Chapter 7
Diagnosis and Differential Diagnosis

Taku Yoshio and Hiroshi Okamoto

Abstract Neuropsychiatric systemic lupus erythematosus (NPSLE) is a life-threatening disorder and early diagnosis and proper treatment are critical for the management of patients with this disease. NPSLE can manifest as a range of neurological and psychiatric features, which are classified using the ACR case definitions for 19 neuropsychiatric syndromes. Approximately one-third of all NPSLE events in patients with SLE are primary manifestations of SLE-related autoimmunity, with seizure disorders, cerebrovascular disease, acute confusional state and neuropathy being the most common. Such primary NPSLE events are a consequence either of autoantibodies and inflammatory mediators, or of microvasculopathy and thrombosis. Diagnosis of NPSLE requires the exclusion of other causes, and clinical assessment directs the selection of appropriate examinations. These examinations include measurement of autoantibodies, analysis of cerebrospinal fluid, electrophysiological studies, neuropsychological assessment and neuroimaging to evaluate brain structure and function. This chapter reviews the important key points for the correct diagnosis and the differential diagnosis.

Keywords NPSLE · Diagnosis · Differential diagnosis · Corticosteroid-induced psychiatric disorders (CIPD) · Autoantibodies · Cytokines · Chemokines

T. Yoshio (✉)
Division of Rheumatology and Clinical Immunology, School of Medicine, Jichi Medical University, Shimotsuke-shi, Tochigi, Japan
e-mail: takuyosh@jichi.ac.jp

H. Okamoto
Minami-otsuka institute of technology, Minami-otsuka Clinic, Tokyo, Japan

S. Hirohata (ed.), *Neuropsychiatric Systemic Lupus Erythematosus*,
https://doi.org/10.1007/978-3-319-76496-2_7

7.1 Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory autoimmune disease with a waxing and waning course and a broad spectrum of clinical presentations [1]. The involvement of the nervous system in SLE patients leads to a nonspecific and heterogeneous group of neuropsychiatric manifestations [2]. A major issue in clinical evaluation is the attribution of neuropsychiatric symptoms to SLE. No laboratory or radiological biomarker nor other formal system exists for establishing a diagnosis in neuropsychiatric SLE (NPSLE). In clinical practice, an individual multidisciplinary diagnostic approach based on the suspected cause and severity of symptoms is recommended [3].

In this chapter, we describe the standard classification of NPSLE which was produced by the American College of Rheumatology (ACR) for the diagnosis of NPSLE, risk factors for NPSLE, SLE disease activity, clinical and laboratory examinations for diagnosis of NPSLE, diagnostic approach of NPSLE, guidelines for diagnosis of NPSLE and the important diseases that should be differentiated from NPSLE.

7.2 Classification of NPSLE

Many previous classifications of NPSLE lacked definitions of individual manifestations and standardization for investigation and diagnosis. In 1999, the ACR produced a standard nomenclature and set of case definitions for 19 neuropsychiatric syndromes known to occur in SLE (Table 7.1) [4]. These syndromes can be segregated into central and peripheral nervous system involvement [4], and diffuse and focal neuropsychiatric events [5]. The ACR classification is comprehensive in the scope of neuropsychiatric manifestations it describes, and provides guidance on investigations and diagnostic criteria for each. However, the classification has never intended to be specific for neuropsychiatric events caused exclusively by SLE. Thus, using the ACR classification in clinical practice it is important to attribute events to SLE and nonSLE causes to optimize the care of individual patients presenting with neuropsychiatric events.

7.3 Risk Factors for NPSLE

It is helpful for the diagnosis of NPSLE to bear in mind risk factors for various manifestations of NPSLE. Risk factors consistently associated with NPSLE events are shown as follows:

1. General SLE activity or damage, especially for seizure disorders and severe cognitive dysfunction [6–8].
2. Previous events or other concurrent NPSLE manifestations [9–11].

Table 7.1 Neuropsychiatric syndromes observed in systemic lupus erythematosus

Central nervous system
Focal manifestations
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorders
Diffuse manifestations
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral nervous system
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

Arthritis Rheum 42:599–608, 1999

3. Antiphospholipid antibodies (persistently positive moderate-to-high anticardiolipin or anti β_2-glycoprotein IgG/IgM titers or the lupus anticoagulant), especially for cerebrovascular disease (CVD) [7, 10], seizure disorder [6, 9], moderate-to-severe cognitive dysfunction [8, 12], myelopathy [13] and movement disorder [12].

7.4 SLE Disease Activity

Some studies [14–16], but not all [17, 18], have found an association between increased global SLE disease activity and neuropsychiatric events attributed to SLE. When the association between SLE disease activity index (SLEDAI) and the appearance of NPSLE were previously investigated, NPSLE occurred in the high scores of SLEDAI [19].

The evaluation of SLE disease activity, such as SLEDAI in organ systems other than neuropsychiatric events is important to diagnose NPSLE correctly and ensure appropriate management of neuropsychiatric events in patients with SLE. Such assessment

might also help attribute these events to SLE and non-SLE causes. This association is probably more robust for diffuse rather than focal neuropsychiatric events.

7.5 Diagnostic Approach of NPSLE

Neuropsychiatric events may occur in patients when the presence of SLE or connective tissue disorders other than SLE is not confirmed. It is thus important to assess the presence or absence of SLE and other connective tissue disorders such as Sjogren's syndrome and mixed connective tissue disease. Of equally importance, the clinicians must realize that the presence of antinuclear antibody (ANA) in a patient with neurologic symptoms does not imply that the patient has NPSLE or, for that matter, SLE at all.

The evaluation of SLE patients with (new) signs or symptoms suggestive of NPSLE is comparable to that in non-SLE patients who present with the same neuropsychiatric manifestations [20]. Clinicians need to initially aim to exclude secondary causes such as infections, metabolic or endocrine disturbances and adverse drug reactions (Table 7.2).

The important diseases which should be differentiated from NPSLE are described in the Sect. 7.8.

Table 7.2 Secondary (non-lupus) causes of neuropsychiatric manifestations in systemic lupus erythematosus

Infection	
Medications	
Thrombotic thrombocytopenia purpura	
Hypertension	
Posterior reversible leukoencephalopathy syndrome	
Metabolic disturbance	Hyperglycemia or hypoglycemia
	Electrolyte imbabnces (Na^{+2}, Ca^{+2})
	Uremia
Hypoxemia	
Fever	
Thyroid disease	
Vitamin B12 deficiency	
Atherosclerosis strokes	
Subdural hematoma	
Berry aneurysm or cerebral hemorrhage	
Cerebral lymphoma	
Fibromyalgia	
Reactive depression	
Sleep apnea	
Other primary neurologic or psychiatric diseases	

7.6 Clinical and Laboratory Examination for the Diagnosis of NPSLE

No single test can diagnose NPSLE. After excluding secondary causes, the diagnosis of NPSLE can only be confirmed if a patient's neuropsychiatric symptoms can be corroborated with objective abnormalities in the neuropsychological examination, cerebrospinal fluid (CSF) examination, neuroimaging studies, electroencephalography, and/or biopsy. Therefore, a methodologic work-up is essential for the patient with SLE who complains of neuropsychiatric symptoms [21, 22].

A careful and thorough history taking and physical examination, including a complete neurologic and mental status (psychiatric) evaluation, must be performed on each patient.

7.6.1 Clinical and Laboratory Tests

In SLE patients who have neuropsychiatric symptoms, the clinical and laboratory tests which are necessary to confirm the diagnosis of NPSLE and to exclude other causes are shown in Table 7.3. A complete blood count and urinalysis should be obtained for disease activity and to rule out infection. If thrombocytopenia is present, the blood smear should be examined for schistocytes to exclude thrombotic thrombocytopenia purpura.

Blood chemistry tests, including electrolytes, creatinine, glucose, and liver-associated enzymes, are obtained to exclude metabolic abnormalities that can cause neurologic dysfunction. Complement (C3/C4, or CH50) determinations, anti-dsDNA antibodies and anti-Sm antibodies should be obtained to assess disease activity. The presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-β_2 glycoprotein I antibodies) should be also determined.

Other tests for hypercoagulable states, including factor V Leiden, protein C and S levels, serum antithrombin III levels, and prothrombin 20210A mutation, may be indicated in selected patients. Most patients with SLE will have an elevated erythrocyte sedimentation rate and a normal or mildly elevated C-reactive protein. A significantly elevated C-reactive protein (>6 mg/dL) usually indicates systemic vasculitis or infection. A fasting lipid profile and homocysteine levels are obtained to establish vascular risk factors.

Table 7.3 Laboratory evaluation and diagnostic imaging of patients with systemic lupus erythematosus and neuropsychiatric manifestations

Complete blood count and peripheral blood smear	
Blood chemistry and serology	Electrolytes, creatinine, glucose, liver-associated enzymes
	C3/C4 and/or CH50
	Anti-dsDNA antibodies
	Anti-Sm antibodies
	Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, anti-β2 glycoprotein I)
Urinalysis	
Cerebrospinal fluid [CSF]	Cell count, protein, glucose, gram stain, other special stains including India ink (*Cryptococcus*), venereal disease research laboratory test and cultures (including polymerase chain reaction for herpes simplex virus, varicella zoster virus, and JC viruses).
	IgG levels, Q-albumin ratio, oligoclonal bands, IgG index
Brain and/or spinal cord magnetic resonance imaging [MRI]	T1/T2-weighted imaging
	A fluid-attenuated inversion recovery sequence [FLAIR]
	Diffusion weighted imaging [DWI]
	A gadolinium-enhanced T1-weighted sequence
Electroencephalography	
Other tests	C-reactive protein
	Serum and CSF antineuronal antibodies
	Serum and CSF neuromyelitis optica [NMO] IgG/ anti-aquaporin 4 antibodies
	Serum and CSF anti-ribosomal P protein antibodies
	Serum and CSF anti-NR2 glutamate receptor antibodies
	Computed tomography [CT] of brain
	CT or magnetic resonance angiogram [MRA]
	Cerebral angiography
	Single photon emission computed tomography [SPECT]
	Positron emission tomography
	18F–fluro-d-glucose positron emission tomography [FDG-PET]

7.6.2 Autoantibodies

More than 20 autoantibodies in the serum and CSF have been reported to be associated with NPSLE [23–25]. They have been detected by a variety of methods using multiple different substrates. Over one half of them are autoantibodies that react to brain antigens, whereas the remaining are systemic autoantibodies. However, many of these autoantibodies are not routinely available and remain investigational.

Notably, the five autoantibodies that are clinically available (antiphospholipid, anti-ribosomal P protein, antineuronal, anti-NR2 glutamate receptor, and neuromyelitis optica (NMO) IgG/anti-aquaporin 4 antibodies) deserve further attention.

7.6.3 CSF Tests

CSF analysis is useful in all patients with SLE who have had a change in neurologic status, particularly to exclude infection or other secondary causes of CNS dysfunction. In patients with NPSLE, CSF results may be unremarkable (50%). However, patients with NPSLE may have such abnormalities that are helpful in confirming the diagnosis and guiding management. Consensus panels recommend that routine CSF tests, IgG index, and oligoclonal bands be determined on all patients suspected of having NPSLE [4, 21].

7.6.3.1 Routine CSF Tests

Routine CSF tests include cell count with differentiation, protein, glucose, Gram stain, other special stains including India ink (*Cryptococcus*), venereal disease research laboratory test and cultures (including polymerase chain reaction for herpes simplex virus, varicella zoster virus, and JC viruses, if indicated).

Pleocytosis (more than 100 cells per high-power field) and elevated protein (70–110 mg/dL) are found in some patients with active NPSLE. Protein abnormalities are common (22% to 50%) than pleocytosis (6% to 34%) [26]. Neutrophilic pleocytosis with elevated protein suggests cerebral vasculitis with ischemia if infection is ruled out. Patients with antiphospholipid antibodies and neurologic thromboembolic events frequently have elevated protein levels with mild or no pleocytosis.

The CSF glucose level is rarely (3% to 8%) decreased (30 to 40 mg/dL) in NPSLE. CSF pleocytosis, elevated protein levels, and low glucose should always raise suspicion of an acute or chronic infection before attributing these abnormalities to NPSLE.

7.6.3.2 CSF Immunologic Tests

CSF IgG levels are elevated in 69% to 96% of patients with NPSLE, and a level greater than 6 mg/dL almost always indicates NPSLE, although it is present in only 40% of patients with NPSLE. An elevated CSF Q-albumin ratio, indicating a break in the blood brain barrier, has been noted in up to one third of patients, especially those with progressive encephalopathy, transverse myelitis, and strokes [22, 26]. Several groups have now confirmed that an elevated lgG index, the presence of oligoclonal bands or both are observed in up to 80% of patients, particularly in those with diffuse manifestations, such as encephalopathy and psychosis [22, 26, 27]. Patients with focal manifestations, such as stroke due to antiphospholipid

antibodies, typically do not have an elevated IgG index or oligoclonal bands, unless they also have a coexistent encephalopathy (complex presentation) [22]. These abnormalities have been shown to normalize in some patients after successful therapy [22, 27].

7.6.3.3 CSF Autoantibodies

Using neuroblastoma cells as the antigen source, CSF levels of antineuronal antibodies were found to be significantly elevated in patients with lupus psychosis compared with those with nonpsychotic NPSLE or non-SLE controls [28].

Furthermore, 90% of the patients with diffuse manifestations of psychosis, encephalopathy or generalized seizures had elevated lgG antineuronal antibodies, compared with only 25% of patients with focal manifestations of hemiparesis or chorea. Notably the antineuronal antibodies were concentrated eightfold in the CSF, relative to its concentration in paired serum samples [29].

7.6.3.4 CSF Cytokine and Chemokine

Several cytokines (interleukin [IL]-6, interferon-α and granulocyte-colony stimulating factor) and chemokines (IL-8, interferon-γ-inducible-10, monocyte chemotactic protein-1) and matrix metalloproteinase-9 have been reported to be elevated in the CSF of patients with active NPSLE and may be important in the pathogenesis [30, 31]. Measurements of these mediators, especially IL-6, may be useful in the diagnosis and to monitor immunologic activity and neuronal damage. The intrathecal ratio of IP-10 to MCP-1 is significantly higher in patients with NPSLE than in patients with SLE without CNS symptoms. This IP-10/MCP-1 could be a useful marker of NPSLE [32, 33].

7.6.4 Neuroimaging Studies

Neuroimaging may detect NPSLE involvement and exclude other (neurosurgical, infectious) causes. The imaging technique of choice is magnetic resonance imaging (MRI) with 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 hyperintensity focal lesions on T2-weighted images in subcortical and periventricular white matter, usually in the frontal-parietal regions. Unfortunately, these MRI lesions are also present in many patients without neuropsychiatric manifestations (specificity 60–82%) [34–36].

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 [37, 38], magnetisation transfer imaging [39, 40], diffusion tensor MRI [41], perfusion-weighted imaging) or radionuclide brain scanning (single photon emission computed tomography (SPECT) [42, 43], or positron emission tomography [44]. These imaging studies may reveal additional white matter and grey matter abnormalities, which, however, have modest specificity for NPSLE.

7.6.5 Electroencephalography

Conventional electroencephalography (EEG) is abnormal in 60% to 91% of adult and pediatric patients with NPSLE [26]. The most common finding is diffuse slowing with increased beta and delta background activity. Focal abnormalities and seizure activity can also be seen. Unfortunately, the EEG findings are not specific for NPSLE, and other disorders, including metabolic encephalopathies and drug effects, can give similar findings. Furthermore, up to 50% of patients with SLE without active NPSLE can have abnormal EEG. Consequently, a single abnormal EEG has limited diagnostic value for NPSLE. On occasion, however, an EEG may be very helpful, revealing unsuspected seizure activity, which was not clinically apparent.

7.7 Guidelines for Diagnosis of NPSLE

The EULAR standing committee for clinical affairs developed the recommendations for the management of SLE with neuropsychiatric manifestations [21]. The guidelines for the diagnosis that this committee recommended are shown in Table 7.4 (A part of Table 7.3 EULAR recommendations for the management of NPSLE is cited and revised and a part of supplementary Table S2, available online only, is also added [21]). When the clinicians diagnose NPSLE in the patients with SLE who have neuropsychological symptoms, these guidelines may be useful for the diagnostic tools.

Furthermore, we show the important key points for the diagnosis of various neuropsychological syndromes, such as headaches, cerebrovascular disease, cognitive dysfunction, seizure disorders, movement disorders, acute confusional states, psychosis, myelopathy, cranial neuropathy and peripheral nervous system disorders.

Table 7.4 EULAR recommendations for the diagnosis of neuropsychiatric systemic lupus erythematosus

Statement
General NPSLE
NPSLE
Neuropsychiatric events may precede, coincide, or follow the diagnosis of SLE but commonly (50–60%) occur within the first year after SLE diagnosis, in the presence of generalized disease activity (40–50%).
Cumulative incidence
Common (5–15% cumulative incidence) manifestations include CVD and seizures; relatively uncommon (1–5%): Severe cognitive dysfunction, major depression, ACS and peripheral nervous disorders; rare (<1%) are psychosis, myelitis, chorea, cranial neuropathies and aseptic meningitis.
Risk factors
Strong (fivefold increase) risk factors consistently associated with primary NPSLE are generalized SLE activity, previous severe NPSLE manifestations (especially for cognitive dysfunction and seizures), and antiphospholipid antibodies (especially for CVD, seizures, chorea).
Diagnostic work-up
In SLE patients with new or unexplained symptoms or signs suggestive of neuropsychiatric disease, initial diagnostic work-up should be similar to that in non-SLE patients presenting with the same manifestations.
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.
The recommended MRI protocol (brain and spinal cord) includes conventional MRI sequences (T1/T2, FLAIR), DWI, and gadolinium-enhanced T1 sequences.
Specific NPSLE disorders
CVD
Atherosclerotic/thrombotic/embolic CVD is common, hemorrhagic stroke is rare, and stroke caused by vasculitis is very rare in SLE patients; accordingly, immunosuppressive therapy is rarely indicated
Cognitive dysfunction
More common in Caucasians (10–20%) than in Asian (1–2%).
Mild or moderate cognitive dysfunction is common in SLE but severe cognitive impairment resulting in functional compromise is relatively uncommon (3–5%) and should be confirmed by neuropsychological tests in collaboration with a clinical neuropsychologist when available.
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.
Acute confusional state (ACS)
Rates ranging 1.8–4.7% (including ‘organic brain syndrome’ cases).
Often in presence of generalized disease activity.
Type: hypo- or hyper-aroused states, ranging from delirium to coma.

(continued)

Table 7.4 (continued)

Statement
In Japan the frequency of ACS is highest among diffuse psychiatric symptoms.
Lumbar puncture for CSF analysis and MRI should be considered to exclude non-SLE causes, especially infection.
The measurement of CSF IL-6 may be useful for the diagnosis of ACS, because the elevated levels in CSF IL-6 have been reported.
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.
Myelopathy
Type: acute transverse myelopathy (most common), longitudinal myelopathy (>4 spinal cord segments affected, continuous or separate). The diagnostic work-up includes gadolinium-enhanced MRI and CSF analysis.
Optic neuritis is commonly bilateral in SLE
The diagnostic work-up should include a complete ophthalmological evaluation (including funduscopy and fluoroangiography), MRI and visual evoked potentials.
Optic neuritis needs to be distinguished from ischemic optic neuropathy, which is usually unilateral, especially in patients with antiphospholipid antibodies.
Peripheral neuropathy
Peripheral neuropathy often co-exists with other neuropsychiatric manifestations and is diagnosed with electromyography and NCS.

ACS acute confusional state, *CNS* central nervous system, *CSF* cerebrospinal fluid, *CVD* cerebrovascular disease, *DWI* diffusion-weighted imaging, *EEG* electroencephagraphy, *FLAIR* fluid-attenuating inversion recovery sequence, *IL-6* interleukin-6, *MRI* magnetic resonance imaging, *NCS* nerve conduction studies, *NPSLE* neuropsychiatric systemic lupus erythematosus, *SLE* systemic lupus erythematosus, *T1/T2* T1/T2-weighted imaging

7.7.1 Headache

As the definition of lupus headaches five types of migraine, tension, cluster, headache from intracranial hypertension, and non-specific intractable headache are shown by the ACR [4]. Fragoso-Loyo H et al. have proposed that headache from intracranial hypertension and intractable non-specific headache are of an inflammatory nature and should remain as NPSLE syndromes, however, migraine is non-inflammatory and might be excluded from this nomenclature [45].

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 [46]. It is necessary to exclude aseptic or septic meningitis, sinus thrombosis (especially in patients with antiphospholipid antibod-

ies), cerebral or subarachnoid hemorrhage. In the absence of high-risk features from the medical history and the physical examination (including fever or concomitant infection, immunosuppression, presence of antiphospholipid antibodies, use of anticoagulants, focal neurological signs, altered mental status, meningismus and generalized SLE activity), headache alone in an SLE patient requires no further investigation beyond the evaluation, if any, that would have been performed for non-SLE patients.

7.7.2 Cerebrovascular Disease

Ischemic stroke and/or TIA comprise over 80% of cerebrovascular disease (CVD) cases, whereas central nervous system (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 titers of antiphospholipid antibodies, heart valve disease, systemic hypertension and old age.

In an acute stroke, MRI DWI excludes hemorrhage, assesses the degree of brain injury, and identifies the vascular lesion responsible for the ischemic deficit. Magnetic resonance angiography, angiography of computed tomography, or conventional angiography may help to characterize the vascular lesions and detect brain vasculature aneurysms in subarachnoid hemorrhage.

7.7.3 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% [47, 48]. Most commonly affected domains are attention, visual memory, verbal memory, executive function and psychomotor speed.

ACR has proposed a 1 h battery of neuropsychological tests for diagnosing cognitive dysfunction in SLE (sensitivity 80%, specificity 81%) [4]. The computer-based automated neuropsychological assessment metrics system has also been used. Indications for brain MRI include the followings: age less than 60 years, rapid unexplained or moderate-to-severe cognitive decline, recent and significant head trauma, new onset of other neurological symptoms or signs, and development of cognitive dysfunction in the setting of immunosuppressive or antiplatelet/anticoagulation therapy. Cerebral atrophy, the number and size of white matter lesions, and cerebral infarcts have been correlated with the severity of cognitive dysfunction [47, 49–51].

7.7.4 Seizure Disorders

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

EEG abnormalities are common (60–70%) in SLE patients with seizure disorder, but typical epileptiform EEG patterns are only present in 24–50% and are predictive of seizure recurrence (positive predictive value 73%, negative predictive value 79%) [52, 53]. MRI can identify structural lesions causally related to seizure disorder and may reveal abnormalities such as cerebral atrophy (40%) and white matter lesions (50–55%). CSF examination is only useful to exclude infection.

7.7.5 Movement Disorders

Chorea (irregular, involuntary and jerky movements involving any part of the body in random sequence) is the best documented movement disorder in SLE, and has been associated with antiphospholipid antibodies and/or antiphospholipid syndrome. Brain imaging should be considered when other focal neurological signs are present or secondary causes of chorea need to be excluded. Most patients (55–65%) experience a single episode of chorea that subsides within days to a few months.

7.7.6 Acute Confusional State

Acute confusional state (ACS) is characterized by acute onset, fluctuating level of consciousness with decreased attention. Patients should be extensively evaluated for underlying precipitating conditions, especially infections and metabolic disturbances. CSF examination is recommended to exclude CNS infection and EEG may help diagnose underlying seizure disorder. Brain imaging is indicated if the patient has focal neurological signs, history of head trauma or malignancy, fever, or when the initial diagnostic work-up has failed to reveal any obvious cause of the ACS. Brain SPECT is sensitive (93%) and may help monitor response to treatment [54].

7.7.7 Psychosis

Lupus psychosis is characterized by delusions (false beliefs refuted by objective evidence) or hallucinations (perceptions in the absence of external stimuli). Although antiribosomal P protein antibodies have been associated with psychosis in prospective studies [55, 56], a meta-analysis has reported limited diagnostic accuracy (sensitivity 25–27%, specificity 75–80%) [57].

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 [58].

7.7.8 Myelopathy

SLE myelopathy presents as rapidly evolving transverse myelitis but ischemic/thrombotic myelopathy can also occur. Patients may present with signs of grey matter (lower motor neuron) dysfunction (flaccidity and hyporeflexia) or signs of white matter (upper motor neuron) dysfunction (spasticity and hyperreflexia); the latter can be associated more with neuromyelitis optica (NMO) and antiphospholipid [59]. Other major NPSLE manifestations are present in one third of cases, with optic neuritis being the most common (21–48%). Contrast-enhanced spinal cord MRI is useful to exclude cord compression and to detect T2-weighted hyperintensity lesions (70–93%). The involvement of more than four spinal cord segments indicates longitudinal myelopathy. This finding may be further investigated with determination of serum NMO IgG/anti-aquaporin 4 antibodies, which help diagnose co-existing NMO [60]. Brain MRI should be performed when other NPSLE symptoms or signs co-exist and in the differential diagnosis of demyelinating disorders. Mild-to-moderate CSF abnormalities are common (50–70%) but non-specific, while microbiological studies are important to exclude infectious myelitis.

7.7.9 Cranial Neuropathy

Most frequent cranial neuropathies involve the eighth, the oculomotor (third, fourth and sixth), and less commonly the fifth and seventh cranial nerves. Other neurological conditions, such as brainstem stroke and meningitis, should be excluded. Optic neuropathy includes inflammatory optic neuritis and ischemic/thrombotic optic neuropathy. Fundoscopy may reveal optic disc edema (30–40%) and visual field examination may show central or arcuate defects. Visual-evoked potentials may detect bilateral optic nerve damage before it is clinically apparent. Fluoroangiography should be performed when vaso-occlusive retinopathy is suspected. Co-existing transverse myelitis or seizure disorder may suggest an underlying inflammatory basis, while optic neuropathy with an altitudinal field defect, associated with

antiphospholipid antibodies, renders an ischemic/thrombotic mechanism more likely. The diagnosis is supported by contrast-enhanced MRI showing optic nerve enhancement in 60–70%, while brain MRI abnormalities are also common (67%).

7.7.10 Peripheral Nervous System Disorders

Peripheral nervous system disorders include polyneuropathy (2–3%) and less commonly mononeuropathy (single, multiplex), acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plexopathy, and present with altered sensation, pain, muscle weakness or atrophy. CNS involvement should be excluded by neuroimaging when focal neurological signs, gait disturbance, visual or urinary disorder, increased tendon reflexes and/or muscle tone are present. Nerve conduction studies and needle electromyography can identify mononeuropathies, differentiate multiple mononeuropathy versus polyneuropathy and distinguish axonal neuropathies from demyelinating neuropathies. CSF analysis is useful for diagnosis of inflammatory demyelinating polyradiculoneuropathy. Nerve biopsy is rarely needed to establish the diagnosis. If electrodiagnostic studies are normal, small-fiber neuropathy may be diagnosed by skin biopsy demonstrating loss of intraepidermal nerve fibers [61].

7.8 The Important Diseases for Differential Diagnosis

In this section, the diseases that should be differentiated from NPSLE are described.

7.8.1 Psychiatric Manifestations after Steroid Therapy

When the new-onset psychiatric manifestations appear in patients with SLE after the initiation of corticosteroid therapy (the dose of prednisone 1 mg/kg or more) or the increase of corticosteroid therapy, such as pulse intravenous methylprednisolone (1 g/day for 3 days), it is very difficult to determine whether these psychiatric manifestations are caused by SLE itself (NPSLE) or induced by steroids (corticosteroid-induced psychiatric disorders [CIPD]) [62]. CIPD occurs in 10% of patients treated with prednisone 1 mg/kg or more and it manifests primarily as mood disorder, such as manic or depressive state (93%), rather than psychosis [63].

It has been reported that CSF IL-6 levels are increased in patients with NPSLE, but not in SLE patients without NPSLE or with CIPD. Thus, the measurement of CSF IL-6 is useful for the differential diagnosis between NPSLE and CIPD [64]. The corticosteroid therapy may deteriorate psychiatric symptoms by reducing the brain blood flow, leading to the development of CIPD. The physicians should not

reduce the steroid dose or cease the steroid therapy in case of CIPD in order to avoid the exacerbation of SLE disease activity.

7.8.2 Neuromyelitis Optica

Neuromyelitis optica (NMO), also known as Devic syndrome, is a severe demyelinating disorder of the CNS that causes longitudinal transverse myelitis of at least three vertebral segments and recurrent optic neuritis. NMO has been reported in patients with SLE [65], which is associated with NMO-specific autoantibodies whose antigenic target is aquaporin 4 [66], the most abundant water channel in the CNS [67]. Although NMO is a rare clinical presentation, suspicion of this syndrome in a patient with SLE warrants the measurement of IgG anti-aquaporin 4 antibodies.

7.8.3 Reversible Posterior Leukoencephalopathy Syndrome

Over the past decade, reversible posterior leukoencephalopathy syndrome (RPLS) has been recognized as an important secondary cause of neurologic dysfunction [68]. At onset, patients with SLE typically have seizures (75% to 100%), accelerated hypertension (90% to 95%), acute renal failure (85% to 90%), headache (70%), blurred vision (45% to 50%), and/or cortical blindness (30%). Notably, over 75% have had augmentation of their immunosuppressants (intravenous methylprednisolone, intravenous cyclophosphamide) within an average of 7 days before the development of RPLS. The majority (61%) have evidence of brain MRI abnormalities involving the posterior lobe circulation caused by vasogenic edema. Therapy includes prompt control of the blood pressure. Further increase in immunosuppressive therapy is contraindicated and potentially detrimental. Long-term anticonvulsant use is rarely needed once neuroimaging abnormalities resolve after an average of 25 days. With early recognition and prompt therapy, full neurologic recovery usually occurs.

7.8.4 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, deadly demyelinating disease of the CNS, which is caused by a reactivation of the DNA polyomavirus, the John Cunningham virus (JCV), and occurs in immunosuppressed hosts. Of note, most SLE patients who develop PML have been either subjected or are concomitantly under immunosuppressant therapy [69].

MRI is the most sensitive imaging method for the investigation of suspected PML, typical lesions appearing hyperintensity on FLAIR and T2-weighted sequences [70]. Isolation of the JCV in brain tissue confirms the diagnosis of PML. Polymerase chain reaction (PCR) analysis of CSF for the presence of JCV has also been proved useful in the diagnosis of PML [71, 72]. Typically the patients with PML present with cognitive impairment, altered mental status, aphasia, focal motor deficits, cortical blindness and behavioral changes [73, 74].

PML must be considered in the differential diagnosis of SLE patients presenting with unexplained neurologic symptoms or signs, and a low threshold for performing PCR analysis of CSF for JCV must be maintained. Furthermore, since negative PCR results do not exclude the diagnosis of PML, brain tissue biopsy should be considered in patients in whom clinical suspicion of PML remains high, despite negative results on PCR analysis of CSF for JCV.

7.9 Summary

Neuropsychiatric symptoms constitute an uncommon and poorly understood event in SLE patients, and pose a diagnostic challenge to the physician. Management of NPSLE patients has not evolved substantially in the last decades and is characterized by the lack of good evidence to date. It seems reasonable that increased understanding of the pathogenesis of NPSLE as well as the specific findings for NPSLE will promote the possibility of discovery of the diagnostic tools for the rapidly targeted therapy.

References

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110–21.
2. Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers. Nat Rev Neurol. 2014;10:579–96.
3. Zirkzee EJ, et al. Prospective study of clinical phenotypes in neuropsychiatric systemic lupus erythematosus; multidisciplinary approach to diagnosis and therapy. J Rheumatol. 2012;39:2118–26.
4. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999; 42:599–608.
5. Hanly JG, et al. Autoantibodies and neuropsychiatric events at the time of systemic lupus erythematosus diagnosis: results from an international inception cohort study. Arthritis Rheum. 2008;58:843–53.
6. Andrade RM, et al. Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV). Ann Rheum Dis. 2008;67:829–34.
7. Mikdashi J, Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. Rheumatology. 2004;43:1555–60.
8. Tomietto P, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 2007;57:1461–72.
9. Appenzeller S, et al. Epileptic seizures in systemic lupus erythematosus. Neurology. 2004;63:1808–12.

10. Buján S, et al. Contribution of the initial features of systemic lupus erythematosus to the clinical evolution and survival of a cohort of Mediterranean patients. Ann Rheum Dis. 2003;62:859–65.
11. Mikdashi J, et al. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. Neurology. 2005;64:2102–7.
12. Sanna G, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol. 2003;30:985–92.
13. Mok MY, et al. Antiphospholipid antibody profiles and their clinical associations in Chinese patients with systemic lupus erythematosus. J Rheumatol. 2005;32:622–8.
14. Govoni M, et al. Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. Rheumatology (Oxford). 2012;51:157–68.
15. Florica B, et al. Peripheral neuropathy in patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2011;41:203–11.
16. Toledano P, et al. Neuropsychiatric systemic lupus erythematosus: magnetic resonance imaging findings and correlation with clinical and immunological features. Autoimmun Rev. 2013;12:1166–70.
17. Jarpa E, et al. Common mental disorders and psychological distress in systemic lupus erythematosus are not associated with disease activity. Lupus. 2011;20:58–66.
18. Shimojima Y, et al. Relationship between clinical factors and neuropsychiatric manifestations in systemic lupus erythematosus. Clin Rheumatol. 2005;24:469–75.
19. Morrison E, et al. Neuropsychiatric systemic lupus erythematosus: association with global disease activity. Lupus. 2014;23:370–7.
20. Bertsias G, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR Standing Committee for International Clinical Studies including therapeutics. Ann Rheum Dis. 2008;67:195–205.
21. Bertsias GK, et al. 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. Ann Rheum Dis. 2010;69:195–205.
22. West SG, et al. Neuropsychiatric lupus erythematosus: a 10-year prospective study on the value of diagnostic tests. Am J Med. 1995;99:153–63.
23. Zandman-Goddard G, et al. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. Semin Arthritis Rheum. 2007;36:297–315.
24. Kimura A, et al. Antibodies in patients with neuropsychiatric systemic lupus erythematosus. Neurology. 2010;74:1372–9.
25. Hanley JG, et al. Autoantibodies and neuropsychiatric events at the time of systemic lupus erythematosus diagnosis: results from an international inception cohort study. Arthritis Rheum. 2008;58:843–53.
26. West S. The nervous system. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 7th ed. Phiadelphia: Lippincott-Williams & Wilkins; 2007. p. 707–46.
27. Hirohata S, Taketani TA. Serial study of changes in intrathecal immunoglobulin synthesis in a patient with central nervous system systemic lupus erythematosus. J Rheumatol. 1987;14:1055–7.
28. Isshi K, Hirohata S. Differential roles of the anti-ribosomal P antibody and antineuronal antibody in the pathogenesis of central nervous system involvement in systemic lupus erythematosus. Arthritis Rheum. 1998;41:1819–27.
29. Bluestein HG, et al. Cerebrospinal fluid antibodies to neuronal cells: association with neuropsychiatric manifestations of systemic lupus erythematosus. Am J Med. 1981;70:240–6.
30. Okamoto H, et al. Cytokines and chemokines in neuropsychiatric syndromes of systemic lupus erythematosus. J Biomed Biotechnol. 2010;2010:268436.
31. Yoshio T, et al. IL-6, IL-8, IP-10, MCP-1 and G-CSF are significantly increased in cerebrospinal fluid but not in sera of patients with central neuropsychiatric lupus erythematosus. Lupus. 2016;25:997–1003.

32. Aranow C, et al. Pathogenesis of the nervous system. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 8th ed. Philadelphia: Lippincott-Williams & Wilkins; 2013. p. 363–7.
33. Okamoto H, et al. IP-10/MCP-1 ratio in CSF is an useful diagnostic marker of neuropsychiatric lupus patients. Rheumatology. 2006;45:232–4.
34. Kozora E, et al. Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 1998;41:41–7.
35. Nomura K, et al. Asymptomatic cerebrovascular lesions detected by magnetic resonance imaging in patients with systemic lupus erythematosus lacking a history of neuropsychiatric events. Intern Med. 1999;38:785–95.
36. Sibbitt WL, et al. Magnetic resonance and computed tomographic imaging in the evaluation of acute neuropsychiatric disease in systemiclupus erythematosus. Ann Rheum Dis. 1989;48:1014–22.
37. Appenzeller S, et al. Evidence of reversible axonal dysfunction in systemic lupus erythematosus: a proton MRS study. Brain. 2005;128(Pt 12):2933–40.
38. Axford JS, et al. Sensitivity of quantitative (1) H magnetic resonance spectroscopy of the brain in detecting early neuronal damage in systemic lupus erythematosus. Ann Rheum Dis. 2001;60:106–11.
39. Bosma GP, et al. Multisequence magnetic resonance imaging study of neuropsychiatric systemic lupus erythematosus. Arthritis Rheum. 2004;50:3195–202.
40. Steens SC, et al. Selective gray matter damage in neuropsychiatric lupus. Arthritis Rheum. 2004;50:2877–81.
41. Hughes M, et al. Diffusion tensor imaging in patients with acute onset of neuropsychiatric systemic lupus erythematosus: a prospective study of apparent diffusion coefficient, fractional anisotropy values, and eigenvalues in different regions of the brain. Acta Radiol. 2007;48:213–22.
42. Castellino G, et al. Single photon emission computed tomography and magnetic resonance imaging evaluation in SLE patients with and without neuropsychiatric involvement. Rheumatology. 2008;47:319–23.
43. Zhang X, et al. Diagnostic value of single-photon-emission computed tomography in severe central nervous system involvement of systemic lupus erythematosus: a case-control study. Arthritis Rheum. 2005;53:845–9.
44. Weiner SM, et al. Diagnosis and monitoring of central nervous system involvement in systemic lupus erythematosus: value of F-18 fluorodeoxyglucose PET. Ann Rheum Dis. 2000;59:377–85.
45. Fragoso-Loyo H, et al. Inflammatory profile in cerebrospinal fluid of patients with headache as a manifestation of neuropsychiatric systemic lupus erythematosus. Rheumatology. 2013;52:2218–22.
46. Mitsikostas DD, et al. A meta-analysis for headache in systemic lupus erythematosus: the evidence and the myth. Brain. 2004;127(Pt 5):1200–9.
47. Tomietto P, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 2007;57:1461–72.
48. Panopalis P, et al. Impact of memory impairment on employment status in persons with systemic lupus erythematosus. Arthritis Rheum. 2007;57:1453–60.
49. Ainiala H, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study. Scand J Rheumatol. 2005;34:376–82.
50. Lapteva L, et al. Anti-N-methyl-d-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2505–14.
51. Waterloo K, et al. Neuropsychological dysfunction in systemic lupus erythematosus is not associated with changes in cerebral blood flow. J Neurol. 2001;248:595–602.
52. Appenzeller S, et al. Epileptic seizures in systemic lupus erythema- tosus. Neurology. 2004;63:1808–12.

53. González-Duarte A, et al. Clinical description of seizures in patients with systemic lupus erythematosus. Eur Neurol. 2008;59:320–3.
54. Tokunaga M, et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis. 2007;66:470–5.
55. Briani C, et al. Neurolupus is associated with anti-ribosomal P protein antibodies: an inception cohort study. J Autoimmun. 2009;32:79–84.
56. Hanly JG, et al. Autoantibodies and neuropsychiatric events at the time of systemic lupus erythematosus diagnosis: results from an international inception cohort study. Arthritis Rheum. 2008;58:843–53.
57. Karassa FB, et al. Accuracy of anti-ribosomal P protein antibody testing for the diagnosis of neuropsychiatric systemic lupus erythematosus: an international meta-analysis. Arthritis Rheum. 2006;54:312–24.
58. Kodama K, et al. Single photon emission computed tomography in systemic lupus erythematosus with psychiatric symptoms. J Neurol Neurosurg Psychiatry. 1995;58:307–11.
59. Birnbaum J, et al. Distinct subtypes of myelitis in systemic lupus erythematosus. Arthritis Rheum. 2009;60:3378–87.
60. Pittock SJ, et al. Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol. 2008;65:78–83.
61. Tseng MT, et al. Skin denervation and cutaneous vasculitis in systemic lupus erythematosus. Brain. 2006;129(Pt 4):977–85.
62. Chau SY, Mok CC. Factors predictive of corticosteroid psychosis in patients with systemic lupus erythematosus. Neurology. 2003;61:104–7.
63. Nishimura K, et al. New-onset psychiatric disorders after corticosteroid therapy in systemic lupus erythematosus: an observational case-series study. J Neurol. 2014;261:2150–8.
64. Katsumata Y, et al. Diagnostic reliability of cerebral spinal fluid tests for acute confusional state (delirium) in patients with systemic lupus erythematosus: interleukin 6 (IL-6), IL-8, interferon-alpha, IgG index, and Q-albumin. J Rheumatol. 2007;34:2010–7.
65. Birnbaum J, Kerr D. Devic's syndrome in a woman with systemic lupus erythematosus: diagnostic and therapeutic implications of testing for the neuromyelitis optica IgG autoantibody. Arthritis Rheum. 2007;57:347–51.
66. Waters P, et al. Aquaporin-4 antibodies in neuromyelitis optica and longitudinally extensive transverse myelitis. Arch Neurol. 2008;65:913–9.
67. Lennon VA, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005;202:473–7.
68. Budhoo A, Mody GM. The spectrum of posterior reversible encephalopathy in systemic lupus erythematosus. Clin Rheumatol. 2015;34:2127–34.
69. Calabrese LH, et al. M. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum. 2007;56:2116–28.
70. De Gascun CF, Carr MJ. Human polyomavirus r eactivation: disease pathogenesis and treatment approaches. Clin Dev Immunol. 2013;2013:373579.
71. Cinque P, et al. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis. 2009;9:625–36.
72. d'Arminio Monforte A, et al. A comparison of brain biopsy and CSF-PCR in the diagnosis of CNS lesions in AIDS patients. J Neurol. 1997;244:35–9.
73. Garrels K, et al. Progressive multifocal leukoencephalopathy: clinical and MR response to treatment. AJNR Am J Neuroradiol. 1996;17:597–600.
74. Smith AB, et al. From the archives of the AFIP: central nervous system infections associated with human immunodeficiency virus infection: radiologic-pathologic correlation. Radiographics. 2008;28:2033–58.