EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs

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Notes

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► Additional data (supplementary tables) are published online only. To view these files please visit the journal online (http://ard.bmj.com).

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ABSTRACT

Objectives To develop recommendations for the diagnosis, prevention and treatment of neuropsychiatric systemic lupus erythematosus (NPSLE) manifestations.

Methods The authors compiled questions on prevalence and risk factors, diagnosis and monitoring, therapy and prognosis of NPSLE. A systematic literature search was performed and evidence was categorised based on sample size and study design.

Results Systemic lupus erythematosus (SLE) patients are at increased risk of several neuropsychiatric manifestations. Common (cumulative incidence >5%) manifestations include cerebrovascular disease (CVD) and seizures; relatively uncommon (1–5%) are severe cognitive dysfunction, major depression, acute confusional state (ACS), peripheral nervous disorders psychosis. Strong risk factors (at least fivefold increased risk) are previous or concurrent severe NPSLE (for cognitive dysfunction, seizures) and antiphospholipid antibodies (for CVD, seizures, chorea). The diagnostic work-up of suspected NPSLE is comparable to that in patients without SLE who present with the same manifestations, and aims to exclude causes unrelated to SLE. Investigations include cerebrospinal fluid analysis (to exclude central nervous system infection), EEG (to diagnose seizure disorder), neuropsychological tests (to assess cognitive dysfunction), nerve conduction studies (for peripheral neuropathy) and MRI (T1/T2, fluid-attenuating inversion recovery, diffusion-weighted imaging, enhanced T1 sequence). Glucocorticoids and immunosuppressive therapy are indicated when NPSLE is thought to reflect an inflammatory process (optic neuritis, transverse myelitis, peripheral neuropathy, refractory seizures, psychosis, ACS) and in the presence of generalised lupus activity. Antiplatelet/anticoagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly thrombotic CVD.

Conclusions Neuropsychiatric manifestations in SLE patients should be first evaluated and treated as in patients without SLE, and secondarily attributed to SLE and treated accordingly.

In 1999, the American College of Rheumatology (ACR) research committee published a set of case definitions for neuropsychiatric systemic lupus erythematosus (NPSLE) manifestations,[1] which involve the central and the peripheral nervous system and that range from overt manifestations such as stroke, seizures and psychosis, to more subtle abnormalities of cognitive function (see supplementary table S1, available online only). Multiple pathological mechanisms are implicated in NPSLE, including antiphospholipid or other autoantibody-mediated vascular or neuronal injury, intrathecal production of inflammatory mediators and accelerated atherosclerosis. Despite substantial advances in the understanding of lupus, NPSLE continues to pose diagnostic and therapeutic challenges to practising physicians. The indicated diagnostic work-up remains unclear, therapies are empiric, and the prognosis after an neuropsychiatric event is often difficult to determine. We sought to develop recommendations for the management of systemic lupus erythematosus (SLE) patients presenting with neuropsychiatric manifestations using an evidence-based approach followed by expert consensus.

METHODS

The European League Against Rheumatism (EULAR) standardised operating procedures were followed and the expert committee created a list of research questions that were further edited for literature search (table 1 and supplementary file, available online only). A systematic search of PubMed was performed using an array of relevant terms,[2] and all English language publications up to January 2009 were considered. Evidence was graded based on the design and validity of available studies and the strength of the statements was graded A–D (table 2). Following discussions, the committee arrived at 15 final statements (table 3). Each member of the committee rated their agreement with each statement, based on the research evidence presented and their own expertise. The guidelines fulfil all 23 items of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument.

RESULTS

General NPSLE

Prevalence of NPSLE

Most (50–60%) NPSLE events occur at disease onset or within the first year after SLE onset,

commonly (40–50%) in the presence of generalised disease activity. Data from cohort studies indicate a cumulative incidence of NPSLE of 30–40% (supplementary table S2, available online only). Manifestations such as headache, mood disorders, anxiety and mild cognitive dysfunction are common, but do not usually reflect overt central nervous system (CNS) lupus activity. By excluding these manifestations and polyneuropathy without electrophysiological confirmation, reported NPSLE frequency decreases by half and the specificity of the ACR nomenclature increases from 46% to 93%.[3 4]

Risk factors for NPSLE

Risk factors consistently associated with NPSLE events include (supplementary table S3, available online only): (1) general SLE activity or damage, especially for seizure disorders and severe cognitive dysfunction[5–7]; (2) previous events or other concurrent NPSLE manifestations[8–10]; and (3) antiphospholipid antibodies (persistently positive moderate-to-high anticardiolipin or anti β2-glycoprotein IgG/IgM titres or the lupus anticoagulant), especially for cerebrovascular disease (CVD),[6 9] seizure disorder,[5 8] moderate-to-severe cognitive dysfunction,[7 11] myelopathy[12] and movement disorder.[11]

Diagnosis of NPSLE

The evaluation of SLE patients with (new) signs or symptoms suggestive of neuropsychiatric disease is comparable to that in non-SLE patients who present with the same manifestations,[2] and initially aims to exclude secondary causes such as infections, metabolic or endocrine disturbances and adverse drug reactions (supplementary table S4, available online only).

Cerebrospinal fluid (CSF) examination (including PCR for herpes simplex virus (HSV) and JC virus as indicated) may help to exclude CNS infection in patients with fever or other signs and symptoms suggestive of infection; mild CSF abnormalities are common (40–50%) but are not specific to the NPSLE manifestations. EEG studies may help to diagnose underlying seizure disorder. Neuroimaging may detect NPSLE involvement and exclude other (neurosurgical, infectious) causes. The imaging technique of choice is MRI (T1/T2-weighted imaging, a fluid-attenuating inversion recovery sequence, diffusion-weighted imaging (DWI) and a gadolinium-enhanced T1-weighted sequence). The average sensitivity of MRI in active NPSLE is 57% (64% in major vs 30% in minor NPSLE, 76% in focal vs 51% in diffuse NPSLE). The most frequent pathological pattern is small punctate hyperintense T2-weighted focal lesions in subcortical and periventricular white matter (WM), usually in the frontal-parietal regions. Unfortunately, these MRI lesions are also present in many patients without neuropsychiatric manifestations (specificity 60–82%).[13–15]

When conventional MRI is normal or does not provide an explanation for the signs and symptoms, advanced neuroimaging may be performed. Modalities to be considered (based on availability and local expertise) include quantitative MRI (magnetic resonance spectroscopy,[16 17] magnetisation transfer imaging,[18 19] diffusion tensor MRI,[20] perfusion-weighted imaging) or radionuclide brain scanning (single photon emission computed tomography (SPECT),[21 22] or positron emission tomography[23]). These imaging studies may reveal additional WM and grey matter abnormalities, which, however, have modest specificity for NPSLE.

Management of NPSLE

General management involves the correction of aggravating factors and symptomatic therapy when appropriate (supplementary table S5, available online only). Specific therapy depends upon the nature of the underlying process (inflammatory or thrombotic). The committee concluded that in selected cases differentiation between these processes may not be feasible and in some patients both mechanisms may be operant. When NPSLE is thought to reflect an inflammatory/neurotoxic process (especially aseptic meningitis, optic neuritis, transverse myelitis, peripheral neuropathy, refractory seizures, psychosis, acute confusional state; ACS) and in the presence of generalised

Table 1 Selected questions on NPSLE for the literature search

Prevalence and risk factors
What is the prevalence of neuropsychiatric manifestations in SLE patients and how much more common are they compared to people without SLE?
Are any of the classic risk factors for the neuropsychiatric manifestations more common in SLE patients?
Are there any risk factors that are specific to SLE patients only?
Screening, diagnosis and monitoring
Should the screening and diagnostic work-up and monitoring for SLE patients with neuropsychiatric manifestations differ from that in non-SLE patients and if so, what particular tests should be applied and in which settings or indications?
Prevention and treatment
Are there any treatment interventions that need to be specifically considered in SLE patients with neuropsychiatric manifestations, and if so, with what diagnostic documentation and with what threshold of initiation, dosage, duration, contraindications?
Prognosis
Is prognosis different in SLE patients with neuropsychiatric manifestations compared to non-SLE patients regarding the manifestation itself and the disease in general?

NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

Table 2 Category of evidence and strength of statements rating scales

Category of evidence	
Diagnostic/prognostic studies	**Intervention studies**
1 The available evidence is *strong* and includes consistent results from well-designed, well-conducted studies	At least one RCT or meta-analysis of RCT
2 The available evidence is *sufficient* to determine effects, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies, inconsistency of findings across individual studies, limited generalisability of findings	Controlled (non-randomised) studies
3 The available evidence is *insufficient* due to the limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence, lack of information on important outcomes	Descriptive studies, such as comparative studies, correlation studies, or case–control studies

Strength of statements	
A	Based on category 1 evidence
B	Based on category 2 evidence, or extrapolated recommendations from category 1 evidence
C	Based on category 3 evidence, or extrapolated recommendations from category 2 evidence
D	Expert opinion or standard of care

RCT, randomised controlled trial.

Table 3 EULAR recommendations for the management of NPSLE

Statement	Category of evidence	Strength of statement	Agreement score
General NPSLE			
NPSLE			
Neuropsychiatric events may precede, coincide, or follow the diagnosis of SLE but commonly (50–60%) occur within the first year after SLE diagnosis, in the presence of generalised disease activity (40–50%)	2	B	8.2
Cumulative incidence			
Common (5–15% cumulative incidence) manifestations include CVD and seizures; Relatively uncommon (1–5%): severe cognitive dysfunction, major depression, ACS and peripheral nervous disorders; Rare (<1%) are psychosis, myelitis, chorea, cranial neuropathies and aseptic meningitis.	2	B	8.4
Risk factors			
Strong (fivefold increase) risk factors consistently associated with primary NPSLE are generalised SLE activity, previous severe NPSLE manifestations (especially for cognitive dysfunction and seizures), and antiphospholipid antibodies (especially for CVD, seizures, chorea)	2	B	9.1
Diagnostic work-up			
In SLE patients with new or unexplained symptoms or signs suggestive of neuropsychiatric disease, initial diagnostic work-up should be similar to that in non-SLE patients presenting with the same manifestations	2	D	9.7
Depending upon the type of neuropsychiatric manifestation, this may include lumbar puncture and CSF analysis (primarily to exclude CNS infection), EEG, neuropsychological assessment of cognitive function, NCS, and neuroimaging (MRI) to assess brain structure and function	2	D	9.8
The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences	1	A	9.4
Therapy			
Glucocorticoids and immunosuppressive therapy are indicated for neuropsychiatric manifestations felt to reflect an immune/inflammatory process (eg, ACS, aseptic meningitis, myelitis, cranial and peripheral neuropathies and psychosis) following exclusions of non-SLE-related causes	1	A	9.1
Antiplatelet/anticoagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly in thrombotic CVD	2	B	9.6
The use of symptomatic therapies (eg, anticonvulsants, antidepressants) and the treatment of aggravating factors (eg, infection, hypertension and metabolic abnormalities) should also be considered	3	D	9.8
Antiplatelet agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titres	2	D	8.8
Specific NPSLE disorders			
CVD			
Atherosclerotic/thrombotic/embolic CVD is common, haemorrhagic stroke is rare, and stroke caused by vasculitis is very rare in SLE patients; accordingly, immunosuppressive therapy is rarely indicated	2	B	9.1
Long-term anticoagulation should be considered in patients with stroke who fulfil the classification criteria for antiphospholipid syndrome for secondary prevention of recurrent stroke which commonly occurs	2	C	9.4
Cognitive dysfunction			
Mild or moderate cognitive dysfunction is common in SLE but severe cognitive impairment resulting in functional compromise is relatively uncommon and should be confirmed by neuropsychological tests in collaboration with a clinical neuropsychologist when available	2	B	9.3
Management of both SLE and non-SLE-associated factors as well as psycho-educational support may prevent further deterioration of cognitive dysfunction; progressive cognitive decline develops only in a minority of patients	2	C	9.2
Seizure disorder			
Single seizures are common in SLE patients and have been related to disease activity. Chance of recurrence is comparable to that in the general population	2	B	8.4
The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG	2	D	9.5
In the absence of MRI lesions related to seizures and definite epileptic abnormalities on EEG following recovery from the seizure, withholding of AED after a single seizure should be considered. Long-term anti-epileptic therapy may be considered for recurrent seizures	3	D	9.3
For most patients without generalised disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures	3	D	9.0
Anticoagulation may be considered in patients with antiphospholipid antibodies	3	D	8.4
Movement disorders (chorea)			
In addition to symptomatic therapy for persistent symptoms (dopamine antagonists), antiplatelet agents may be considered in SLE patients with antiphospholipid antibodies	3	D	8.9
Glucocorticoids/immunosuppressive and/or anticoagulation therapy may be considered in severe cases when generalised disease activity and/or thrombotic manifestations are present	3	D	9.0
ACS			
Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection	3	D	9.6
Glucocorticoids and immunosuppressive therapy may be considered in severe cases	3	D	9.0
Major depression and psychosis			
Major depression attributed to SLE alone is relatively uncommon while psychosis is rare; although steroid-induced psychosis may occur this is very rare	2	B	9.1
There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression	2	B	8.7
Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalised disease activity	3	D	8.8

Continued

Table 3 Continued

Statement	Category of evidence	Strength of statement	Agreement score
Myelopathy			
The diagnostic work-up includes gadolinium-enhanced MRI and cerebrospinal fluid analysis	2	D	9.5
Timely (as soon as possible) induction therapy with high-dose glucocorticoids followed by intravenous cyclophosphamide should be instituted		A	9.4
Maintenance therapy with less intensive immunosuppression to prevent recurrence may be considered	3	D	9.3
Optic neuritis is commonly bilateral in SLE			
The diagnostic work-up should include a complete ophthalmological evaluation (including funduscopy and fluoroangiography), MRI and visual evoked potentials	3	D	9.5
Optic neuritis needs to be distinguished from ischaemic optic neuropathy, which is usually unilateral, especially in patients with antiphospholipid antibodies	3	D	9.3
Glucocorticoids (intravenous methylprednisolone) alone or in combination with immunosuppressive agents should be considered, but failures are common	1	A	9.1
Peripheral neuropathy			
Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and NCS	3	D	9.1
Combination therapy with glucocorticoids and immunosuppressive agents may be considered in severe cases	1	A	8.8

ACS, acute confusional state; AED, anti-epilectic drug; CNS, central nervous system; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuating inversion recovery sequence; NCS, nerve conduction studies; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

lupus activity, management includes glucocorticoids alone or in combination with immunosuppressants (azathioprine or cyclophosphamide).[24 25] In severe NPSLE refractory to standard immunosuppressive therapy, among other treatments, plasma exchange,[26 27] intravenous immunoglobulin,[28–30] and rituximab (anti-CD20 monoclonal antibody)[31] have been used.

Antiplatelet and/or anticoagulation therapy is recommended for NPSLE related to antiphospholipid antibodies, especially for thrombotic CVD. Anticoagulation may be superior to antiplatelet therapy for secondary prevention of arterial events (including stroke/transient ischaemic attack; TIA) in antiphospholipid antibody syndrome (APS).[32–35] Antiplatelet/anticoagulation therapy has also been used in antiphospholipid-associated ischaemic optic neuropathy and chorea, as well as in myelopathy refractory to immunosuppressive therapy.[36–38] Data from cohort studies,[39–41] but not from a randomised controlled trial (RCT),[42] support a potential benefit from antiplatelet agents in the primary prevention of CVD (and other thrombotic events) in SLE patients with persistently positive, moderate-to-high titres of antiphospholipid (HR 0.98–0.99 per month of aspirin therapy).

Specific NPSLE manifestations

Headache

Although headache is frequently reported by SLE patients, several studies and a meta-analysis of epidemiological data[43] found no evidence of an increased prevalence or a unique type of headache in SLE. Caution is needed to exclude aseptic or septic meningitis, sinus thrombosis (especially in patients with antiphospholipid antibodies), cerebral or subarachnoid haemorrhage. In the absence of high-risk features from the medical history and the physical examination (including fever or concomitant infection, immunosuppression, presence of antiphospholipid, use of anticoagulants, focal neurological signs, altered mental status, meningismus and generalised SLE activity), headache alone in a SLE patient requires no further investigation beyond the evaluation, if any, that would have been performed for non-SLE patients.

Cerebrovascular disease

Ischaemic stroke and/or TIA comprise over 80% of CVD cases, whereas CNS vasculitis is rare. CVD occurs commonly (50–60%) in the context of high disease activity and/or damage; other strong risk factors are persistently positive moderate-to-high titres of antiphospholipid antibodies, heart valve disease, systemic hypertension and old age.

In acute stroke, MRI/DWI excludes haemorrhage, assesses the degree of brain injury, and identifies the vascular lesion responsible for the ischaemic deficit. Magnetic resonance angiography, CT angiography, or conventional angiography may help to characterise the vascular lesions and detect brain vasculature aneurysms in subarachnoid haemorrhage.

The acute management of SLE stroke or TIA is similar to that in the general population. A stroke specialist consultation is necessary to identify patients who are candidates for thombolytic or surgical therapy; unless contraindicated, aspirin should be initiated. Secondary prevention includes tight control of cardiovascular risk factors, antiplatelet therapy and carotid endarterectomy when indicated. Generalised lupus activity may be controlled with glucocorticoids and/or immunosuppressive therapy. In patients with persistently positive moderate-to-high titres of antiphospholipid antibodies, chronic oral anticoagulation therapy should be considered.[32 33] Two RCT of 114 and 109 patients with mixed (primary and SLE-related) APS have demonstrated no superiority of high-intensity warfarin (target international normalised ratio (INR) 3.1–4.0) over moderate-intensity warfarin (target INR 2.0–3.0) for secondary thromboprophylaxis, but the risk of minor bleeding was increased in the high-intensity arm (28% vs 11%).[44 45] Conversely, retrospective studies that included larger numbers of patients with arterial thrombosis or stroke concluded that high-intensity anticoagulation may be more effective without increasing the risk of major bleeding.[32 33 46] Accordingly, and based on the results of a systematic review of epidemiological studies,[35] some experts recommend that SLE patients with ischaemic stroke fulfilling the criteria for APS should receive long-term anticoagulation treatment with a target INR of 3.0–4.0,[47 48] but this is still a matter of debate.[49]

Cognitive dysfunction

Most SLE patients have a mild-to-moderate degree of cognitive dysfunction with an overall benign course, and severe cognitive dysfunction develops only in 3–5%.[7 50] Most commonly affected domains are attention, visual memory, verbal memory, executive function and psychomotor speed.

ACR has proposed a 1 h battery of neuropsychological tests for diagnosing cognitive dysfunction in SLE (sensitivity 80%,

specificity 81%).[1] The computer-based automated neuropsychological assessment metrics system has also been used. Indications for brain MRI include: age less than 60 years, rapid unexplained or moderate-to-severe cognitive decline, recent and significant head trauma, new onset of other neurological symptoms or signs, and development of cognitive dysfunction in the setting of immunosuppressive or antiplatelet/anticoagulation therapy. Cerebral atrophy, the number and size of WM lesions, and cerebral infarcts have been correlated with the severity of cognitive dysfunction.[7 51–53]

Management involves treatment of any exacerbating causes, especially anxiety and depression, and control of cardiovascular risk factors. Although a single study has reported a favourable association between regular aspirin use and cognitive function in older diabetes patients with SLE,[54] the efficacy of antiplatelet therapy has not been established. Psycho-educational group interventions have demonstrated improvements in memory function and the ability to perform daily activities (mean cognitive symptoms inventory score improved from 2.1 to 1.7).[55 56] Glucocorticoids and/or immunosuppressive therapy may be considered to control concurrent SLE or other NPSLE activity.[57 58] APS patients with cognitive dysfunction may benefit from anticoagulation therapy but evidence comes from a single, uncontrolled study.[59]

Seizure disorders

Most seizures in SLE represent single isolated events; recurrent seizures (epilepsy) are less common (12–22%) but have a significant impact on morbidity and mortality. Patients can experience generalised tonic–clonic seizures (67–88%) or partial (complex) seizures.

EEG abnormalities are common (60–70%) in SLE patients with seizure disorder, but typical epileptiform EEG patterns are only present in 24–50% and are predictive of seizure recurrence (positive predictive value 73%, negative predictive value 79%).[8 60] MRI can identify structural lesions causally related to seizure disorder and may reveal abnormalities such as cerebral atrophy (40%) and WM lesions (50–55%). CSF examination is only useful to exclude infection.

Anti-epileptic drug (AED) therapy is not necessary in patients with single or infrequent seizures, unless high-risk features for recurrences are present, such as two or more unprovoked seizures occurring with at least 24 h interval, serious brain injury, brain MRI structural abnormalities causally linked to seizures, focal neurological signs, partial seizure and epileptiform EEG. Approximately a quarter of SLE patients will require a second AED to control seizure activity.[60] If seizures are thought to reflect an acute inflammatory event or if a concomitant lupus flare is present, glucocorticoids alone or in combination with immunosuppressive therapy may be given. The combination of pulse intravenous methylprednisolone and intravenous cyclophosphamide has shown effectiveness in refractory seizures in the context of generalised lupus activity.[25]

Movement disorders

Chorea (irregular, involuntary and jerky movements involving any part of the body in random sequence) is the best documented movement disorder in SLE, and has been associated with antiphospholipid antibodies and/or APS. Brain imaging should be considered when other focal neurological signs are present or to exclude secondary causes of chorea. Most patients (55–65%) experience a single episode of chorea that subsides within days to a few months. Symptomatic therapy with dopamine antagonists is usually effective and glucocorticoids in combination with immunosuppressive agents (azathioprine, cyclophosphamide) may be used to control NPSLE disease activity. Antiplatelet and/or anticoagulation therapy is administered in antiphospholipid-positive patients, especially when other antiphospholipid/APS-related manifestations are present.[36 61 62]

Acute confusional state

ACS is characterised by acute onset, fluctuating level of consciousness with decreased attention. Patients should be extensively evaluated for underlying precipitating conditions, especially infections and metabolic disturbances. CSF examination is recommended to exclude CNS infection and EEG may help diagnose underlying seizure disorder. Brain imaging is indicated if the patient has focal neurological signs, history of head trauma or malignancy, fever, or when the initial diagnostic work-up has failed to reveal any obvious cause of the ACS. Brain SPECT is sensitive (93%) and may help monitor response to treatment.[31]

Management requires addressing and correcting the underlying causes. Drug treatment with haloperidol or atypical antipsychotics is used only when other interventions are ineffective in controlling agitation and an underlying cause of ACS has been excluded. A combination of glucocorticoids with immunosuppressive agents is effective in most patients (response rates up to 70%).[25 63 64] Plasma exchange therapy (synchronised with intravenous cyclophosphamide)[26 27] and rituximab have been used in refractory cases.

Psychiatric disorders

Lupus psychosis is characterised by delusions (false beliefs refuted by objective evidence) or hallucinations (perceptions in the absence of external stimuli). Corticosteroid-induced psychiatric disease occurs in 10% of patients treated with prednisone 1 mg/kg or more and it manifests primarily as mood disorder (93%) rather than psychosis.[65] Although anti-ribosomal-P antibodies have been associated with psychiatric SLE in prospective studies,[66 67] a meta-analysis has reported limited diagnostic accuracy (sensitivity 25–27%, specificity 75–80%).[68]

Brain MRI has modest sensitivity (50–70%) and specificity (40–67%) for lupus psychosis, and should be considered when additional neurological symptoms or signs are present. Brain SPECT identifies perfusion deficits in severe cases (80–100%) and residual hypoperfusion during clinical remission correlates with future relapse.[69]

Management involves antidepressive and/or antipsychotic agents as indicated. Biofeedback-assisted cognitive behavioural treatment has a favourable impact on depressive symptoms.[70] In generalised SLE activity, the combination of glucocorticoids and immunosuppressive therapy (usually cyclophosphamide, followed by maintenance with azathioprine) results in a significant improvement (60–80% response) although relapses may occur (up to 50%).[64 71–73] In refractory cases, rituximab has caused a rapid significant improvement of psychiatric manifestations.[31] Most psychiatric episodes resolve within 2–4 weeks and only 20% of SLE patients develop a chronic mild psychotic disorder.

Myelopathy

SLE myelopathy presents as rapidly evolving transverse myelitis but ischaemic/thrombotic myelopathy can also occur. Patients may present with signs of grey matter (lower motor neuron) dysfunction (flaccidity and hyporeflexia) or WM (upper motor neuron) dysfunction (spasticity and hyperreflexia); the latter can be associated more with neuromyelitis optica (NMO) and antiphospholipid.[74] Other major NPSLE manifestations are present in one third of cases, with optic neuritis being the most common (21–48%). Contrast-enhanced spinal cord MRI is

useful to exclude cord compression and to detect T2-weighted hyperintense lesions (70–93%). The involvement of more than three spinal cord segments indicates longitudinal myelopathy. This finding may be further investigated with determination of serum NMO IgG (aquaporin) antibodies, which help diagnose co-existing NMO.[75] Brain MRI should be performed when other NPSLE symptoms or signs co-exist and in the differential diagnosis of demyelinating disorders (supplementary table S6, available online only). Mild-to-moderate CSF abnormalities are common (50–70%) but non-specific and microbiological studies are important to exclude infectious myelitis.

Although an intensely inflammatory CSF resembling meningitis (bacterial or HSV) necessitates antimicrobial/antiviral therapy, high-dose glucocorticoids may be given early while awaiting MRI confirmation, and continued if infection has been ruled out. The combination of intravenous methylprednisolone and intravenous cyclophosphamide can be effective in SLE myelitis if used promptly, within the first few hours, and neurological response paralleled by MRI improvement occurs within a few days to 3 weeks. Relapses are common (50–60%) during corticosteroid dose reduction, underscoring the need for maintenance immunosuppressive therapy. Plasma exchange therapy has been used in severe cases[26 27 76] and anticoagulation therapy in antiphospholipid-positive myelopathy with good results.[37 38] Factors associated with severe neurological deficit include extensive spinal cord MRI lesions, reduced muscle strength or sphincter dysfunction at presentation, antiphospholipid antibodies, and delay (>2 weeks) in the initiation of therapy.[76 77]

Cranial neuropathy

Most frequent cranial neuropathies involve the eighth, the oculomotor (third, fourth and sixth), and less commonly the fifth and seventh nerves. Other neurological conditions, such as brainstem stroke and meningitis, should be excluded. Optic neuropathy includes inflammatory optic neuritis and ischaemic/thrombotic optic neuropathy. Funduscopy may reveal optic disc oedema (30–40%) and visual field examination may show central or arcuate defects. Visual-evoked potentials may detect bilateral optic nerve damage before it is clinically apparent. Fluoroangiography should be performed when vaso-occlusive retinopathy is suspected. Co-existing transverse myelitis or seizure disorder may suggest an underlying inflammatory basis, while optic neuropathy with an altitudinal field defect, associated with antiphospholipid antibodies, renders an ischaemic/thrombotic mechanism more likely. The diagnosis is supported by contrast-enhanced MRI showing optic nerve enhancement in 60–70%, while brain MRI abnormalities are also common (67%). Pulse intravenous methylprednisolone in combination with intravenous cyclophosphamide is recommended.[25] SLE-related optic neuritis is associated with poor visual outcome and only 30% of patients maintain a visual acuity greater than 20/25. Relapses may occur and merit chronic immunosuppressive therapy. Anticoagulation may be considered in antiphospholipid-positive patients not responding to immunosuppressive therapy.

Peripheral nervous system disorders

These include polyneuropathy (2–3%) and less commonly mononeuropathy (single, multiplex), acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plexopathy, and present with altered sensation, pain, muscle weakness or atrophy. CNS involvement should be excluded by neuroimaging when focal neurological signs, gait disturbance, visual or urinary disorder, increased tendon reflexes and/or muscle tone are present. Nerve conduction studies (NCS) and needle electromyography can identify mononeuropathies, differentiate multiple mononeuropathy versus polyneuropathy and distinguish axonal from demyelinating neuropathies. CSF analysis is useful in inflammatory demyelinating polyradiculoneuropathy. Nerve biopsy is rarely needed to establish the diagnosis. If electrodiagnostic studies are normal, small-fibre neuropathy may be diagnosed by skin biopsy demonstrating loss of intraepidermal nerve fibres.[78]

Glucocorticoids alone or with immunosuppressive therapy have been used with good results (60–75% response rate). Intravenous immunoglobulin, plasma exchange, and rituximab have been used in severe cases. Peripheral neuropathy has been reported to be a significant predictor of damage in SLE, but a single longitudinal study found that, over a 7-year period, NCS parameters remained unchanged in most (67%) patients.[79]

DISCUSSION

We have developed recommendations for the management of NPSLE patients based upon a systematic review of over 1000 published studies and expert opinion. There is currently no good quality evidence to guide several diagnostic, primary prevention, therapeutic and monitoring decisions in NPSLE, emphasising the need for further research. Nonetheless, consideration of the existing evidence by the expert panel has led to the formulation of NPSLE recommendations with excellent agreement among experts (average 9.1 out of 10, table 3).

We found a considerable variability in reported NPSLE prevalence, which is also due to the rarity of many of the neuropsychiatric syndromes. We categorised NPSLE in order of frequency using estimates of their cumulative incidence based on data from individual studies. After excluding mild neuropsychiatric manifestations, common (cumulative incidence 5–15%) disorders were CVD and seizures, relatively uncommon (1–5%) were severe cognitive dysfunction, ACS, psychosis and polyneuropathy, while the remaining neuropsychiatric disorders were rare (<1%).

Aetiopathogenic mechanisms involved in NPSLE include vascular injury of intracranial vessels,[22 80] autoantibodies to neuronal antigens, ribosomes and phospholipid-associated proteins[81–83] and the intracranial generation of inflammatory mediators.[84 85] We identified risk factors associated with NPSLE, as a tool for clinicians to suspect SLE as the underlying cause of a neuropsychiatric event (table 4). General SLE activity or damage, past or concurrent NPSLE and persistently positive antiphospholipid antibodies in moderate-to-high titres were the most significant predictors. These observations provide the rationale for primary and secondary prevention strategies.

In the absence of a diagnostic gold standard for most NPSLE syndromes, numerous serological, CSF and imaging investigations have been used to support the clinical diagnosis. Herein, we have provided estimates of the sensitivity, specificity and diagnostic accuracy of most of these investigations for the diagnosis of various NPSLE syndromes, and have prioritised them according to the clinical setting. Neuroimaging is rapidly evolving and newer brain imaging techniques are increasingly used in NPSLE. Based upon existing evidence and expert opinion, we recommend the use of advanced MRI techniques and/or functional neuroimaging in cases of normal MRI readings or when MRI findings do not correlate with the clinical syndrome. Better biomarkers and neuroimaging tests for SLE-associated neuropsychiatric disease need to be developed that have the capacity to identify the underlying pathological mechanism (ischaemic/thrombotic vs inflammatory) and guide therapeutic decisions.

Table 4 Illustrative cases of SLE patients presenting with neuropsychiatric manifestations

	Management based on EULAR recommendations
Case 1	
48-Year-old woman with SLE and history of single seizure; serology notable for anti-ds DNA (+), antiphospholipid (–) Presents with progressive memory decline and difficulties with speech and complex task completion Non-CNS SLEDAI: 8; Brain MRI: periventricular WM focal T2-weighted hyperintensities	This patient has possible cognitive dysfunction. Risk factors include previous major NPSLE (seizure) and generalised SLE activity. Neuropsychological testing (1 h ACR battery) diagnosed moderate cognitive dysfunction. Brain MRI was performed due to the young age and the progressive cognitive decline reported by the patient. She received glucocorticoids and azathioprine due to generalised SLE activity and brain MRI lesions. Follow-up neuropsychological examination after 6 months.
Case 2	
38-Year-old woman with history of SLE nephritis (class III); serology: anti-dsDNA (+), antiphospholipid (–) Smoker, dyslipidemia (LDL-C 150 mg/dl) Presents with right hemiparesis and motor aphasia Modest lupus activity (SLEDAI: 6)	This patient has ischaemic stroke. Brain MRI with DWI showed ischaemic lesions (left middle cerebral artery) and the MRA revealed thrombosis of the left internal carotid and the left middle cerebral arteries. Carotid artery ultrasound showed mild atherosclerotic lesions. The patient was started on aspirin and statin, and she was advised to stop smoking. Blood pressure was controlled by ACE-inhibitor. Disease activity was controlled with low-dose glucocorticoids and hydroxychloroquine.
Case 3	
16-Year-old woman presents with fever and generalised tonic-clonic seizures/status epilepticus CSF examination with mild pleocytosis and increased protein; negative gram stain and PCR for HSV Arthritis, malar rash, alopecia, lymphadenopathy Serology: ANA 1:640, anti-dsDNA (+), antiphospholipid (–)	This patient has SLE with seizure disorder. Brain MRI was normal and the EEG revealed epileptiform activity. The patient received anti-epileptic therapy (phenobarbital), and glucocorticoids, hydroxychloroquine, and azathioprine to control disease activity. She was scheduled for a follow-up EEG to guide duration of AED therapy.
Case 4	
31-Year-old woman with SLE. Major depression progressively deteriorating for the last year interfering with work. Mild SLE activity (malar rash, mild arthritis)	This patient has mood disorder (major depression) with poor response to various antidepressants. Brain MRI—performed due to her severe, progressive symptoms—was normal. Disease activity was controlled with glucocorticoids and azathioprine with moderate improvement in her depression.
Case 5	
28-Year-old woman with SLE and several weeks of new-onset headaches of moderate severity. No focal neurological signs or fever. Clinical: arthritis, malar rash	This patient has headache with some concerning features (new-onset, persistent moderate severity). Brain MRI showed subcortical WM focal hyperintensities. The patient received short-course of low-dose glucocorticoids with clinical improvement.
Now presents with tingling sensation in the hands in the absence of arthritis; antiphospholipid (–)	Needle electromyography and NCS were unremarkable. Spinal cord MRI revealed longitudinal myelitis (C2–C7, T1). Mild CSF abnormalities (7 cells/hpf, protein 66 mg/dl, IgG index (–)). The patient received pulses IV-MP and immunosuppressive therapy.
Case 6	
23-Year-old man with SLE, mild arthralgias and a previous history of discoid rash and serositis He presents with left hemiparesis. No history of hypertension or smoking. Serology: anti-DNA (–), C3, C4: normal, LAC: positive, aCL IgG: 55 GPL, no hyperlipidemia	This patient has stroke in the context of SLE-related APS. Brain MRI revealed infarct in the right parietal lobe. Treated with oral anticoagulants (target INR 3.1–4). Low dose of glucocorticoids was continued with gradual tapering and hydroxychloroquine was added. After 3 years of follow-up, no new cerebrovascular events were reported.

aCL, anticardiolipin antibodies; AED, anti-epileptic drug; ANA, antinuclear antibody; APS, antiphospholipid syndrome; CSF, cerebrospinal fluid; CNS, central nervous system; DWI, diffusion-weighted imaging; EULAR, European League Against Rheumatism; GPL, IgG anticardiolipin unit (1 GPL units = 1 μg affinity-purified IgG ACA from an original index serum sample); HSV, herpes simplex virus; INR, international normalised ratio; IV-MP, intravenous methylprednisolone; LAC, lupus anticoagulant; LDL-C, low-density lipoprotein cholesterol; MRA, magnetic resonance angiography; NCS, nerve conduction studies; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; WM, white matter.

Current therapeutic strategies in NPSLE include the use of immunosuppressive therapies when the underlying pathogenesis is considered primarily inflammatory or there is evidence of generalised SLE activity, antiplatelet/antithrombotic therapy when persistently positive moderate-to-high titres of antiphospholipid antibodies or other APS features are present, appropriate symptomatic interventions as indicated, and the treatment of non-SLE factors. The effectiveness of many interventions, however, should be further defined in future RCT.

Clinical practice recommendations require a framework to assess their quality, and to ensure that potential biases have been adequately addressed, are both internally and externally valid, and that are feasible in daily practice. We have ensured that the current guidelines fulfill satisfactorily the AGREE instrument. Following this first round of recommendations, we intend to update them every 3 years with the inclusion of patients and individuals from other relevant professions, and the development of tools that will facilitate the dissemination and implementation of the recommendations.

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