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

G K Bertsias,1 J P A Ioannidis,2 M Aringer,3 E Bollard,4 S Bombardieri,5 J N Bruce,6 R Cervera,7 M Dalakas,8 A Doria,9 J G Hanly,10 T W J Huizinga,11 D Isenberg,12 C Kallenberg,13 J C Piette,14 M Schneider,15 N Scolding,16 J Smolen,17 A Stara,18 I Tassiulas,19 M Tektonidou,20 A Tincani,21 M A van Buchem,22 R van Vollenhoven,23 M Ward,24 C Gordon,25 D T Boumpas1

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 neuropathy and 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. Antithrombotic therapy is indicated when NPSLE manifests as stroke, seizures and psychosis, and 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 I and supplementary file, available online only). A systematic search of PubMed was performed using an array of relevant terms, 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 polynuropathy 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 11 seizure disorder,5 8 moderate-to-severe cognitive dysfunction,7 11 myelopathy12 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 fewer 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
Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of severe cases.

Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection.

The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences.

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.

Antiplaeee/anti-coagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly in thrombotic CVD.

The use of symptomatic therapies (eg, anticonvulsants, antidepressants) and the treatment of aggravating factors (eg, infection, hypertension and metabolic abnormalities) should also be considered.

Antiplaeee agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titres.

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.

Long-term anti-coagulation should be considered in patients with stroke who fulfil the classification criteria for antiphospholipid syndrome for secondary prevention of recurrent stroke which commonly occurs.

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.

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.

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.

The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG.

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.

For most patients without generalised disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures.

Anticoagulation may be considered in patients with antiphospholipid antibodies.

Movement disorders (chorea)

In addition to symptomatic therapy for persistent symptoms (dopamine antagonists), antiplatelet agents may be considered in SLE patients with antiphospholipid antibodies.

Glucocorticoids/immunosuppressive and/or anti-coagulation therapy may be considered in severe cases when generalised disease activity and/or thrombotic manifestations are present.

ACS

Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection.

Glucocorticoids and immunosuppressive therapy may be considered in severe cases.

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.

There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression.

Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalised disease activity.

Table 3  EULAR recommendations for the management of NPSLE

<table>
<thead>
<tr>
<th>Statement</th>
<th>Category of evidence</th>
<th>Strength of statement</th>
<th>Agreement score</th>
</tr>
</thead>
<tbody>
<tr>
<td>General NPSLE: NPSLE</td>
<td>2</td>
<td>B</td>
<td>8.2</td>
</tr>
<tr>
<td>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%)</td>
<td>2</td>
<td>B</td>
<td>8.4</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 (&lt;1%) are psychosis, myelitis, chorea, cranial neuropathies and aseptic meningitis.</td>
<td>2</td>
<td>B</td>
<td>8.4</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td>2</td>
<td>B</td>
<td>9.1</td>
</tr>
<tr>
<td>Diagnostic work-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>D</td>
<td>9.7</td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>D</td>
<td>9.8</td>
</tr>
<tr>
<td>The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences</td>
<td>1</td>
<td>A</td>
<td>9.4</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>1</td>
<td>A</td>
<td>9.1</td>
</tr>
<tr>
<td>Antiplatelet/anti-coagulation therapy is indicated when manifestations are related to antiphospholipid antibodies, particularly in thrombotic CVD</td>
<td>2</td>
<td>B</td>
<td>9.6</td>
</tr>
<tr>
<td>The use of symptomatic therapies (eg, anticonvulsants, antidepressants) and the treatment of aggravating factors (eg, infection, hypertension and metabolic abnormalities) should also be considered</td>
<td>3</td>
<td>D</td>
<td>9.8</td>
</tr>
<tr>
<td>Antiplaeee agents may be considered for primary prevention in SLE patients with persistently positive, moderate or high, antiphospholipid antibody titres</td>
<td>2</td>
<td>D</td>
<td>8.8</td>
</tr>
<tr>
<td>Specific NPSLE disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>B</td>
<td>9.1</td>
</tr>
<tr>
<td>Long-term anti-coagulation should be considered in patients with stroke who fulfil the classification criteria for antiphospholipid syndrome for secondary prevention of recurrent stroke which commonly occurs</td>
<td>2</td>
<td>C</td>
<td>9.4</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>B</td>
<td>9.3</td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>C</td>
<td>9.2</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>2</td>
<td>B</td>
<td>8.4</td>
</tr>
<tr>
<td>The diagnostic work-up aims to exclude structural brain disease and inflammatory or metabolic conditions and includes MRI and EEG</td>
<td>2</td>
<td>D</td>
<td>9.5</td>
</tr>
<tr>
<td>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</td>
<td>3</td>
<td>D</td>
<td>9.3</td>
</tr>
<tr>
<td>For most patients without generalised disease activity, immunosuppressive therapy is not indicated for prevention of recurrences or control of refractory seizures</td>
<td>3</td>
<td>D</td>
<td>9.0</td>
</tr>
<tr>
<td>Anticoagulation may be considered in patients with antiphospholipid antibodies</td>
<td>3</td>
<td>D</td>
<td>8.4</td>
</tr>
<tr>
<td>Movement disorders (chorea)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In addition to symptomatic therapy for persistent symptoms (dopamine antagonists), antiplatelet agents may be considered in SLE patients with antiphospholipid antibodies</td>
<td>3</td>
<td>D</td>
<td>8.9</td>
</tr>
<tr>
<td>Glucocorticoids/immunosuppressive and/or anti-coagulation therapy may be considered in severe cases when generalised disease activity and/or thrombotic manifestations are present</td>
<td>3</td>
<td>D</td>
<td>9.0</td>
</tr>
<tr>
<td>ACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection</td>
<td>3</td>
<td>D</td>
<td>9.6</td>
</tr>
<tr>
<td>Glucocorticoids and immunosuppressive therapy may be considered in severe cases</td>
<td>3</td>
<td>D</td>
<td>9.0</td>
</tr>
<tr>
<td>Major depression and psychosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression attributed to SLE alone is relatively uncommon while psychosis is rare; although steroid-induced psychosis may occur this is very rare</td>
<td>2</td>
<td>B</td>
<td>9.1</td>
</tr>
<tr>
<td>There is no strong evidence to support the diagnostic utility of serological markers or brain imaging in major depression</td>
<td>2</td>
<td>B</td>
<td>8.7</td>
</tr>
<tr>
<td>Glucocorticoids and immunosuppressive therapy may be considered in SLE-associated psychosis, especially in presence of generalised disease activity</td>
<td>3</td>
<td>D</td>
<td>8.8</td>
</tr>
</tbody>
</table>
Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and nerve conduction studies (NCS). The diagnostic work-up should include a complete ophthalmological evaluation (including funduscopy and fluoroangiography), MRI and visual evoked potentials (VEP) for diagnosing cognitive dysfunction in SLE (sensitivity 80%, specificity 85%).

In severe NPSLE refractory to standard immunosuppressive therapy, among other treatments, plasma exchange, intravenous immunoglobulin, and rituximab (anti-CD20 monoclonal antibody) 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. In patients with persistently positive moderate-to-high titres of antiphospholipid antibodies, chronic oral anticoagulation therapy should be considered.

**Specific NPSLE manifestations**

**Headache**

Although headache is frequently reported by SLE patients, several studies and a meta-analysis of epidemiological data 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 thrombolytic 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. 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%). 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.

**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%. 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 60%) and a 2 h battery (sensitivity 85%, specificity 85%).
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, 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 dysfunction 51–53).

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%).74 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.59

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...
MRI abnormalities are also common (67%). Pulse intravenous more likely. The diagnosis is supported by contrast-enhanced lipid antibodies, renders an ischaemic/thrombotic mechanism with an altitudinal field defect, associated with antiphospholipid antibodies in moderate-to-high titres were the most significant predictors. These observations provide the rationale for primary and secondary prevention strategies.

These include polyneuropathy (2–5%) 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.

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.

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 and the cranial nerves, increased intracranial pressure, and white matter changes associated with inflammation. The diagnosis of NPSLE is based on a combination of clinical, laboratory, and imaging findings. NPSLE is a heterogeneous condition with a wide range of clinical presentations and outcomes. The management of NPSLE is challenging, and there is a need for further research to improve diagnostic accuracy and develop effective treatment strategies.
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, antplatelet/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.

### Author affiliations

1. Rheumatology, Clinical Immunology and Allergy, University of Crete, Heraklion, Greece
2. Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioanna School of Medicine, Ioanna, Greece
3. Department of Medicine III, Division of Rheumatology, University Medical Center Carl Gustav Carus, Technical University of Dresden, Dresden, Germany
4. Division of Neurology, Leiden University Medical Center, Leiden, The Netherlands
5. Cattedra di Reumatologia, Università di Pisa, Pisa, Italy
6. Arc Epidemiology Unit, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK
7. Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain
8. Clinical Neurosciences, Neuromuscular Diseases, Imperial College, London, UK
9. Division of Rheumatology, Clinical and Experimental Medicine, University of Padova, Padova, Italy
10. Division of Rheumatology, Department of Medicine and Department of Pathology, Capital Health and Dalhousie University, Halifax, Canada
11. Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
12. Centre for Rheumatology, University College London Hospitals, London, UK
13. Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, The Netherlands
14. Service de médecine interne, centre hospitalier universitaire Pitié-Salpêtrière, Université Pierre-et-Marie-Curie, Paris, France
15. Rheumatology, Heinrich-Heine-University, Düsseldorf, Germany
16. Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK
17. Department of Rheumatology, Medical University of Vienna, Vienna, Austria
18. Patient representative
19. Hospital for Special Surgery, New York, USA
20. Division of Rheumatology, University of Athens, Athens, Greece
21. Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy
22. Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

### Table 4: Illustrative cases of SLE patients presenting with neuropsychiatric manifestations

<table>
<thead>
<tr>
<th>Case</th>
<th>Management based on EULAR recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>48-Year-old woman with SLE and history of single seizure; serology notable for anti-ds DNA (+), antiphospholipid (–)</td>
</tr>
<tr>
<td>Case 2</td>
<td>38-Year-old woman with history of SLE nephritis (class III); serology; anti-dsDNA (+), antiphospholipid (–)</td>
</tr>
<tr>
<td>Case 3</td>
<td>16-Year-old woman presents with fever and generalised tonic-clonic seizures/status epilepticus</td>
</tr>
<tr>
<td>Case 4</td>
<td>31-Year-old woman with SLE; major depression progressively deteriorating for the last year interfering with work. Mild SLE activity (malar rash, mild arthritis)</td>
</tr>
<tr>
<td>Case 5</td>
<td>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</td>
</tr>
<tr>
<td>Case 6</td>
<td>23-Year-old man with SLE, mild arthralgias and a previous history of discoid rash and serositis</td>
</tr>
</tbody>
</table>

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.
Provenance and peer review
This study was funded by the European League Against Rheumatism.

REFERENCES


