging clinical features, in terms of frequency or severity, in the management of SLE-related CNS involvement. Furthermore, we will remark on some syndromes of particular interest that may occur as heralding manifestations of the disease or complicate its course, and we will highlight their principal differential diagnosis. As mentioned above, a multidisciplinary approach with expert opinions is advised in the management of these conditions.

Headache

Results from a meta-analysis highlight that headache is frequently reported in SLE and accounts for more than 50% of the all NP events (migraine was reported by 32% and tension-type headache by 23% of patients). Although it should be noted that pooled data showed the prevalence of all headache types was not different from controls [103].

Usually, headache is secondary to other causes besides lupus and is associated with abnormalities of the eye (e.g., glaucoma), ear (e.g., mastoiditis), sinus (e.g., sinusitis), teeth (e.g., dental granuloma), temporomandibular joint (e.g., pain syndrome), cervical spine (e.g., osthoarthritis) and fibromyalgia, which must be looked for and properly treated.

No particular pathogenic mechanism of headache in SLE patients has been identified. Usually it does not require further investigation and it should be classified according to IHS criteria and managed as a primary headache. However, headache might be the heralding symptom of a more complex CNS syndrome, such as septic or aseptic meningitis including those associated with nonsteroidal anti-inflammatory use, pseudotumor cerebri and cranial neuropathy. Therefore, cases of acute occurrence or modification of an existing chronic headache associated with high-risk factors (severe headache refractory to analgesic drugs, sudden onset, vomiting, fever, immunosuppression, aPL positivity) and alarm signs (sign of infection, meningeal signs, papilledema, focal neurologic signs, decreased level of consciousness) must be viewed cautiously, and must be managed and treated accordingly.

Headache in SLE often responds to the same interventions as non-SLE headache. Prophylactic agents such as low-dose tricyclic antidepressants, low-dose aspirin and valproic acid are sometimes useful for decreasing chronic headache frequency.

Cognitive dysfunction

Cognitive dysfunction is a common complaint in SLE patients (10–40%). Even in childhood-onset SLE cognitive impairment is not uncommon and should not be overlooked [104]. According to the ACR nomenclature a patient's report of cognitive dysfunction should be categorized as 'objective' (tested and verified), 'subjective – not tested' or 'subjective – tested and not verified'.

Once detected, through neuropsychological tests, cognitive dysfunction must be classified according to the type (domain of deficit: simple attention, complex attention, memory, visual–spatial processing, language, reasoning/problem solving, psychomotor speed or executive functions), severity (mild, moderate and severe) and duration [1]. Usually cognitive dysfunctions are not cumulative over time and have variable impact on employment, functional outcome and quality of life, with severe cognitive impairment described in only 3–8% of SLE patients [105,106].

Screening of patients complaining of cognitive deficits should include the use of validated tools investigating attention, information processing, learning, memory and executive function (e.g., Mini-Mental State Examination) but the final diagnosis must be done through accurate neuropsychological testing, such as the One-Hour Neuropsychological Battery for SLE, carried

out and interpreted by a neuropsychologist. The computer-based Automated Neuropsychological Assessment Metrics system may also be used [107]. Since mood and psychological factors influence a patient's report of cognitive dysfunction as well as performance on neuropsychological tests, all patients reporting cognitive dysfunction should also be assessed by a psychiatrist in order to evaluate and exclude the occurrence of a psychiatric illness, such as depression, which may determine pseudodementia.

A brain MRI might be performed in order to highlight abnormalities predictive of cognitive deficit severity and progression, such as cortical atrophy, white matter focal lesions and cerebral infarcts, especially in the presence of other known risk factors such as aPL (odds ratio [OR]: 1.9–4.9), high disease activity (SLEDAI >16; OR: 13.6), high cumulative dose of glucocorticosteroids, hypertension (OR: 4.7), older age and dyslipidemia [43]. In selected patients with normal MRI and new onset of cognitive dysfunction a functional neuroimaging assay (e.g., H-MRS or SPECT) should be performed at baseline and follow-up in order to demonstrate abnormal brain metabolism or hypoperfusion and their changes after therapy.

Management of SLE patients with cognitive dysfunction include identification and treatment of any associated (e.g., metabolic disturbances, drug abuse or withdrawal) or aggravating (e.g., hypertension or dyslipidemia) causes of impairment. Pharmacologic therapy for SLE-associated cognitive dysfunction still lacks evidence from controlled studies. There has been only one double-blind, paired, placebo-controlled study published [108]. Treatment with 0.5 mg/kg/day prednisone for 21 days, followed by steroid tapering, has been reported to improve cognition in five out of eight patients naive to corticosteroids within the previous 6 months with mild-to-moderate disease activity. However, no data are available on long-term follow-up in order to clarify the benefit of corticosteroids after withdrawal or tapering. Moreover, a high cumulative dose of prednisone is associated with decreased cognitive functioning in patients with SLE, although it is not clear there is a true association and it cannot be excluded that the use of high prednisone doses is because of more severe disease, which may more severely affect cognitive functioning. Therefore, corticosteroid use must be considered only in patients with high disease activity. Antiplatelet and anticoagulation therapy might be helpful in patients with persistent positivity for aPL and progressive cognitive impairment mostly in the presence of MRI abnormalities and other vascular risk factors [109,110]. Low-dose aspirin may also be useful for chronic cognitive dysfunction in NPSLE in the absence of aPL. Cognitive rehabilitation is an alternative or complementary therapeutic approach [111] and can be particularly satisfactory in those patients who had partial or complete recovery from a previous episode of cognitive dysfunction but still self-perceived cognitive disturbances.

Cerebrovascular disease

During the disease course, 5–10% of lupus patients develop CVD. Acute ischemic stroke and transient ischemic attack (80–90%) are more frequent than multifocal disease (5–10%), intracranial hemorrhage (1–5%) and sinus thrombosis (1–2%). CVD is a cause of increased mortality and disability in SLE patients compared with the general population and, despite acute ischemic stroke being more frequently observed, deaths due to cerebral infarctions appeared less commonly than hemorrhages and other types of cerebrovascular events [112].

Patients with SLE carry a high risk of CVD, which cannot be explained only by traditional cardiovascular risk factors, such as age (hazard ratio [HR]: 1.07 per year of age), dyslipidemia (HR: 1.09 per 10 mg/dl serum total cholesterol above normal value), hypertension (HR: 3.2), obesity, smoking, diabetes or carotid plaque, and are partly due to accelerated atherosclerosis typical of the disease [37,40,42,47]. Disease specific risk factors are persistently positive aPL (OR: 3.3–22.2), previous CVD (OR: 16.3), high disease activity (SLEDAI >6; HR: 2.1) and valvular heart disease, in particular Libman–Sacks endocarditis [37,40,42,47]. All the modifiable risk factors must be carefully assessed at screening, monitored and managed according to the existing guidelines promoting weight control and tailored physical activity.

The clinical presentation of CVD depends on the type and the extent of events and may vary from asymptomatic to lethal neurologic syndrome as seen in brain stem infarction or in multivascular stroke. Diagnosis should be confirmed through brain imaging. CT scan may help to exclude hemorrhage whilst MRI should be performed to confirm cerebral infarction and define the extent of injury. DWI sequences improve the sensitivity of MRI in the early diagnosis of acute ischemic and hemorrhagic stroke. CT or magnetic resonance angiography may detect brain aneurisms as a cause of hemorrhage.

Cardiovascular imaging, including transthoracic echocardiogram, transesophageal echocardiogram and carotid ultrasound are critical in the evaluation of CVD in SLE and should be part of every suspected ischemic CNS event in SLE patients.

The acute management and rehabilitation of CVD in SLE is similar to that in non-SLE patients. Primary prophylaxis in patients who are aPL negative is limited to managing primary risk factors and eventually adding hydroxychloroquine, which also confers additional thromboprophylaxis, to control disease activity. Results from studies on primary prophylaxis of thrombotic CVD in asymptomatic patients carrying aPL are scant and seem to exclude benefit from low-dose aspirin [102]. However, in presence of persistently positive aPL it may advisable to add antiplatelet therapy (low-dose aspirin) and hydroxychloroquine, especially when additional thrombosis risk factors are present [100,101]. Secondary prevention in aPL-negative patients include long-term antiplatelet therapy and tight control of traditional cardiovascular risk factors [58]. In persistently positive aPL patients with a history of previous thrombosis, including CVD, long-term anticoagulation must be prescribed as a secondary prevention. The level of anticoagulation is still debated because there is a higher risk of bleeding and hemorrhagic complications in patients undergoing intensive anticoagulation treatment. It has been suggested that the international normalized ratio should be titrated to 2.0–3.0 in the absence of risk factors (previous arterial thrombosis, including ischemic stroke, severe venous or recurrent thrombosis) for new thrombotic events, whilst it should be maintained at 3.0 or between 3.0 and 4.0 in patients with risk factors [100,101,113]. CVD due to vasculitits is extremely rare, therefore immunosuppression is not recommended.

Seizures

Seizures are one of the 1997 ACR revised criteria for the classification of SLE. Seizures, distinct as focal or generalized, may occur in 8–15% of patients as an isolated episode (60%) or as epilepsy (40%), which is defined as a chronic disorder characterized by an abnormal tendency for recurrent unprovoked seizures. Isolated seizures, not associated with focal stroke, are usually characterized by diffuse slowing on EEG indicating diffuse encephalopathy; epilepsy is usually characterized by anatomically restricted focal spikes. Isolated seizures are most often associated with active SLE and respond to therapy for SLE; epilepsy typically is not associated with current active SLE and responds to anticonvulsants.

Secondary causes of seizures include fever, infection, drugs, metabolic disturbances, hypoxemia and hypertension, and these causes must be considered and treated. Posterior reversible encephalopathy syndrome (PRES) is a rare condition recently recognized in SLE patients and mainly characterized by seizures, among other neurologic manifestations (headache, acute confusional state and visual loss), and transient posterior changes on brain MRI consistent with cerebral edema [114]. The role of SLE in PRES, which is associated with hypertension (95%), nephritis (90%) and recent starting of immunosuppressive therapy (55%), is still unclear and under debate [115]. Some cases of PRES complicated by intracranial hemorrhage have been reported, however, after early identification and prompt treatment of precipitating condition the evolution of PRES is usually rapidly favorable [115,116].

Brain MRI must be performed to highlight the presence of malignancies, vascular abnormalities and other anatomical changes that might cause seizures. An EEG should be performed in every patient presenting with a first episode of seizures. However, typical epileptiform patterns, which represent a risk for the development of epilepsy, only occur in 25–50% of patients.

After a single episode of unprovoked seizures in the absence of lupus activity the prescription of chronic therapy with an anticonvulsant should be delayed. In the presence of risk factors for recurrence of seizures, such as previous stroke (HR: 2.4) and persistently positive moderate-to-high titers of anticardiolipin IgG (HR: 2.2), anticonvulsants might be considered [40]. If the seizures occurred as an isolated event during an SLE flare, or in presence of high disease activity, corticosteroids and immunosuppressant must be prescribed. In cases of epilepsy anticonvulsants may help in preventing recurrence with or without steroids and immunosuppressants. The mechanism for seizures in SLE patients with aPL has been related to focal cerebral ischemia or to a direct aPL-mediated effect on neurons, and this may explain why antiplatelet and anticoagulation therapy has been anecdotally reported to be effective in recurrent refractory unprovoked seizures [99].

Psychosis

Psychosis, in the absence of offending drugs or electrolyte imbalance, is included in the 1997 ACR revised criteria for the classification of SLE

and its frequency ranges from 2 to 7%. In half of cases psychosis is the initial presenting feature of SLE and it recurs in only 10–20% of patients after treatment [117]. The differential diagnosis of psychosis needs a psychiatric evaluation and includes: drug-induced psychotic disorder (e.g., high-dose corticosteroids), psychosis due to illicit substance abuse, schizophrenia, mania and brief psychotic disorder secondary to a stressful event or trauma. Acute confusional state, otherwise known as delirium, which is included in the 1999 ACR nomenclature for NPSLE and is characterized by fluctuating levels of consciousness, reduced attention and disturbances of cognition, mood and behavior, must be distinguished from psychosis. Psychosis typically presents with delusions, with or without paranoid ideation, and/or auditory, visual and olfactory hallucinations [117].

The diagnostic work-up in patients with psychosis consists of CSF examination to exclude CNS infections and brain MRI to detect organic lesions. The detection of antiribosomal-P antibodies in serum has low sensitivity (25%) and moderate specificity (75–80%) and should not be used for diagnostic purposes [23]. As brain SPECT scan shows hypoperfusion areas in 80–100% of patients with overt psychosis. In acute psychosis associated with NPSLE activity methylprednisolone pulses (500–100 mg daily for 3 days) followed by a high dose of oral prednisone (35–50 mg) and cyclophosphamide pulses (500 mg every 2 weeks for 3 months according to severity and clinical response) followed by maintenance with azathioprine is recommended [92,117]. In psychosis refractory to conventional immunosuppressive treatment plasma exchange or rituximab may be effective options [95,96]. Antipsychotics should be prescribed according to guidelines, especially in relapsing cases.

Myelopathy

Myelopathy represents a rare feature of NPSLE occurring in approximately 1% of patients as transverse myelitis or ischemic myelopathy, and is the first clinical manifestation of the disease in some patients [118,119]. It usually has a rapid onset (hours or days), with bilateral weakness of the legs that may be asymmetric, with or without arm involvement and with or without sensory impairment with cord level similar to that of motor weakness. Bowel and bladder dysfunction may also be present. Flaccidity and hyporeflexia indicate gray matter involvement, usually associated with fever and urinary retention as prodromes of irreversible paraplegia, and allow earlier diagnosis and treatment in SLE patients and must not be confused with other conditions. Patients with spasticity and hyperreflexia, consistent with white matter involvement, are more likely to meet criteria for neuromyelitis optica and to have antiphospholipid antibodies [120]. Neuromyelitis optica (NMO) is an idiopathic inflammatory demyelinating disease of the CNS predominantly affecting optic nerves and spinal cord, characterized by longitudinal extensive and rapidly progressive transverse myelitis and MRI lesions extending for more than three contiguous vertebra and positivity for the serum antibody biomarker NMO-IgG (antiaquaporin-4) [121]. Similarly to NMO, myelopathy in SLE is highly associated with optic neuritis (30–40%).

Cerebrospinal fluid examination should investigate the presence of viral or bacterial infection. Spinal cord MRI with gadolinium is useful in the differential diagnosis of cord compression (e.g., malignancies, vascular malformation, abscess, stenosis and herniated disc) and in detection of T_2-weighted hyperintense lesions (70–90%). When a longitudinal myelopathy is present, the association with NMO must be suspected and a search for NMO-Ig should be performed in the sera of patients. Brain MRI might be performed to exclude a co-occurring demyelinating syndrome. Early diagnosis and intervention predict a good outcome whilst severity of initial motor deficits, extensive MRI lesions and sphincter dysfunction are risk factors for disability, which occurs in 55–65% of patients [122].

Management of myelopathy in SLE should include promptly high-dose methylprednisolone pulses (500–1000 mg daily for 3 days), associated with antivirals or antimicrobials until exclusion of infection by CSF microbiological culture or PCR for viral genome and confirmation of myelopathy through spinal cord MRI. After exclusion of infection the antiviral and antimicrobial therapy must be suspended and pulses of cyclophosphamide (500 mg every 2 weeks for 3 months or monthly doses of 750 mg/m^2 body surface for 3–6 months according to severity and clinical response) quickly added in association with oral prednisone. Because of the high risk of relapses cyclophosphamide therapy should be followed by treatment with immunosuppressants such as azathioprine. Recently an observational study in six SLE patients suggested that a treatment regimen of rituximab and methylprednisolone

pulses could be beneficial in preventing permanent neurological damage in severe lupus myelopathy [123]. Plasma exchange has been reported to be efficacious in severe myelopathy [95]. The use of antiplatelet or anticoagulation therapy in patients with persistently positive aPL without previous thrombosis is controversial, but should be considered in focal myelitis and refractory cases [119,124]. Clinical course and response to therapy may appear in a few hours to a few days after starting treatment but most of the time can only be appreciated after weeks or months. Neurological rehabilitation should be started early during treatment.

Demyelinating syndrome

The occurrence of demyelinating syndromes in SLE is extremely rare (<1%) but may represent an extremely challenging condition for both clinicians and patients with a very high rate of residual disability. Usually a demyelinating syndrome starts with weakness and sensory loss in one or more limbs associated with areas of damage in brain white matter presenting as T_2-weighted hyperintense lesions on MRI and sometimes showing contrast enhancement and variable progression rate. It may also present with transverse myelitis, cranial neuropathies including optic neuritis, diplopia due to VI nerve palsies or brain stem disease characterized by vertigo, vomiting, ataxia, diplopia, dysarthria or dysphagia. Pyramidal syndrome may coexist but mainly in late stage.

Differential diagnosis is mandatory to exclude infections or other causes of demyelinating syndromes.

Progressive multifocal leukoencephalopathy is a rare, typically fatal, CNS demyelinating disease that results from reactivation of the JCV, which occurs more commonly in SLE than in other rheumatic diseases and has been associated with high levels of immunosuppression [125]. The characteristic MRI findings of progressive multifocal leukoencephalopathy include a lesion in the white matter of the brain, sparing the cortex and deep nuclei, that exhibits neither a mass effect nor contrast enhancement [126]. Lesions can appear atypically in the brainstem and cerebellum. The gold standard for diagnosis is the CSF detection of JCV DNA and treatment is based on antiviral agents, but the disease has a high mortality rate and devastating neurologic sequelae [125].

Multiple sclerosis (MS) might be differentiated from NPSLE because of the different MRI findings in the brain and spinal cord. Brain subcortical T_2-weighted hyperintense lesions predominate in SLE whereas periventricular, corpus callosum, brain stem, basal ganglia and cerebellar lesions are more common in MS. Usually spinal cord MRI lesions in MS do not show cord swelling, are confined to two vertebral segments and have a diameter of less than half of the spinal cord. Gadolinium contrast enhancement may help in differentiating new MS lesions from past MS lesions and antiphospholipid syndrome lesions. Multiple oligoclonal bands may be found in SLE (25–55%) but are more specific to MS (80–90%), especially if they are found in high number (i.e., >5). Visual evoked potentials typically show delayed conduction but well-preserved wave form in patients with MS [127]. The diagnosis of concomitant MS and SLE is particularly hazardous. The therapy for MS may make SLE worse; however, therapy for SLE may make MS better. Most cases of MS superimposed on SLE are actually SLE with antiphospholipid syndrome, Libman–Sacks endocarditis or the sclerosis of primary Sjogren's syndrome.

Other conditions to be considered in the differential diagnosis of demyelinating syndromes are sarcoidosis, subacute sclerosing panencephalitis, neurosyphilis and CNS lymphoma.

Reports of therapy in SLE-related demyelinating syndromes are anecdotal. In patients with active brain MRI lesions and progressive and relapsing syndromes, we recommend treatment with methylprednisolone (500–1000 mg daily for 3 days), cyclophosphamide pulses (500 mg every 2 weeks for 3 months or 750 mg/m^2 body surface monthly for 3–6 months) and plasma exchange, if available, followed by oral prednisone and immunosuppressants as steroid-sparing agents.

Conclusion

In conclusion, the occurrence of NPSLE still represents a diagnostic and therapeutic challenge for patients and clinicians due to the high level of decline in quality of life, morbidity, disability and mortality.

The presented data reflect how challenging it is diagnose NP events related to SLE versus other etiologies, highlighting the need for thorough differential diagnosis. At present, there is no gold standard or a standardized algorithm of attribution for CNS involvement in SLE.

Correct NPSLE management needs a multidisciplinary approach involving an expert in the field, with treatment tailored to the patient and type of NP event, and with the aim of increasing quality of life.

Pathogenic and clinical perspectives highlight that the risk of NPSLE is mediated by a number of elements that involve not only factors associated with SLE, but also a range of general modifiable risk factors. Preventative strategies will therefore need to address all potential risk factors of relevance in order to optimize NPSLE management.

Despite the lack of randomized controlled trials, the pharmacologic approach to NPSLE is based on the underlying pathogenic mechanism. Corticosteroids and immunosuppressants are required in inflammatory or antibody-mediated conditions whereas antimalarial, antiplatelet and anticoagulant therapy must be considered in primary and secondary prophylaxis of thromboembolic disorders. Symptomatic therapy may be useful in specific syndromes.

Future perspective

Despite a sizeable amount of investigational papers and guidelines on NPSLE being published in the last 20 years by a high number of researchers and physicians, and although our knowledge in the field has quickly moved forward since the publication of the 1999 ACR nomenclature and case definition for NPSLE, we have "miles to go before we sleep", according to a still significant editorial by Robin Brey and Michelle Petri [128].

Considering the low prevalence of each NPSLE syndrome in the general population, future development in the management of SLE-related CNS involvement will likely come from longitudinal multicenter studies able to cluster a sufficiently high number of patients. A better understanding of the pathogenic mechanisms of disease, the identification of biomarkers for NPSLE, the availability of new tools for diagnosis and attribution of NP events, and the design of specific double-blind, randomized controlled trial testing the efficacy of both old and newly available therapeutic agents are points of interest in the next 5–10 years.

The development of new attribution algorithms and the improvement of existent algorithms, taking into account the epidemiology, associated risk factors to the development of NPSLE and the sensitivity and specificity of diagnostic tools, will assist rather than substitute clinicians in the decision-making process when dealing with CNS involvement in SLE patients [59,129].

Results from new neuroimaging assays such as extra sequences placed into the MRI protocols or new application for well-known techniques such as the use of radiolabeled CNS drugs with SPECT in the functional imaging need to be validated in larger study and most importantly their potential role must be proved in selected NPSLE syndrome [130–133]. Furthermore, cardiac and cardiovascular imaging is underutilized in the evaluation of NPSLE and is to be encouraged.

Long-term prospective studies and double-blind randomized trials must be properly designed, possibly together with patient delegates, in order to define a better therapeutic approach for each NPSLE syndrome. Primary and secondary end points must take into account the efficacy of therapy in terms of event prevention, resolution and risk of relapses but might also be targeted to acceptable standardized levels of quality of life. Prevention regimens consisting in a better and tighter control of associated modifiable risk factors should be tested in order to understand their power to reduce the onset of new NPSLE event.

Moreover, taking into account the potential risks due to high cumulative doses of steroids, the efficacy of the currently recommended high-dose steroid therapeutic approach for major NPSLE syndrome needs to be challenged against other regimens of low-dose or steroid-free therapy based on immunosuppressants such as mycophenolate mofetil and new biotechnological agents. At the same time, the role of the long-term use of antiplatelet and anticoagulation therapy in persistently positive aPL patients must be better understood and they need to be deeply investigated in order to verify and quantify their preventive and curative potential.

Finally, in the next 10–15 years, it will be possible to clinically examine the therapeutic effect of structural 'mimetope' peptides blocking the antigen-binding site of supposed pathogenic antibodies such as the known antiribosomal-P and anti-NMDAR antibodies or some newly recognized antibodies and preventing their pathogenic interaction with tissue antigens [133–136].

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Executive summary

Epidemiology

- According to the 1999 American College of Rheumatology (ACR) nomenclature, neuropsychiatric systemic lupus erythematosus (NPSLE) has a prevalence ranging from 37 to 91%. However, recently developed sets of decision rules defined only 18–31% of events as attributable to SLE.
- NPSLE should be classified for scientific and clinical purpose according to the 1999 ACR nomenclature and case definition until more sensitive and specific attribution algorithms and classification criteria are developed.

Pathogenesis

- CNS vasculitis occurs in only 7–13% of cases and major infarcts in 10–22% of the cases, whereas thrombotic and hemorrhagic microangiopathy (65–83%) and microinfarcts (35–71%) are major findings in post-mortem neuropathologic analysis.
- Focal manifestations such as cerebrovascular disease are considered to be mainly associated with the thrombotic effect of antiphospholipid antibodies (aPL) and microembolism from Libman–Sacks endocarditis.
- Diffuse manifestations such as psychiatric syndromes are considered as secondary to the 'neurotoxic' effect of cytokines and antibodies directed against the cerebral structure, and they gain access to the CNS through blood–brain barrier defects.
- The breakdown of the blood–brain barrier is considered as secondary to ischemia, caused by antiphospholipid antibodies and Libman–Sacks endocarditis, or to inflammatory endothelium activation, caused by either systemic inflammation due to SLE or co-occurring conditions such as infection, nicotine dependence and hypertension.

Risk factors

- Major risk factors for NPSLE development are high disease activity or damage, previous events or other co-occurring NPSLE manifestations, and persistently positive moderate-to-high titers of anticardiolipin or anti-β2-glycoprotein IgG/IgM or the lupus anticoagulant.

Impact

- CNS involvement in SLE accounts for the high level of decline in quality of life, morbidity, disability and mortality.

Diagnosis

- Diagnostic work-up should be tailored to each individual patient according to the type, underlying pathogenic mechanism and severity of the NPSLE event.
- The presence of mimicking or aggravating conditions must be determined as the first step in the NPSLE diagnostic work-up.
- A multidisciplinary approach including the intervention of expert rheumatologists, cardiologists, neurologists, psychiatrists and neuropsychologists is recommended.

Management

- The first step in NPSLE management is the prompt identification and treatment of CNS disease-associated risk factors and contributing causes.
- Pharmacological treatment must be tailored to each patient according to the type, underlying pathogenic mechanism and severity of NPSLE manifestations.
- Symptomatic therapy, such as anticonvulsants, antidepressants and antipsychotics, might be helpful in appropriate syndromes with or without the addition of steroids and immunosuppressants.
- Methylprednisolone and cyclophosphamide pulses followed by oral prednisone and immunosuppressants as steroid-sparing agents should be used in severe cases.
- In refractory cases plasma exchange, intravenous immunoglobulin and rituximab might be successfully used.
- More data are needed on the efficacy of new biotechnologic agents, mycophenolate mofetil and intrathecal dexamethasone plus methotrexate.

Future perspective

- Identification of biomarkers for NPSLE, the availability of new tools for diagnosis and attribution of neuropsychiatric events, and the design of specific double-blind, randomized controlled trials testing the efficacy of both old and newly available therapeutic agents will help the field to evolve in the next 5–10 years.

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