Neurologic and neuropsychiatric manifestations of systemic lupus erythematosus

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INTRODUCTION AND GENERAL PRINCIPLES

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ, including the nervous system. Estimates of the incidence and prevalence of neurologic and psychiatric symptoms among patients with SLE vary greatly, due in large part to heterogeneity in definitions and methodology. In the aggregate, studies report that approximately one-third to one-half of SLE patients report neurologic or neuropsychiatric symptomatology [1-4]. Most studies do not clearly distinguish between symptoms that are causally associated with SLE versus those that are due to comorbid conditions.

Neuropsychiatric events may precede, occur concomitantly with, or follow the diagnosis of SLE. However, most events are accompanied by other SLE disease activity and occur close to the time of diagnosis [5].

The presentation of neurologic symptoms in SLE presents a distinct clinical challenge. Some, but not all, neurologic or psychiatric problems are caused by SLE; some will be comorbid, and some will be related to complications of treatment. Thus, the differential diagnosis is often extensive and will include entities that are severe, disabling, and life-threatening as well as those that are self-limited. While the attribution of neurologic symptoms to SLE may influence decisions about disease-modifying treatments, timely recognition of neuropsychiatric comorbidity in SLE patients is also important to provide appropriate symptomatic management. Neuropsychiatric symptoms, whether causally associated or comorbid, negatively impact the quality of life in

patients with SLE. In addition, these symptoms appear to identify patients with a higher mortality than those without neuropsychiatric symptoms [2,6-8].

For most phenotypic manifestations of neuropsychiatric SLE (NPSLE), no biomarkers or diagnostic tests are specific enough to attribute neurologic diagnosis to SLE. Diagnosis of NPSLE almost always requires rigorous exclusion of other causes. Clinicians should take a detailed history, perform a comprehensive physical examination including hypothesis-driven neurologic and mental status examinations as appropriate, and "localize" the lesion or lesions neuroanatomically. Localization and characterization of the clinical syndrome should guide the differential diagnosis and strategies for testing.

Because of the inherent complexities in regard to diagnosis and management, these patients are most appropriately managed by both rheumatologists and neurologists.

This topic will review the neurologic and neuropsychiatric manifestations of SLE. Other aspects of the clinical presentation, diagnosis, and management of SLE are discussed separately.

- (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults".)
- (See "Overview of the management and prognosis of systemic lupus erythematosus in adults".)

NOMENCLATURE

The term "neuropsychiatric SLE" (NPSLE) refers to primary, direct, pathologic involvement of affected neuroanatomy by the disease process of SLE, such as from inflammation or thrombosis [9]. In the literature, this is sometimes referred to as primary NPSLE. Patients with SLE can also experience secondary neuropsychiatric complications related to having SLE, such as central nervous system (CNS) infection associated with immunosuppression or neuropsychiatric symptoms secondary to medication; such complications are sometimes referred to as secondary NPSLE.

Revisions to the American College of Rheumatology (ACR) nomenclature and case definitions for 19 NPSLE syndromes in 2001 narrowed the original definitions, increasing the specificity for causally associated syndromes (table 1) [9,10].

From a clinical practice standpoint, we find it most useful to consider each syndrome individually rather than consider NPSLE as a monolithic entity; each clinical syndrome has a different potential causal relationship(s) with SLE, differential diagnosis, and treatment plan.

Use of older terms such as "lupus cerebritis" and "lupus sclerosis" are discouraged due to uncertainty or ambiguity on the basis and absence of clear-cut pathology.

EPIDEMIOLOGY AND PATHOGENESIS

Prevalence estimates for neuropsychiatric SLE (NPSLE) using available classification criteria vary, with published studies generally estimating that between 20 to 40 percent of patients have some evidence of nervous system involvement [1-3,11].

The occurrence of a particular neurologic or psychiatric syndrome in someone with SLE does not necessarily imply SLE is the underlying cause, particularly with relatively common syndromes. Some neurologic symptoms may be coincidental, others may arise from complications of treatment or comorbidity. A few syndromes (eg, neuromyelitis optica spectrum disorder [NMOSD]) are believed to reflect a concurrent autoimmune disorder.

For neurologic complications that are believed to be directly associated with SLE, the pathogenesis is heterogeneous depending on the specific syndrome and is not well understood in all cases. Both inflammatory and noninflammatory mechanisms are proposed:

- Some neurologic syndromes clearly appear to be caused by a primary inflammatory process; pathogenic autoantibodies, cell-mediated inflammation, and cytokine-mediated mechanisms have all been proposed mechanisms. Examples of neuroinflammatory syndromes include myelitis, optic neuritis, aseptic meningitis, and some acute confusional states and psychosis episodes associated with a cerebrospinal fluid (CSF) pleocytosis.

  Several candidate biomarkers have been proposed. These include a wide range of cytokines, chemokines, and other inflammatory markers with variable associations with SLE activity. Most have not been reliably translated for clinical use, nor have they been widely accepted as clinical diagnostics, with the exception of aquaporin-4 antibodies (for overlap with NMOSD) and antiphospholipid antibodies (aPL) [12,13].

  Some autoantibodies have been associated with various neurologic syndromes [14,15], including anti-DNA antibodies that cross-react with the NR2 subunit (and particularly the GluN2A subunit) of the N-methyl-D-aspartate receptor (NMDAR) and may play a role in the pathogenesis of cognitive impairment and the acute confusional state [16-18]. These antibodies are different from antineuronal autoantibodies to the NR1 subunit that cause anti-NMDAR antibody encephalitis [19], which has not been associated with SLE except as a rare comorbid disease. While some reports have documented the presence of anti-U1 ribonucleoprotein (RNP) antibodies [20] and antiribosomal P antibodies [21], the role of

these antibodies in producing neurologic disease is speculative. By contrast, there is strong evidence associating stroke with aPL in the context of antiphospholipid syndrome (APS) [12,22] and aquaporin-4 immunoglobulin G (IgG) and NMOSD in patients with SLE [23,24].

- Vascular disease mediates some neurologic complications. A central nervous system (CNS) vasculitis is uncommon, composing only 7 percent of 57 neuropathology cases studied at the University of California, Los Angeles (UCLA) between 1955 and 1976 [25].

  More commonly seen is a noninflammatory vasculopathy, variously described as a destructive or proliferative hyalinization process involving small blood vessels (arterioles and capillaries) [26]. Studies suggest that blood-brain barrier dysfunction may contribute to pathologic entry of cytokines and autoantibodies into the CNS, leading to a bland vasculopathy with rare inflammatory infiltrates [27]. Blood-brain barrier dysfunction can result from a variety of causes, including immune-complex deposition, inflammatory cytokines, tobacco smoke, and hypertension [27]. In some cases, vasculopathy may also relate in part to hypertension and chronic kidney disease.

CLINICAL SYNDROMES

Stroke — Stroke has been reported in up to 19 percent of patients with SLE [28,29] and contributes to the early mortality observed in the disease [6,7,11,30-32]. Patients with SLE appear to have a 1.5- to 3-fold higher risk of stroke than matched population controls [33-35]. In rare cases, stroke occurs as a first manifestation of SLE [36].

Stroke subtypes — All stroke subtypes occur in patients with SLE. In a meta-analysis pooling cohort studies, the relative risk of stroke in SLE is approximately twofold higher for ischemic stroke, threefold higher for intracerebral hemorrhage, and almost fourfold higher for subarachnoid hemorrhage (SAH); the relative risk was highest in patients less than age 50 years [37]. Other studies have found that SLE is not associated with an increased risk of SAH [38].

Several mechanisms are implicated in the pathogenesis of stroke in the setting of SLE:

- Antiphospholipid antibodies (aPL) are detectable in approximately 30 to 40 percent of patients with SLE. There is a strong association between aPL and stroke in SLE patients, but not all of these patients have antiphospholipid syndrome (APS) [39,40]. APS describes a clinical autoimmune syndrome characterized by venous or arterial thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of aPL. Not all

patients with APS have SLE. (See "Clinical manifestations of antiphospholipid syndrome", section on 'Neurologic involvement'.)

aPL can predispose to ischemic stroke as a result of in situ arterial thrombosis or (in approximately one-third to one-half of patients) cardiogenic embolism in the setting of nonbacterial thrombotic endocarditis (NBTE). aPL are also a risk factor for cerebral venous thrombosis (image 1 and image 2). (See "Clinical manifestations of antiphospholipid syndrome", section on 'Neurologic involvement' and "Cerebral venous thrombosis: Etiology, clinical features, and diagnosis".)

- Cardioembolic stroke in SLE can occur with valvular disease (ie, NBTE). aPL are commonly present in this setting, but NBTE can also occur in patients with SLE who do not have aPL. (See "Non-coronary cardiac manifestations of systemic lupus erythematosus in adults", section on 'Valvular disease'.)

  Cardiogenic embolism also can occur in the setting of atrial fibrillation, present in up to 10 percent of patients with SLE. (See "Non-coronary cardiac manifestations of systemic lupus erythematosus in adults", section on 'Cardiac arrhythmias'.)

- Atherosclerosis contributes to the stroke burden in patients with SLE, who have a higher burden of comorbid hypertension and other risk factors [34]. (See "Coronary heart disease in systemic lupus erythematosus", section on 'Traditional risk factors'.)

- A noninflammatory microangiopathy, characterized by small vessel hyalinization and associated microinfarction, is a common neuropathologic finding in patients with SLE. Often referred to as a vasculopathy, these lesions correspond to white matter hyperintensities, which are commonly reported on magnetic resonance imaging (MRI) in patients with SLE [25,41].

- Central nervous system (CNS) vasculitis is rare in SLE, but reported in a few case reports [25,26]. Vasculitis is typically suggested by a beading appearance of affected vessels on digital subtraction or magnetic resonance angiography (MRA) [41-44], abnormal vessel wall enhancement on high-resolution vessel wall MRI [45], or gadolinium-enhancing parenchymal or leptomeningeal lesions on brain MRI; the presence of vasculitis can be supported by evidence of inflammation on cerebrospinal fluid (CSF) examination. Confirmation requires pathologic examination, although this is uncommonly done in the context of neuropsychiatric SLE (NPSLE) evaluation. In one case, putative vasculitis was associated with cerebral infarction as well as aneurysm formation and SAH [46]. (See "Primary angiitis of the central nervous system in adults", section on 'Neuroimaging'.)

- Thrombotic thrombocytopenia purpura (TTP) is a rare but life-threatening cause of stroke in SLE. (See "Hematologic manifestations of systemic lupus erythematosus" and "Diagnosis of immune TTP", section on 'Neurologic and other organ involvement'.)

- The increased risk of hemorrhagic stroke in SLE may relate in part to hypertension (including related to renovascular disease), coagulopathies related to the disease, and the use of anticoagulation in those with APS [34]. (See "Hematologic manifestations of systemic lupus erythematosus".)

Evaluation and management

- **Acute stroke management** – Acute stroke evaluation and management are not specific to SLE and are discussed separately. Thrombolytic therapy and mechanical thrombectomy can be used in patients with SLE when indicated [47-49]. (See "Initial assessment and management of acute stroke".)

- **Evaluation for ischemic stroke subtype** – Identifying the cause of ischemic stroke is important because effective secondary prevention is determined by the stroke subtype. Because there are diverse stroke mechanisms in SLE, the initial evaluation should be broad and include in most patients:

  - Contrast-enhanced MRI and/or computed tomography (CT) of the brain. (See "Neuroimaging of acute stroke".)

  - Vascular imaging of the extracranial and intracranial arteries. Noninvasive options include ultrasound (carotid duplex and transcranial Doppler), MRA, and CT angiography (CTA). (See "Neuroimaging of acute stroke".)

  - Echocardiography, usually transthoracic echocardiography (TTE) as the first study. (See "Overview of the evaluation of stroke", section on 'Echocardiography'.)

  - Hypercoagulable studies, especially testing for aPL. (See "Overview of the evaluation of stroke", section on 'Hypercoagulable studies' and "Diagnosis of antiphospholipid syndrome", section on 'Antiphospholipid antibody testing'.)

  - Ambulatory cardiac event monitoring to examine for occult atrial fibrillation. (See "Overview of the evaluation of stroke", section on 'Monitoring for subclinical atrial fibrillation'.)

  In patients in whom the stroke etiology remains obscure after initial workup, additional testing may include spinal fluid examination, transesophageal echocardiography (which

may be more sensitive than TTE for NBTE), digital subtraction angiography (which may be more sensitive for vasculitic changes), and more extensive testing for hypercoagulability. While the presence of greater SLE disease activity may prompt consideration of CSF examination, high-resolution vessel wall MRI, or conventional angiography, and/or inform treatment decisions [50], quiescent SLE disease activity does not necessarily exclude the presence of underlying CNS inflammatory disease. (See 'Attribution of a clinical syndrome to SLE' below.)

- **Secondary stroke prevention** – The appropriate secondary prevention measures are determined by the stroke subtype. (See "Overview of secondary prevention for specific causes of ischemic stroke and transient ischemic attack" and "Management of antiphospholipid syndrome", section on 'Secondary thrombosis prevention' and "Management of antiphospholipid syndrome", section on 'Long-term anticoagulation'.)

  Hydroxychloroquine or chloroquine is indicated for most patients with SLE independent of stroke history and may reduce thrombotic events, although reduction in stroke incidence specifically has not been demonstrated. (See "Antimalarial drugs in the treatment of rheumatic disease", section on 'Noninfectious indications for antimalarials' and "Overview of the management and prognosis of systemic lupus erythematosus in adults", section on 'Approach to drug therapy'.)

  For rare patients in whom an acute inflammatory etiology such as CNS vasculitis is strongly suspected or confirmed, immunosuppressive therapies such as high-dose intravenous ("pulse") glucocorticoids and intravenous cyclophosphamide are typically used as they are for patients with primary angiitis of the CNS [51]. (See "Primary angiitis of the central nervous system in adults", section on 'Treatment of PACNS'.)

Primary stroke prevention — Despite the higher risk of stroke in patients with SLE, the role for primary preventive treatment with aspirin or other therapies is uncertain, even if aPL are present. (See "Management of antiphospholipid syndrome", section on 'Primary thrombosis prevention'.)

All patients with SLE should be evaluated for traditional and SLE-specific risk factors for vascular disease; these should be managed to lower the risk of stroke as well as coronary heart disease [35]. This is discussed in detail separately. (See "Coronary heart disease in systemic lupus erythematosus", section on 'Prevention and treatment'.)

Seizures — Various cohort studies have reported that between 4 and 12 percent of patients with SLE have a seizure over the course of study follow-up, which ranged from one to eight years [52-57].

Risk factors for incident seizures in patients with SLE have been reported to include positive aPL, glucocorticoid treatment, and disease activity [53,55,58,59]. Metabolic disturbances (such as uremia), hypertension, infections, stroke, vasculopathy, drug toxicity, or rarely reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome (PRES), may play a role in some patients.

- **Clinical features** – Seizures are most often localization related (focal) and manifest with episodes of impaired awareness (complex partial seizures) or, in the case of focal seizures, evolve to bilateral tonic-clonic seizures (secondary generalization).

- **Evaluation** – SLE should not be presumed to be the sole cause of a seizure, and patients with new-onset seizures should undergo evaluation similar to that undertaken for a patient without SLE (including MRI and electroencephalography [EEG]). Evaluation of SLE disease activity may be helpful to inform diagnosis and concurrent management. (See "Evaluation and management of the first seizure in adults".)

  Patients who present with seizure in the setting of altered mental status should be evaluated as outlined below. (See 'Evaluation and diagnosis' below.)

- **Treatment** – Decisions about antiseizure therapy should be based on seizure-specific risk factors together with individualized patient considerations and preferences. (See "Initial treatment of epilepsy in adults".)

  Immunosuppressive therapy is generally not indicated for patients who present with a seizure in the absence of other evidence of CNS inflammation. At least one observational study suggests that hydroxychloroquine treatment may reduce the risk of seizure recurrence in SLE [60].

  Immunosuppressive therapy may be considered in unusual patients with refractory seizures after rigorous evaluation for CNS infection. One clinical trial evaluated immunosuppressive therapy in 32 patients with a variety of severe manifestations of NPSLE; 11 patients had seizures [61]. Seizure frequency decreased from baseline in all patients who received intravenous pulse methylprednisolone followed by intravenous pulse cyclophosphamide, but only two of the five patients who received intermittent intravenous pulse methylprednisolone experienced decreased seizure frequency.

Altered mental status — Acute mental status change in an SLE patient is a medical emergency and should lead to emergent evaluation to determine the cause and initiate appropriate treatment (table 2).

Clinical features — Two overlapping syndromes are recognized.

Acute confusional state or delirium — Delirium is characterized by an acute to subacute (hours to days) development of disturbances of attention, arousal, and cognition, often with an inability to focus or maintain linear thinking, as well as memory deficits and changes in affect.

Psychosis — Psychosis is characterized by a disordered thought process, delusions, and hallucinations. In this setting, patients also have heightened arousal. Psychotic events occur in up to 1 to 2 percent of SLE patients according to cohort studies, and usually occur early in the course of disease (typically within one to three years) [2,62,63]. Most episodes of psychosis (93 percent in one cohort) do not recur [62].

Causes — The differential diagnosis of altered mental status is broad, and workup should proceed considering both potential SLE-related and non-SLE causes (table 2).

Altered mental status can occur as an independent phenomenon not directly related to SLE, with causes including other metabolic conditions, drug intoxication and withdrawal, as well as primary psychiatric disease [64]. (See "Diagnosis of delirium and confusional states" and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)

SLE-related considerations include:

- **An SLE-related neuroinflammatory process, so-called "lupus psychosis"** – In some patients with SLE, an acute confusional state (delirium) appears to result from inflammation within the CNS. This is often referred to as "lupus psychosis." In large cohort studies with four to nine years of follow-up, lupus psychosis was reported to occur in 1 to 1.5 percent of patients [62,63]. Younger age and male sex may be risk factors. Elevated levels of several cytokines, including interleukin (IL) 6, IL-8, interferon (IFN) alpha, and IFN-gamma, have been noted in some cases; however, clinically useful biomarkers remain to be elucidated [62,64].

  No specific abnormalities are usually noted on brain MRI in these patients; studies are often normal or show nonspecific white matter changes and/or atrophy [64].

  CSF examination may be normal or may show evidence of inflammation, such as a pleocytosis, elevated total protein content, elevated IgG index, and the presence of CSF oligoclonal bands, which are unmatched in a corresponding serum sample [64]. While a mildly low CSF glucose level (usually >30 mg/dL) is sometimes observed in patients with lupus psychosis, hypoglycorrhachia is most commonly associated with CNS infection (bacterial, mycobacterial, fungal) or carcinoma [65,66].

- **Acute cerebrovascular events** – In addition to macrovascular strokes, microvascular processes resulting from TTP or catastrophic APS should be considered. (See 'Stroke' above.)

- **Seizure** – Epileptic seizures can sometimes manifest as acute confusion or psychosis as an ictal or postictal phenomenon. (See 'Seizures' above and "Focal epilepsy: Causes and clinical features".)

- **Electrolyte abnormalities and uremia** – (See "Diagnosis of delirium and confusional states".)

- **Infection** – Both CNS and systemic infection (pneumonia, urinary tract infection, bacteremia) can cause mental status changes. These are important diagnostic considerations in SLE patients with acute altered mental status, due to immunosuppression risk. (See "Diagnosis of delirium and confusional states".)

- **Medication toxicities** – The most common medication effect causing mental status change in SLE is glucocorticoid-induced psychosis [64]. Glucocorticoid-induced neuropsychiatric disturbances, which include delirium, cognitive impairment, and depression as well as psychosis, appear to be dose dependent, with an increased risk with a prednisone equivalent dose of ≥40 mg/day [64,67,68]. Symptoms usually occur during the first six weeks of treatment. Neuropsychiatric symptoms generally resolve with discontinuation of glucocorticoids but may recur with reexposure [64]. (See "Major adverse effects of systemic glucocorticoids", section on 'Neuropsychiatric effects'.)

- **Complications of hypertension and renovascular disease including RPLS** – (See 'Treatment complications and associated conditions' below.)

- **Macrophage activation syndrome (MAS)** – MAS refers to hemophagocytic lymphohistiocytosis (HLH) occurring in the setting of a rheumatologic disorder such as SLE. In addition to the usual laboratory abnormalities such as cytopenias, high serum ferritin level, and elevated liver function tests, neurologic abnormalities such as mental status changes can occur in up to one-third of patients with MAS. (See "Clinical features and diagnosis of hemophagocytic lymphohistiocytosis".)

Evaluation and diagnosis — The evaluation is directed toward identifying potential underlying causes as discussed above (table 2) and should include:

- A careful history and physical examination, including a review of medications to identify those, such as glucocorticoids, that can be associated with mental status changes.

- Laboratory investigations to identify metabolic derangements and infections. Initial laboratory studies should include electrolytes, blood urea nitrogen (BUN), creatinine, liver function tests, complete blood count (CBC), thyroid-stimulating hormone (TSH), ammonia, urinalysis, and consideration of serum and urine toxicology testing. Blood and urine cultures should be obtained.

- Neuroimaging, including brain CT in the acute setting to evaluate for strokes or bleeding. MRI should be performed if a cause is not quickly identified.

- EEG to evaluate for subclinical seizure activity as well as evidence of encephalopathy.

- A lumbar puncture and CSF analysis should be performed in patients with acute mental status change and should be done urgently if there is fever or other signs and symptoms of infection. If a pleocytosis is detected, then a broad range of infections should be considered and tested for. (See "Clinical features and diagnosis of acute bacterial meningitis in adults", section on 'Cerebrospinal fluid analysis'.)

  Testing for oligoclonal bands and IgG index evaluation, which require corresponding serum samples to be sent at the time of CSF examination, can be helpful to evaluate for evidence of CNS inflammation.

  In the absence of an identified pathogen, the CSF should be further evaluated for autoimmune encephalitis, malignancy, and less common causes of infections.

  - (See "Autoimmune (including paraneoplastic) encephalitis: Clinical features and diagnosis".)
  - (See "Viral encephalitis in adults", section on 'Diagnosis' and "Viral encephalitis in adults", section on 'Differential diagnosis'.)
  - (See "Clinical features and diagnosis of leptomeningeal disease from solid tumors", section on 'Diagnostic evaluation'.)

The attribution of an acute confusional state or psychosis to an SLE-associated neuroinflammatory process (ie, lupus psychosis) requires that other causes are excluded with the workup described above. There is no specific test that confirms the diagnosis of lupus psychosis. Evidence of concomitant SLE disease activity increases the likelihood of a neuroinflammatory etiology, and a thorough assessment of SLE clinical and serologic activity should be performed [62]. This evaluation is described below. (See 'Attribution of a clinical syndrome to SLE' below.)

Treatment of lupus psychosis — Immunosuppressive therapy is typically used to treat the acute confusional state, known as lupus psychosis.

In patients with severe symptoms and in whom suspicion for active SLE is high, we suggest initiating treatment with high-dose intravenous ("pulse") glucocorticoids along with an evaluation for non-SLE causes (table 2). After non-SLE diagnoses have been excluded, immunosuppressive agents such as cyclophosphamide or mycophenolate can be added as steroid-sparing therapies [62,69-71]. Intravenous immune globulin (IVIG) and rituximab have also been used in refractory cases [72,73]. There are no trials to guide therapy; the choice among the individual agents may be influenced by the presence of other SLE manifestations as well as patient-specific factors (eg, other comorbidities). (See "Overview of the management and prognosis of systemic lupus erythematosus in adults", section on 'Approach to drug therapy'.)

Antipsychotic drugs are also often prescribed concurrently to manage symptoms [70]. (See "Psychosis in adults: Initial management", section on 'Antipsychotic therapy'.)

Lupus psychosis appears to have a good prognosis for long-term recovery; the frequency of recurrent episodes has been reported to range from 2 of 28 patients in one series to 18 of 59 patients in another [62,64].

Cognitive impairment

- **Epidemiology** – Patient reports of difficulty with cognition and objective cognitive impairment are common in patients with SLE. In one meta-analysis of studies in which neuropsychological testing was performed in 2463 unselected patients with SLE, 38 percent were estimated to have cognitive dysfunction [74]. Available longitudinal studies suggest that cognitive function is generally stable over 5 to 10 years in SLE [75-79]. However, administrative database studies show that SLE may be a risk factor for dementia [80,81]. For example, one population-based study using health insurance claims found that SLE is a risk factor for dementia with an incidence rate of 357 versus 180 per 100,000 patient-years (adjusted hazard ratio [HR] 2.14) [82]. However, studies using administrative data should be interpreted with caution given the significant risks of selection bias and misclassification.

- **Pathogenesis** – The neuropathologic substrate of cognitive impairment in SLE is unclear and likely heterogeneous, but could relate in part in some cases to greater cerebral microvascular injury and white matter microstructural damage with SLE. Observational studies using quantitative volumetric MRI have observed greater relative regional brain atrophy (including in the temporal lobes and hippocampal pathways) in people with SLE

and cognitive dysfunction compared with unaffected controls, as well as evidence of microstructural white matter abnormalities [83-86].

A range of vascular abnormalities, including white matter hyperintensities, lacunar infarcts, and microhemorrhages, are reported with varying frequency on MRI studies in these patients [85,86]. The observation that aPL positivity is associated with cognitive impairment in patients with SLE also supports a vascular mechanism in some cases [80,87]. Chronic kidney disease and chronic medication toxicity can also produce cognitive impairment in some patients.

- **Clinical features** – SLE patients often complain of "brain fog," a nonspecific and nonlocalizing description of cognitive dysfunction or slowing; not all of these patients will have objective cognitive impairment on testing.

  In one study, cognitive domains affected in glucocorticoid-naïve patients with SLE included attention/concentration, working memory, executive functioning, and processing speed [88]. Verbal memory appeared to be relatively intact, a finding that contrasts with studies in patients taking glucocorticoids in whom deficits in verbal memory are often prominent [89-91]. These cognitive domains are described separately. (See "The mental status examination in adults".)

- **Evaluation and differential diagnosis** – The evaluation of cognitive complaints in patients with SLE typically starts with assessment of severity and patterns of deficit with more formal testing. In patients with documented impairments, further evaluation examines potential causes and may include examination of medication lists, laboratory testing, psychological and sleep evaluations, and neuroimaging.

  Use of bedside screening tools, such as the Montreal Cognitive Assessment (MoCA), is important to document objective impairment, to characterize the severity and patterns of deficits, and to monitor change over time [92,93]. (See "Mental status scales to evaluate cognition" and "Evaluation of cognitive impairment and dementia", section on 'Cognitive testing'.)

  Formal neuropsychological (cognitive) testing is also helpful to evaluate cognitive dysfunction in SLE, particularly when cognitive complaints are substantial enough to negatively affect quality of life or are progressive [94]. Testing can identify patterns of deficits in affected cognitive domains, quantitate the extent of impairment, and help to guide differential diagnosis and treatment. (See "Evaluation of cognitive impairment and dementia", section on 'Neuropsychological testing'.)

For patients with cognitive impairment, evaluation for other potential causes is imperative; these include metabolic and endocrinologic abnormalities and medication effects (including glucocorticoids, pain or neuropsychiatric medications, anticholinergics, and others). (See "Evaluation of cognitive impairment and dementia", section on 'Laboratory testing' and "Major adverse effects of systemic glucocorticoids", section on 'Neuropsychiatric effects'.)

In addition, comorbid mood or anxiety disorders are prevalent in patients with SLE, particularly among patients with cognitive complaints [74,95-99]. Because such disorders are treatable, it is important to consider and evaluate for these diagnoses in patients with cognitive impairment. (See "Evaluation of cognitive impairment and dementia", section on 'Screening for depression' and "Evaluation of cognitive impairment and dementia", section on 'Dementia mimics'.)

Sleep disturbances, such as insomnia and obstructive sleep apnea, can also cause or contribute to cognitive dysfunction, including in SLE [100], and should be considered.

Neuroimaging is indicated to evaluate for evidence of a structural cause, including one that may be separate from or comorbid with SLE, particularly if impairments are interfering with function or are progressive. Brain MRI findings in people with SLE with cognitive dysfunction are variable; these studies are often normal or demonstrate nonspecific white matter hyperintensities [85,86,101]. (See "Evaluation of cognitive impairment and dementia", section on 'Neuroimaging' and "Etiology, clinical manifestations, and diagnosis of vascular dementia", section on 'Neuroimaging'.)

CSF examination is not typically performed to evaluate cognitive deficits, but it should be considered if the deficits develop acutely (see 'Altered mental status' above), are severe, are rapidly progressive, or occur in the context of other concerning focal neurologic signs or symptoms.

- **Prognosis** – Data on long-term follow-up of patients with cognitive impairment in SLE are limited. In the absence of an identified contributing factor, cognitive impairment in SLE tends to present insidiously and can persist chronically; however, it tends not to progress like typical neurodegenerative dementias [74]. In one Italian cohort study, most of the 43 patients with SLE and cognitive impairment showed improvement at 10 years of follow-up [75].

- **Management** – Unless there is clear evidence of an active CNS inflammatory process based on MRI or CSF examination or evidence of other features of worsening SLE activity,

cognitive dysfunction in isolation is generally not an indication to initiate or escalate immunosuppression.

In the absence of a treatable cause or comorbid disorder such as medication toxicity, depression, anxiety, or a sleep disorder, there is currently no disease-specific recommended treatment for cognitive impairment in patients with SLE. Because of the higher risk of vasculopathy in SLE and likely contribution to cognitive dysfunction in some patients with SLE, it is reasonable to focus on reducing cardiovascular risk factors as part of comprehensive management. (See "Treatment of vascular cognitive impairment and dementia", section on 'Vascular risk modification'.)

Obesity and physical inactivity have also been associated with cognitive impairment in patients with SLE and may be amenable to intervention [102]. (See "Management of the patient with dementia", section on 'Exercise programs'.)

Inflammatory and demyelinating disease — Demyelinating disease is defined as an NPSLE syndrome in the American College of Rheumatology (ACR) nomenclature. In some cases, this likely represents a direct manifestation of SLE; in others, the occurrence of a demyelinating event can reflect a comorbid autoimmune condition, such as neuromyelitis optica spectrum disorder (NMOSD) or multiple sclerosis.

Optic neuritis — Optic neuritis occurs in up to 1 percent of SLE patients [103]. While the causal relationship of SLE and optic neuritis is largely unclear, some of these patients do not have another clearly identified alternate cause associated with CNS inflammation.

- **Clinical features** – Patients present with acute vision loss, usually with a central or paracentral scotoma, often with pain with eye movement [103]. Physical examination usually shows a relative afferent pupillary defect (unless there is no relative difference in visual impairment between eyes), and there may be disc edema (papillitis) [104]. Brain MRI with gadolinium contrast and dedicated orbital sequences with fat saturation can demonstrate optic nerve enhancement. Optic neuritis associated with SLE is more frequently bilateral than in non-SLE patients [105-107]. The presentation and evaluation of patients presenting with optic neuritis are described separately. (See "Optic neuritis: Pathophysiology, clinical features, and diagnosis".)

- **Differential diagnosis** – A subset of cases of optic neuritis in people with SLE are now known to be associated with either aquaporin-4 antibodies or myelin oligodendrocyte glycoprotein (MOG) autoantibodies as a manifestation of comorbid NMOSD [108]. Patients with optic neuritis and SLE should be evaluated for these antibodies. (see "Neuromyelitis optica spectrum disorder (NMOSD): Clinical features and diagnosis").

Comorbid multiple sclerosis should also be considered. (See "Optic neuritis: Pathophysiology, clinical features, and diagnosis", section on 'Magnetic resonance imaging'.)

Other alternative diagnoses should be considered:

- Optic neuropathy in SLE can also be ischemic, including a possible association with APS [109]. Fluorescein angiography may help distinguish between some cases of optic neuritis and ischemic optic neuropathy, which often results from thrombosis or vasculitis. (See "Clinical manifestations of antiphospholipid syndrome", section on 'Ocular involvement'.)

- It is also important to consider infectious causes of optic nerve dysfunction or its mimics, particularly herpes virus infections, which can occur secondary to the immunosuppressed state of SLE and treatment. Other causes of optic neuropathy are discussed in detail separately. (See "Optic neuropathies", section on 'Infections'.)

- **Acute treatment** – Autoimmune and inflammatory optic neuritis is typically treated with pulse doses of glucocorticoids (1 gram daily of methylprednisolone or bioequivalent oral steroid regimen for three to five consecutive days), usually followed by an oral steroid taper [103]. (See "Optic neuritis: Prognosis and treatment", section on 'Acute treatment'.)

  While data to inform treatment selection for SLE-associated optic neuritis are limited and comparative efficacy data lacking, in patients with severe or refractory disease, acute treatment with plasma exchange may also be used in addition to glucocorticoids, particularly if there is concern for comorbid NMOSD [110]. (See "Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis".)

- **Escalation of treatment of SLE -** SLE optic neuritis is an indication for escalation of immunosuppression for SLE. We often use cyclophosphamide as an induction agent and usually continue it for three to six months [111,112]. Mycophenolate mofetil, azathioprine, or rituximab are reasonable alternatives to control disease activity and prevent recurrences, although data are limited [113-115]. Selection of maintenance preventive therapy is typically based on individualized considerations, including risk tolerance, comorbidities, and patient preference. Maintenance is usually continued for a period of several years to reduce relapse risk. (See "General principles of the use of cyclophosphamide in rheumatic diseases" and "Mycophenolate: Overview of use and adverse effects in the treatment of rheumatic diseases" and "Pharmacology and side effects of azathioprine when used in rheumatic diseases" and "Rituximab: Principles of use and adverse effects in rheumatoid arthritis".)

When there is comorbid NMOSD as the cause of optic neuritis, NMOSD-targeted preventive immunosuppressive agents are typically favored. Because NMOSD has frequent recurrences, long-term therapy is recommended. Rituximab is often used because the drug has been studied both for NMOSD and for other manifestations of SLE. Additional agents can be considered. The long-term management of NMOSD is discussed separately. (See "Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis", section on 'Attack prevention'.)

Myelitis — Myelitis in SLE is a rare but morbid condition, occurring in approximately 1 to 2 percent of SLE patients in some cohorts [1,116].

- **Clinical features and diagnosis** – Patients present with acute to subacute paraparesis or quadriparesis, which is usually bilateral but not always symmetric; sensory impairment localizable to a spinal sensory level; and/or impairment of bowel or bladder function. Prompt evaluation with neuroimaging is essential to exclude compression. The evaluation of patients with acute myelitis is described separately. (See "Transverse myelitis", section on 'History and examination'.)

  In SLE-associated myelitis, MRI often shows T2 hyperintensity of the affected area of the spinal cord and, in the acute setting, gadolinium contrast enhancement (image 3). CSF examination may show a pleocytosis, which is usually lymphocytic. In some patients there can be mild or moderately low (usually >30 mg/dL) CSF glucose [65]. Electromyography/nerve conduction studies (EMG/NCS) may show findings of anterior horn cell loss at affected levels and suprasegmental weakness but are often normal unless there is a myeloradiculitis.

- **Differential diagnosis** – A subset of SLE patients with myelitis has positive antiaquaporin-4 antibodies and therefore has comorbid NMOSD (image 3) [23,24,117-120]; a subset has positive MOG autoantibodies, which could also be a manifestation of comorbid MOG antibody-associated demyelinating disease [117]. (See "Neuromyelitis optica spectrum disorder (NMOSD): Clinical features and diagnosis", section on 'Evaluation and diagnosis'.)

  Comorbid multiple sclerosis should also be considered. (See "Transverse myelitis", section on 'Determining the cause of TM'.)

  Myelitis in patients with SLE can also be infectious secondary to an immunosuppressed state, and a comprehensive CSF evaluation for causes of myelitis in such cases is imperative. (See "Disorders affecting the spinal cord", section on 'Infections'.)

Alternative diagnostic considerations in this setting include spinal cord infarction, which typically presents acutely (ie, stroke-like) and may be associated with antiphospholipid seropositivity [121]. (See "Disorders affecting the spinal cord", section on 'Spinal cord infarction'.)

- **Acute treatment** – Acute autoimmune/inflammatory myelitis is typically treated with pulse dose glucocorticoids, usually followed by an oral steroid taper. Plasma exchange is sometimes also given concurrently for severely affected patients or subsequently for those who do not respond to glucocorticoids, particularly if the myelitis is caused by comorbid NMOSD. (See "Transverse myelitis", section on 'Treatment' and "Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis".)

  The optimal management of transverse myelitis in patients with SLE who do not have comorbid NMOSD or an alternative pathology is uncertain, but it typically involves pulse high-dose glucocorticoids followed by an oral steroid taper, often in combination with cyclophosphamide. Observational studies suggest favorable outcomes with this approach [122-126].

- **Long term treatment** – Treatment with cyclophosphamide is usually continued for three to six months and then switched to a less toxic agent for maintenance therapy such as mycophenolate, azathioprine, or rituximab to control SLE disease activity and reduce the risk of recurrence. The optimal agent is unknown and is based on clinical experience and case reports [127-129]. Treatment with immunosuppression is usually continued for a period of several years to reduce CNS relapse risk, weighing medication risk, tolerability, and overall control of SLE disease activity. (See "General principles of the use of cyclophosphamide in rheumatic diseases" and "Mycophenolate: Overview of use and adverse effects in the treatment of rheumatic diseases" and "Pharmacology and side effects of azathioprine when used in rheumatic diseases" and "Rituximab: Principles of use and adverse effects in rheumatoid arthritis".)

  When there is comorbid NMOSD as the cause of myelitis, NMOSD-targeted preventive immunosuppressive agents are typically favored. Because NMOSD has frequent recurrences, long-term therapy is recommended. Rituximab is often used because the drug has been studied both for NMOSD and for other manifestations of SLE. Additional agents can be considered. The long-term management of NMOSD is discussed separately. (See "Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis", section on 'Attack prevention'.)

Patients with spinal cord infarction who have aPL may benefit from antithrombotic therapy [130]. (See "Management of antiphospholipid syndrome", section on 'Secondary thrombosis prevention' and "Management of antiphospholipid syndrome", section on 'Long-term anticoagulation'.)

- **Prognosis** – The prognosis for transverse myelitis is variable. In a review of 105 patients, 50 and 29 percent had complete and partial recovery, respectively [123]; in another case series, those who presented with urinary retention and persistent flaccidity and hyporeflexia had a greater risk of irreversible paraplegia than those with spasticity and hyperreflexia [65]. (See "Transverse myelitis", section on 'Treatment'.)

Aseptic meningitis — A rare manifestation of SLE, aseptic meningitis typically presents with headache, stiff neck (though usually without frank meningeal signs on physical examination), and a lymphocytic pleocytosis and elevated protein on CSF examination [131-133]. Some patients have concomitant focal or multifocal neurologic symptoms or seizures. MRI may reveal leptomeningeal enhancement or may be normal.

It is important to evaluate for other potential causes, including bacterial and nonbacterial infections, parameningeal processes (which may require spinal cord imaging to evaluate if the syndrome persists), and neoplasia. Adverse effects of medications should also be considered; nonsteroidal antiinflammatory drugs and IVIG can cause aseptic meningitis. (See "Aseptic meningitis in adults".)

This syndrome has been treated successfully with a course of glucocorticoids, once infection has been excluded [131,132].

Chorea — Acute chorea is a rare neurologic syndrome associated with SLE, described in up to 1 percent of patients with SLE [134,135].

- **Clinical features** – This movement disorder is characterized by involuntary, abrupt, brief, nonstereotyped movements, which can be unilateral or bilateral. The onset of chorea may precede the diagnosis of SLE and may coexist with other neurologic syndromes including stroke and/or cognitive impairment [136]. The clinical features and differential diagnosis of chorea are described in detail separately. (See "Overview of chorea".)

- **Evaluation** – Many patients with SLE-associated chorea have aPL, and a subset exhibit small infarctions in the basal ganglia; thus, antibody testing and brain MRI with and without contrast are advised as part of the evaluation, allowing implementation of secondary stroke prevention if appropriate [135,137-139]. In many patients, neuroimaging is normal and a primary inflammatory or antibody-mediated cause is postulated.

The evaluation of chorea not associated with SLE is described separately. (See "Overview of chorea", section on 'Evaluation for the cause of chorea'.)

- **Treatment and prognosis** – Symptom duration is variable. In many cases, the chorea is self-limited and resolves over a few weeks, with or without treatment [138].

  Symptomatic treatments for chorea should be offered; these are described separately. (See "Overview of chorea", section on 'Management of chorea'.)

  Many patients are treated with glucocorticoids empirically [137,140,141]. Other patients with persistent symptoms despite treatment with glucocorticoids and hydroxychloroquine have been successfully managed with IVIG or plasmapheresis [138,142].

  In one series, chorea in SLE patients with aPL was associated with a relatively high risk of future arterial thrombosis (12 of 32 patients); thus, antithrombotic treatment for possible APS should be considered in this context [138]. (See "Management of antiphospholipid syndrome", section on 'Secondary thrombosis prevention' and "Management of antiphospholipid syndrome", section on 'Long-term anticoagulation'.)

Other neurologic and psychiatric symptoms

Headache — Headaches are common in patients with SLE, as they are in the general population, and pooled data from controlled studies show that prevalence of various headache types in SLE patients does not differ from controls [143,144]. Although any illness can exacerbate existing primary headache syndromes such as migraine, the available evidence does not support the concept of a "lupus headache," or that headache in SLE is associated with disease activity [144].

- **Chronic headaches** – Chronic headaches are an important cause of morbidity in patients with SLE and should lead to more specific characterization of headache phenotype and targeted evidence-based treatment. In particular, screening for migraine should be considered in patients with SLE, as migraine is common (32 percent of headaches in SLE patients in pooled analyses), is frequently underdiagnosed, and has effective evidence-based treatment [144]. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults" and "Preventive treatment of episodic migraine in adults".)

- **New headaches or change in headache pattern** – Red flags for emergent evaluation in a patient with SLE include a new headache associated with focal neurologic findings, fever, or true encephalopathy, similar to red-flag features in non-SLE patients. (See "Evaluation of

headache in adults", section on 'Need for emergency evaluation' and "Evaluation of the adult with nontraumatic headache in the emergency department".)

Any new severe or unrelenting headache should prompt a diagnostic evaluation for inflammatory or thrombotic causes of headache that occur more commonly in SLE. Cerebral sinus venous thrombosis, especially in patients with aPL, and aseptic meningitis should be considered. Rare patients with SLE can develop idiopathic intracranial hypertension (pseudotumor cerebri), which should be suspected in patients with headache and visual symptoms. (See "Evaluation of headache in adults", section on 'New or recent onset headache' and "Idiopathic intracranial hypertension (pseudotumor cerebri): Clinical features and diagnosis".)

Depression and anxiety disorders — Depression and anxiety are common in SLE, and in some series appear to be more prevalent in SLE than in the general population. In one meta-analysis, the prevalence of major depression in SLE was 24 percent and anxiety 37 percent [145]. Studies have not found a clear association of mood disorders with SLE disease activity, cumulative organ damage from SLE, or autoantibodies [146]. Depression and anxiety may reflect the psychosocial burden of chronic disease.

It is important to recognize, triage, and treat these syndromes to reduce neuropsychiatric morbidity and improve quality of life. It is also important to evaluate for other potential causes and contributors, including medication effects (including chronic glucocorticoid toxicity), endocrine abnormalities, and sleep disorders. (See "Major adverse effects of systemic glucocorticoids", section on 'Neuropsychiatric effects'.)

The evaluation and management of depression and anxiety are discussed separately:

- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Generalized anxiety disorder in adults: Management".)

Fatigue — Fatigue affects 80 to 90 percent of patients [147] and profoundly impacts qualify of life in SLE [148]. The pathogenesis of fatigue in SLE is probably multifactorial in most patients; pain, depression, sleep disorders, reduced exercise tolerance, and stress are common contributors [149]. Hypothyroidism is prevalent in patients with SLE, occurring in 15 to 19 percent of patients, and should be evaluated in patients with prominent fatigue [150-152].

The approach to evaluation and management of fatigue is discussed separately. (See "Approach to the adult patient with fatigue".)

Peripheral nervous system manifestations — A number of neuromuscular disorders may complicate SLE. These are described separately. (See "Manifestations of systemic lupus erythematosus affecting the peripheral nervous system".)

Treatment complications and associated conditions

- **Reversible posterior leukoencephalopathy syndrome** – RPLS, also known as posterior reversible encephalopathy syndrome (PRES), is a clinical and MRI syndrome characterized by acute-onset encephalopathy and/or seizures associated with characteristic MRI findings of vasogenic edema, which are often but not always predominant in the posterior parietal and occipital lobes (image 4 and image 5).

  RPLS is reported to occur in 0.7 percent of patients with SLE, in some cases as a direct complication of the disease or, more likely, as a complication of immunosuppressive therapy and/or associated kidney disease and hypertension [153]. RPLS is described in detail separately. (See "Reversible posterior leukoencephalopathy syndrome".)

- **Progressive multifocal leukoencephalopathy (PML)** – PML is an opportunistic infection of the CNS caused by a reactivation of the JC virus that occurs almost exclusively in immunosuppressed individuals; it is rare in SLE [154].

  PML typically presents with subacute neurologic deficits including altered mental status, visual symptoms such as hemianopia and diplopia, hemiparesis or monoparesis, and appendicular or gait ataxia; some patients have seizures. Brain MRI shows characteristic nonenhancing white matter changes (image 6). Diagnosis is confirmed via JC virus polymerase chain reaction (PCR) on CSF examination or brain biopsy. PML is discussed separately. (See "Progressive multifocal leukoencephalopathy (PML): Epidemiology, clinical manifestations, and diagnosis".)

- **Other serious infections** – Serious infectious complications develop in up to 50 percent of patients with SLE and may include CNS infections, which are usually bacterial but also include opportunistic infections in the setting of chronic immunosuppressive therapy [155]. Cryptococcal meningitis is the most frequent CNS fungal infection in SLE [156]. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Other associated conditions and complications'.)

- **Medication side effects** – Some medications used in the treatment of SLE, particularly glucocorticoids, may have cognitive side effects, which are discussed in the sections above. (See "Major adverse effects of systemic glucocorticoids", section on 'Neuropsychiatric effects'.)

ATTRIBUTION OF A CLINICAL SYNDROME TO SLE

Patients without a prior diagnosis of SLE — SLE is often a diagnostic consideration in patients with a new, unexplained neurologic syndrome.

Clinical suspicion for SLE should be heightened in patients at higher risk epidemiologically for SLE, such as females under the age of 40. In addition, patients with SLE typically have other signs of systemic inflammation, including constitutional symptoms (low-grade fever, severe fatigue), mucocutaneous disease (skin rashes, oral ulcerations, alopecia), musculoskeletal disease (inflammatory arthritis), serositis (pleuritic chest pain, pleural or pericardial rubs), or internal organ dysfunction (renal, hepatic, or pulmonary abnormalities). The presence of an unexplained multisystem disease should prompt evaluation for SLE. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'History and physical examination'.)

In addition to a comprehensive history and physical examination, initial evaluation for possible SLE should include testing for antinuclear antibodies (ANA), ideally by indirect immunofluorescence. A positive ANA test has low specificity for SLE, particularly at low titers; therefore, testing for subserologies that are more specific for SLE, such as anti-double-stranded DNA (anti-dsDNA), anti-Smith, anti-SSA, anti-SSB, and antiribonucleoprotein (anti-RNP) antibodies, as well as serum complements, is recommended when the ANA is positive. Testing for antiphospholipid antibodies (aPL) should also be performed for clinical syndromes associated with their presence (eg, ischemic stroke, chorea). (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Laboratory testing'.)

When this evaluation suggests a possible diagnosis of SLE, further evaluation for SLE disease activity, as described in the next section, can provide further evidence that the neurologic syndrome is attributable to SLE.

Patients with a diagnosis of SLE — In individuals with known SLE and neurologic symptoms, a thorough examination for signs, symptoms, and laboratory markers of SLE disease activity is required; the presence of other evidence of disease activity can increase suspicion that the symptoms may be directly attributable to SLE.

Laboratory investigations should include:

- Complete blood count (CBC) with differential. Cytopenias (eg, leukopenia, lymphopenia, thrombocytopenia) may be observed in active disease. Cytopenias may also reflect drug toxicities.
- Serum chemistries to screen for SLE renal or liver involvement.
- Urine studies including urinalysis with examination of urinary sediment and spot urine protein-to-creatine ratio to evaluate for lupus-related glomerular disease.
- Anti-dsDNA. Titers of anti-dsDNA antibodies often fluctuate with SLE disease activity, particularly in patients with active glomerulonephritis. (See "Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP".)
- Complement levels (C3 and C4). Low C3 and C4 are associated with active SLE, particularly lupus nephritis. (See "Lupus nephritis: Diagnosis and classification".)

Additional evaluation should be directed toward specific manifestations. For example, skin rashes may prompt dermatology consultation and skin biopsy, and suspicion for glomerulonephritis may prompt further renal evaluation and biopsy.

In situations in which inflammatory central nervous system (CNS) involvement is suspected, cerebrospinal fluid (CSF) examination should be performed to evaluate for inflammation and exclude possible infection and other entities in the differential diagnosis of the patient's syndrome. When a lumbar puncture is performed, the following studies should be included:

- Opening pressure (particularly if there is headache or clinical concern for processes that could cause intracranial hypertension).
- Cell count and differential.
- Glucose. A corresponding serum glucose is recommended to compare with CSF, particularly in cases where there may be hyperglycemia, such as with chronic glucocorticoid use or diabetes mellitus.

  Low CSF glucose can be a marker of CNS infection, malignancy, or, less commonly, primary neuroinflammatory processes including those attributed to SLE [65]. The CSF glucose tends to be normal or only mildly low (typically >30 mg/dL) in SLE. Very low values (<30 mg/dL) should prompt investigation for infection (particularly bacterial, mycobacterial, fungal pathogens).

- Total protein.
- IgG index (requires corresponding serum sample).
- Oligoclonal bands (requires corresponding serum sample).
- Cultures and molecular infectious disease diagnostics as indicated.
- Neuronal autoantibodies can also be considered if there is a concern clinically for an autoimmune encephalitis, though these are usually negative with typical SLE.

CSF examinations that show evidence of inflammation (pleocytosis, elevated protein, and/or low glucose), an elevated IgG index, or positive oligoclonal banding (which requires a corresponding serum sample at the time of the CSF examination) can support attribution of neurologic symptoms to active SLE from a primary inflammatory cause [157]. The sensitivity, specificity, and predictive value of these findings alone or in combination, or of the potential for other investigational metrics, such as cytokine levels in CSF, is not known.

Several research groups have developed algorithms for quantitating confidence of attribution of neuropsychiatric events to SLE [1,158-160], but none has yet been widely adopted for research or clinical decision-making.

Although some studies have suggested an association between the presence of antiribosomal P antibodies and SLE, other studies do not support this relationship, and testing for antiribosomal P antibodies is generally not helpful in diagnosing neuropsychiatric involvement of SLE. (See "Antiribosomal P protein antibodies", section on 'Clinical utility of antiribosomal P antibodies'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Systemic lupus erythematosus".)

SUMMARY AND RECOMMENDATIONS

- **Pathogenesis** – The pathogenesis of neurologic manifestations of systemic lupus erythematosus (SLE) is uncertain and may include an inflammatory process or vasculopathy. Secondary factors include side effects of medications, metabolic

complications of organ system failure, and comorbid disorders. (See 'Epidemiology and pathogenesis' above.)

- **Stroke** – Stroke is reported in up to 19 percent of patients with SLE. Stroke mechanisms are heterogeneous in SLE and include arterial and venous thrombosis, cardiogenic embolism, and small vessel infarcts. Vasculitis is an unusual stroke mechanism in this setting. Antiphospholipid antibodies (aPL) are prevalent in patients with stroke and SLE. Appropriate secondary stroke preventive measures are specific to the stroke subtype. (See 'Stroke' above.)

- **Seizures** – Seizures develop in 10 to 20 percent of patients with SLE. The evaluation and management of seizures in the setting of SLE does not typically differ from that in other settings. (See "Evaluation and management of the first seizure in adults".)

- **Acute mental status change** – Acute mental status change may take the form of a delirium or psychosis. The differential diagnosis is extensive and requires an urgent and thorough evaluation to exclude causes that may be SLE related or SLE independent (table 2). (See 'Altered mental status' above.)

  A minority of patients will be considered to have an SLE-related neuroinflammatory event, including so-called "lupus psychosis." This diagnosis requires that other causes of delirium and psychosis are excluded.

  In patients with severe psychosis or agitated delirium and in whom suspicion for active SLE is high, we suggest initiating treatment with high-dose ("pulse") glucocorticoids (**Grade 2C**). This should be concurrent with an evaluation for other causes and symptomatic treatment with antipsychotic drugs (table 2). (See 'Treatment of lupus psychosis' above.)

- **Cognitive dysfunction** – Impairments in mental activities (eg, memory, abstract thinking, and judgment), is prevalent among patients with SLE. Reversible and treatable causes such as medication effects, sleep disorders, and underlying psychiatric comorbidities should be considered and treated. (See 'Cognitive impairment' above.)

- **Inflammatory or demyelinating disease** – Optic neuritis and myelitis occur in SLE. Comorbid autoimmune disease, including neuromyelitis optica spectrum disorder (NMOSD), antimyelin oligodendrocyte glycoprotein (anti-MOG) antibody-associated demyelinating disease, and multiple sclerosis, should also be considered in the differential diagnosis. (See 'Optic neuritis' above and 'Myelitis' above.)

The acute management of these conditions is similar to their treatment in patients without SLE. (See "Optic neuritis: Prognosis and treatment", section on 'Acute treatment' and "Transverse myelitis", section on 'Acute idiopathic TM'.)

For patients with SLE who develop optic neuritis or myelitis not attributed to NMOSD or other comorbid disorder, we suggest escalation of immunosuppressive therapy to control disease activity and prevent relapse (**Grade 2C**). Suggested regimens are discussed above. (See 'Optic neuritis' above and 'Myelitis' above.)

The long-term management of NMOSD and related disorders is discussed separately. (See "Neuromyelitis optica spectrum disorder (NMOSD): Treatment and prognosis".)

- **Rare manifestations** – Other rare neurologic manifestations of SLE include aseptic meningitis and chorea. (See 'Aseptic meningitis' above and 'Chorea' above.)

- **Uncertain disease associations** – Headache, mood and anxiety disorders, and fatigue are common in patients with SLE and are managed similarly to that in patients without SLE. (See 'Other neurologic and psychiatric symptoms' above.)

- **Complications of treatment** – Patients with SLE are subject to complications of its treatment including glucocorticoid-related psychosis, reversible posterior leukoencephalopathy syndrome (RPLS), and others. (See 'Treatment complications and associated conditions' above.)

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