Nervous System and Rheumatology

8

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8.1 Introduction

The nervous system can be affected by many rheumatologic disorders. The involvements are different in various diseases. Some rheumatologic diseases have prominent nervous system features, e.g. SLE, while in others these are minor (Table 8.1).

Patients with rheumatologic disorders can have nervous system involvement secondary to medications including immunosuppressive therapy or related to associated comorbidities. It also can be related or a sequel of the disease process itself.

The objective of this chapter is to provide a systemic approach to patients with various rheumatic conditions presenting with neurological syndromes.

8.1.1 Specific Objectives

By the end of the chapter, the reader should be able to:

1. Recognize different neurological manifestations associated with SLE.
2. Compose a diagnostic approach to SLE patients presenting with acute headache.
3. Compose a diagnostic approach to SLE patients presenting with chronic headache.
4. Manage SLE patients presenting with acute stroke.
5. Recall the different causes of stroke in SLE patients.
6. Recall the differential diagnosis of generalized seizure in SLE patients.
7. Recall the differential diagnosis of focal seizure in SLE patients.
8. Use appropriate investigation for SLE patients presenting with seizure.
9. Recognize SLE patients with seizure who will require long-term antiepileptic medications.
10. Compose a diagnostic approach and manage SLE patients presenting with spinal cord dysfunction.
11. Recognize neurological manifestations of rheumatoid arthritis (RA).
12. Recognize RA patients at high risk of cervical spine disease.
13. Manage RA patients with suspected cervical spine disease.
14. Recognize causes of neuropathy in RA patients.
15. Compose a diagnostic approach to RA patients presenting with neuropathy.
16. Compose a diagnostic approach to patients with neuropathy and skin rash.

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Table 8.1 Neurological involvement in rheumatic diseases

Condition	Neurological syndromes
Antiphospholipid syndrome	Transverse myelopathy, stroke, migraine, memory loss, demyelination, movement disorders
Temporal arteritis/giant cell arteritis and Takayasu's arteritis	Headache, visual loss, papilloedema, amaurosis fugax, stroke
Systemic vasculitis	Peripheral neuropathy, mononeuritis multiplex, stroke, polymyositis, meningoencephalitis
Eosinophilic granulomatosis with polyangiitis	Peripheral or cranial neuropathy, mononeuritis multiplex, encephalopathy
Dermatomyositis—Polymyositis	Proximal myopathy
Mixed connective tissue disease	Proximal myopathy
Rheumatoid arthritis	Rheumatoid vasculitis causing stroke and/or neuropathy, atlantoaxial subluxation, polymyositis; mononeuritis multiplex, peripheral neuropathy
Systemic lupus erythematosus	Aseptic meningitis, demyelinating syndrome, chorea, myelopathy, seizures, anxiety/mood disorders; psychosis, Guillain-Barre' syndrome, plexopathy; cranial and/or peripheral neuropathy, myasthenia gravis, autonomic disorder, stroke, migraine, headache
<i>Behçet's</i> disease	Meningitis, encephalitis, seizure, stroke, headache
Scleroderma	Proximal myopathy, plexopathy, intracerebral inflammation
Ankylosing spondylitis	Spinal stenosis
Granulomatosis with polyangiitis and polyarteritis nodosa	Peripheral or cranial neuropathy, mononeuritis multiplex, ocular disorders
Sjogren's syndrome	Myelopathy, polyneuropathy, motor neurone syndromes, cognitive Dysfunction

Table 8.2 Neuropsychiatric syndromes associated with systemic lupus erythematosus

NPSLE associated with the central nervous system	NPSLE associated with the peripheral nervous system
<ul style="list-style-type: none"> – Aseptic meningitis – Cerebrovascular disease – Demyelinating syndromes – Headaches – Movement disorders (chorea) – Myelopathy – Seizure disorders – Acute confusional state – Anxiety disorders – Cognitive dysfunction – Mood disorders – Psychosis 	<ul style="list-style-type: none"> – Acute inflammatory demyelinating syndromes (Guillain-Barre' syndrome) – Autonomic neuropathy – Mononeuropathy, single or multiplex – Myasthenia gravis – Cranial neuropathy – Plexopathy – polyneuropathy

8.2 Systemic Lupus Erythematosus (SLE)

In 1999, the American College of Rheumatology (ACR) established 19 different neuropsychiatric SLE syndromes (NPSLE) (Table 8.2).

In this chapter, the diagnostic approach to patients with SLE presenting with different neurological complaints will be presented. In general, obtaining good and detailed history and examination will assist to narrow the differential diagnosis and help with obtaining specific diagnostic tests (Table 8.3).

8.2.1 Headache

The prevalence of headache in patients with SLE is reported around 47.1–57% [1–3]. The differential diagnosis and approach to headache in SLE patients is different for acute versus chronic headache (Figs. 8.1 and 8.2). Patients with SLE can present with headache as primary disorders or can be secondary to other causes. The objective is to rule out serious causes before attributing it to primary headache disorder.

Table 8.3 Summary of NPSLE syndromes and differential diagnosis

NPSLE manifestations	Diseases to exclude	Notes
Headache	Aseptic meningitis, CNS infections, venous sinus thrombosis	<p>1. Diagnosis of NPSLE is by exclusion of other important causes by ordering routine tests:</p> <p>a. Laboratory: CBC, electrolyte, renal, and liver function tests</p> <p>b. CSF: WBC, protein, glucose, gram stain and culture, viral PCR</p> <p>c. Imaging: Either CT brain or MRI brain and spinal cord according to the case</p> <p>d. EEG, EMG, NCV</p> <p>2. Treatment is by glucocorticoids and immunosuppressive drugs and anticoagulant in certain conditions</p> <p>– In refractory cases, you can add one or all of the following:</p> <p>a. Plasmapheresis</p> <p>b. Intravenous immunoglobulin</p> <p>c. rituximab</p>
Cognitive dysfunction	Drug side effects, depression, endocrine disorders like adrenal disease, stroke	
Stroke	Thromboembolic causes, cerebral vasculitis	
Seizure	Infection, electrolyte abnormalities, uraemia, hypertension, medication side effects, hypoxia or rarely brain tumour	
Acute confusional state	Metabolic causes like renal or liver failure, CNS infections, medication side effects, seizure, structural lesion, e.g. tumour	
Myelopathy	Infectious myelitis, neuromyelitis optica	
Movement disorders	Hereditary causes like Huntington's, Wilson, metabolic causes, structural like brain tumour	
Peripheral neuropathy	Metabolic causes like diabetes, infectious causes, vitamin deficiency, etc.	

8.2.1.1 Approach

Obtain a careful history of the headache: onset, duration, types, and precipitating, aggravating, and relieving factors. Headache that increases with coughing or sneezing and also that is worse with lying down raises the possibility of raised intracranial pressure. The presence of history of visual obscuration is also suggestive of increased intracranial pressure. Ask about any associated neurological symptoms that will make primary headache unlikely and necessitate neuroimaging. In female patients, ask about the relation of headache to the menstrual cycle. Headaches that worsen in relation to menstrual cycle likely will be migraine related.

In addition, a comprehensive evaluation of SLE itself (current active symptoms like joint pains, skin rashes, and urinary symptoms, duration, organ involvements, and prior NPSLE attacks).

Detailed drug history should be obtained as some may precipitate or worsen headaches, e.g. some nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen can cause aseptic meningitis.

On examination, look carefully for signs of meningitis and focal neurological deficits, and *do not forget* to look for papilledema.

Workup depends on your initial findings (Figs. 8.1 and 8.2).

Indications for neuroimaging:

1. New-onset headache or worsening of pre-existing headache.
2. Features suggestive of increased intracranial pressure from history or examination, e.g. papilledema.
3. Altered level of consciousness.
4. Focal neurological signs and symptoms.
5. Associated seizure.

Treatment depends on the cause of the headache. Patients with venous sinus thrombosis will require treatment with anticoagulants. Meningitis should be treated with antibiotic therapy. If the headache is attributed to primary headache disorders, use abortive therapy as indicated. If primary headache is frequent, preventive therapy should be considered according to the headache type.

Fig. 8.1 Diagnostic approach to SLE patients with acute headache

8.2.2 Stroke

Cerebrovascular diseases account for around 2–17% [2–4] of all NPSLE events.

Approach to SLE patients with acute stroke is the same as in non-SLE patients (Fig. 8.3).

Keep in mind that in SLE patients, further consideration of the aetiology of the events should be

considered. When patients with SLE present with acute neurological deficit within a 4.5-h window, immediate evaluation with brain CT scan is warranted to rule out presence of intracerebral haemorrhage. In absence of contraindication, thrombolytic therapy should be administered. Patient who arrived outside the thrombolytic window should have CT brain before starting antiplatelet therapy. The

Fig. 8.2 Approach to SLE patient with chronic headache

initial workup for any SLE patient with stroke should include:

1. Fasting blood glucose.
2. Fasting lipid profile.
3. Carotid Doppler.
4. Holter monitoring.
5. Echocardiogram.
6. Antiphospholipid antibodies.

Disease activity should be determined (anti-dsDNA level, urinalysis, complement level (C3 and C4), creatinine). Specific treatment for active disease with immunosuppressive therapy should be considered. All patients should get cardiovascular risk factor modifications. In patients with negative antiphospholipid antibodies

and with no indication for anticoagulation such as atrial fibrillation, antiplatelet therapy is the cornerstone for the prevention of further events. Patient with antiphospholipid antibodies should be anticoagulated with warfarin at an INR >3.0 or combined antiplatelet-anticoagulant (INR 2.0–3.0). There is no consensus agreement on this [5].

8.2.3 Seizure

Seizure is a transient neurological dysfunction that results from excessive abnormal discharges of cortical neurons. Seizure can be generalized or focal in onset. The differential diagnosis of generalized-onset seizure is different than focal-onset seizure (Table 8.4).

Fig. 8.3 Approach to SLE patients with acute stroke

Table 8.4 Cause of generalized versus partial onset seizure

Generalized seizure	Partial-onset seizure
Electrolyte imbalance	Venous sinus thrombosis
Medication side effect	Posterior reversible encephalopathy
Uraemia	Limbic encephalitis
Infection	Infection
NPSLE	Stroke

Different aetiological factors can cause seizure in SLE patients (Tables 8.5 and 8.6). The prognosis and the need for further treatment of seizure are dependent on the cause of seizure [6, 7].

8.2.3.1 Tips in History

1. Disease activities.
2. Seizure onset, duration, and postictal events.
3. Determine the seizure type by asking if there was a preceding aura and by taking exact description of seizure from a witness.
4. History of fever.

Table 8.5 Causes of seizure in SLE patients

Electrolyte imbalance
Uraemia
Medication side effect
Posterior reversible encephalopathy
Infection (meningitis, encephalitis, cryptococcal meningitis)
Limbic encephalitis
Venous sinus thrombosis
NPSLE (single unprovoked seizure)

Table 8.6 workup of SLE patients present with single seizure

Electrolytes
Renal profile
Liver profile
CBC
Brain MRI and MRV
EEG

5. Any associated other neurological symptoms or signs.
6. Medication history.
7. History of comorbidities, e.g. hypertension or renal failure.

- 8. Similar events in the past.
- 9. History of prior CNS insults, e.g. stroke.
- 10. Family history of epilepsy.

Treatment with an antiepileptic is not indicated for a single unprovoked seizure and for seizure secondary to metabolic causes. Use an antiepileptic in the presence of recurrent events, abnormal EEG, and abnormal neuroimaging which carry a higher risk of recurrence without treatment.

If seizure happens in a setting of high disease activities, treatment with immunosuppressive therapy is indicated.

8.2.4 Myelopathy

It is a condition that results from inflammation of the spinal cord. Although it is considered rarer than other NPSLE syndromes, its development carries poor functional outcome. The classical presentation is with symptoms of spinal cord dysfunction including motor weakness, sensory loss with sensory level, and loss of sphincter control. The presentation differs according to the specific localization of the cord inflammation (Table 8.7).

Patients with SLE can present with transverse myelitis and rarely can also present with longitudinal myelitis where more four segments of the cord are involved. The development of longitudinal myelitis carries a worse prognosis and mandates aggressive immunosuppressive therapy. In the presence of longitudinal myelitis, brain MRI

should be done to rule out brain demyelination. Anti-NMO antibodies (neuromyelitis optica) should be sent for those patients.

When dealing with patients with symptoms of acute cord dysfunction, one should rule out surgical causes first as an early intervention will affect the outcome (Fig. 8.4). When surgical causes are excluded, patients should have CSF examination to rule out infectious causes of myelitis. Treatment with immunosuppressive therapy should be delayed. Combine it with antiviral therapy until negative culture is obtained.

Different immunosuppressive regimens have been used in patients with myelopathy including pulse steroid therapy with or without intravenous cyclophosphamide or plasmapheresis. Aggressive therapy with combined three modalities can be used for patients with more severe disease especially with longitudinal myelitis, although one case series did not show superior outcome with the combined three modalities [8]. That observation may be explained by the fact that patients who had combined therapy had severe disease at their presentation. In a subgroup of patients with antiphospholipid antibodies, the use of anticoagulation is recommended.

8.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common inflammatory destructive joint disease. Besides its articular manifestations, patients with RA exhibit multiple extra-articular manifestations. The nervous system can be involved at varying degrees in patients with RA [9]. Both central and peripheral nervous system can be involved (Fig. 8.5). Central nervous system involvements can happen in the form of necrotizing vasculitis or as a result from atlantoaxial subluxation. Peripheral nervous system involvement can be primary due vasculitis or secondary to the joint deformities or compression from rheumatoid nodules. Also the nervous system can be involved secondary to drug side effect.

The approach to patients with rheumatoid arthritis and atlantoaxial subluxation as well to patients presenting with neuropathy will be discussed (Fig. 8.6).

Table 8.7 Symptoms and signs of myelopathy according to the spinal level

Cervical cord	Motor weakness affecting four limbs (lower motor neuron signs at the level with upper motor neuron signs below the level of the lesion in chronic stage) Sensory loss below the level with cervical sensory level Loss of sphincter control Respiratory compromise in high cervical lesion
Thoracic cord	Motor weakness below the lesion (usually upper limb preserved unless T1 involved) Sensory loss below the lesion with truncal sensory level Loss of sphincter control

Fig. 8.4 Approach to patient with suspected myelopathy

Fig. 8.5 Causes of neurological manifestations of RA

Fig. 8.6 Approach to RA patient with suspected atlantoaxial subluxation

8.3.1 Atlantoaxial Subluxation

1. RA is the most common inflammatory disorder affecting the cervical spine. The involvement of cervical spine is related to active erosive RA and early age of onset [10].
2. Craniocervical complications arise in 30–50% of patients with RA more than 7 years; however, the atlantoaxial subluxation with myelopathy develops in 2.5% of RA more than 14 years [11].
3. Cervical spine involvements by RA include atlantoaxial subluxation, cranial settling, subaxial subluxation, or combinations of the above.
4. Atlantoaxial subluxation is the most common type of cervical spine affection.
5. The subluxation can be anterior, posterior, or lateral, and the anterior subluxation is the most common type that results from laxity of the primary and secondary ligamentous structures.
6. It is very important to recognize this particular complication especially in neurologically normal patients, as early recognition and treatment will improve outcome.
7. Patients with atlantoaxial subluxation can be asymptomatic, or more commonly involve complaints of neck pain. Patients may present with occipital neuralgia, facial pain, ear pain, or pain in the suboccipital region.
8. In cases where cord compression already developed, patients would present with weakness, sensory symptoms related to the cord compression, as well as loss of sphincter control. (*When you deal with any RA patients presenting with any of the above symptoms, consider atlantoaxial subluxation*).
9. Detailed neurological examination is mandatory with careful evaluation for signs of myelopathy.
10. In order to prevent the development of neurological sequels, an evaluation for possible atlantoaxial subluxation radiologically is mandatory for any patient with RA at presen-

tation and periodically thereafter and prior to any surgical procedures.

11. If atlantoaxial subluxation is suspected, besides assessing the disease activity with DAS-28 score, for example (see Chap. 1), and peripheral joint X-ray, the status of the cervical spine should be assessed. Plain X-ray that includes lateral, anteroposterior, open mouth odontoid views and lateral flexion-extension dynamics is necessary to assess joint stability.

More advanced imaging is required for patients with neurological symptoms to assess multilevel disease. MRI is better than CT scan to evaluate the neurological structures as well as to provide better look at the ligamentous structures.

The mainstay of treatment is early surgical intervention before the onset of severe neurological dysfunction, appropriate and aggressive disease-modifying therapy to control the disease activity, and adequate rehabilitation services to optimize neurological outcome.

8.3.2 Neuropathy

Neuropathy in patients with RA can result from nerve compression or secondary to vasculitis. When RA patients present with symptoms of mononeuropathy, it is essential to differentiate between neuropathy related to nerve compression and vasculitis as the treatment will be different.

Take appropriate history related to neurological complaints. The onset of symptoms, progression, and whether there is sensory and/or motor deficits should be checked. Check if the symptoms are all related to one nerve or multiple nerves (mononeuritis multiplex). Assess RA activity, severity with the presence of erosions on X-rays, functional decline, duration, and medications used for RA. On examination, try to identify the deficit and if you can which nerve is involved (Table 8.8). Examine all other peripheral nerves to assess whether it is a single or multiple processes. Examine the activity of RA and

Table 8.8 Things to look for in common nerve involvements

Nerve	Motor symptoms	Sensory symptoms	Notes
Radial nerve	Wrist drop due to weakness of extensors of the wrist and the fingers. Loss of elbow extension if the upper third of the nerve is affected	Loss of sensation over the anatomical snuff box	Flex the elbow, pronate the forearm, and extend the wrist and the fingers to demonstrate wrist drop if it is not clear
Median nerve	Loss or weakness of the thumb abduction mainly Loss of wrist flexors	Loss of sensation over the palmer aspect of the thumb, index, middle, and lateral half of the little finger and the corresponding part of the palm if it is affected above the wrist	Pen touching test for lesion at the wrist. Ochsner claspings for lesion in the cubital fossa
Ulnar nerve	Weakness of most of the small muscles of the hand which will lead clawing of the hand	Loss of sensation over the little finger the medial half of the ring finger	Froment's test can be used to demonstrate loss of thumb adduction in ulnar nerve affection
Femoral nerve	Weakness in knee extension	Loss of sensation over the medial aspect of the thigh and the leg	
Sciatic nerve	Weakness of all the muscles below the knee that results mainly in foot drop and weakness of the hip flexion	Loss of sensation over the posterior aspect of the thigh, all the aspects of the lower limb below the knee except for the medial aspect of the leg	It divides into the common peroneal nerve and the posterior tibial nerve at the level of the knee
Common peroneal nerve	Foot drop	Usually minimal sensory loss over the lateral aspect of the dorsum of the foot	Loss of eversion is another feature

assess deformity. Look for rheumatoid nodules. Nerve conduction studies (NCS) and electromyogram (EMG) will help to establish the diagnosis of nerve involvements. If it develops in a site of entrapment, e.g. carpal tunnel for median nerve and tarsal tunnel for posterior tibial nerve, the condition is most likely to be related to nerve compression rather than vasculitis and requires supportive care and may require surgical intervention. Neuropathy that develops in a non-compression site is related to vasculitis. Those patients may exhibit mononeuropathy or features of multiple nerve involvement (mononeuritis multiplex). Usually it happens in the setting of active erosive disease and with seropositive disease. Treatment with steroid should be initiated together with the use of disease-modifying therapy to achieve disease control. Patients with RA can also present with features of peripheral neuropathy that can be sensory, sensory-motor, or motor neuropathy. The approach to such patients will be discussed in the next part.

8.4 Neuropathy with Skin Rash

When neuropathy either mononeuropathy, mononeuritis multiplex, or peripheral neuropathy occurs in a setting of skin rash, vasculitis should be considered as an etiological factor. Vasculitis is a condition that results from inflammation of the blood vessels. It can be primary or secondary to other conditions, e.g. connective tissue disease, infection (hepatitis C), hypersensitivity reaction, and paraneoplastic condition. (See Chap. 19 for full details about vasculitis.)

Figure 8.7 shows the diagnostic approach to patient with neuropathy and rash.

8.4.1 Tips in History and Physical Examinations

1. Identify the nature of neuropathy (sensory, sensory-motor, motor, mono, multiple versus peripheral).

Fig. 8.7 Approach to patient with rash and neuropathy

- Symptoms of asthma like shortness of breath may suggest Churg-Strauss syndrome, *eosinophilic granulomatosis with polyangiitis [EGPA]*, or *allergic granulomatosis*.
- Symptoms of renal involvement like periorbital oedema and hypertension may suggest ANCA-associated vasculitis including microscopic polyangiitis and Henoch-Schonlein purpura (HSP).
- The age of the patient may give a clue since HSP is rare in a patient who is older than 18.
- Associated gastrointestinal symptoms are important findings in HSP.
- Symptoms of liver involvement are essential to be established as hepatitis C is associated with cryoglobulinaemic vasculitis and hepatitis B is strong risk factor for polyarteritis nodosa.

7. History of recent use of drugs or recent systemic viral infection that can be associated with hypersensitivity reactions.
8. Symptoms of connective tissue diseases like SLE, RA, and Sjogren disease are suggestive for a secondary cause of vasculitis.
9. Constitutional symptoms can be associated with rheumatologic diseases or solid tumours like lung cancer or lymphoma in what is known as paraneoplastic phenomenon.
10. Family history of similar presentation as some genetically determined disease, e.g. porphyria can present with skin rash and neuropathy.
11. High risk factors, e.g. multiple sexual partner and IV drug abusers, may suggest infections like HIV and/or syphilis.
12. The patient's job is important to exclude exposure to certain toxins.
13. Pay attention to the patient's nutritional status as vitamin deficiencies can lead to neuropathy and rash that might be mistaken for vasculitis.
14. Thorough systemic examination is mandatory to help narrow your differential diagnosis.
6. Serology for hepatitis B and C, HIV, and cryoglobulin level and VDRL to exclude secondary syphilis.
7. Vitamin assays like B12, folate, and E to exclude vitamin deficiency as the cause of patient presentation.
8. Toxicology screen looking for drug toxicities.
9. Look for porphyrins according to which subtype you suspect in the patient.
10. Use the different imaging modalities to look for solid tumour or lymphoma if you think they are the culprit.

8.4.2 Laboratory Investigations and Imaging Modalities

1. CBC, C-reactive protein, and ESR to assess the presence of inflammatory condition in the body like vasculitis and connective tissue disease.
2. NCS and EMG help to categorize the type of neuropathy [12].
3. Nerve biopsy is the ultimate gold standard to diagnose vasculitis as a cause of neuropathy [12].
4. Rheumatologic autoantibody profile like ANA, ANCA, RF, anti-DNA, anti-RO, anti-Jo, and anti-CCP will help identify if vasculitis were secondary to connective tissue disease (see for details in Chap. 4).
5. Assess the patient's liver, renal, thyroid, as well as glucose levels to help narrow the differential diagnosis.

8.4.3 Treatment

1. Immunosuppressive therapy with glucocorticoids is the mainstay of treatment. Depending on disease severity, the addition of cyclophosphamide should be considered to minimize the risk of relapse, morbidity, and mortality [13].
2. Control the precipitating condition in the case of secondary vasculitis in addition to same agents used for primary vasculitis, e.g. DMARDs for connective tissue diseases, antimicrobial for certain infection, discontinuation of the culprit drugs, etc.

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