Neurological consult in Rheumatologically center:

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Neurological Diseases Connective Tissue Diseases and Vasculitides:

- Neurological complications may be direct consequences of connective tissue diseases or may be secondary to other organ involvement or to treatment. Autoimmune inflammatory responses, especially necrotizing vasculitis, characterize connective tissue disorders. The mechanism of vasculitis is uncertain but may involve the deposition of immune complexes in vessel walls or cell-mediated immunity and release of lymphokines; autoantibodies also may be important in some instances.
The common direct CNS manifestations of connective tissue diseases are cognitive or behavioral changes and focal neurological deficits. Peripheral neuropathies also occur and may take the form of a vasculitic neuropathy, distal axonal polyneuropathy, compression neuropathy, sensory neuronopathy, trigeminal sensory neuropathy, acute or chronic demyelinating polyneuropathy, or plexopathy.
The cause of vasculitic neuropathy is nerve infarction from occlusion of the vasa nervorum. A mononeuropathy multiplex develops that becomes increasingly confluent with increasing nerve involvement until it resembles a distal symmetrical polyneuropathy. Nerves in watershed regions that lie between different vascular territories, such as the mid-thigh or mid- to upper arm, are more likely to be involved. Both large and small fibers are affected. Treatment with corticosteroids, often in conjunction with other immunosuppressive therapy, usually is effective (Burns et al., 2007), but intravenous immunoglobulin may be helpful in resistant cases (Levy et al., 2005).
Vasculitis neuropathy:
Systemic Lupus Erythematosus:

- Neurologic and psychiatric symptoms are reported to occur in 10 to 80 percent of patients either prior to the diagnosis of systemic lupus erythematosus (SLE) or during the course of their illness.
Nervous system involvement in SLE was initially thought to be due to vasculitis. This idea was challenged, however, by investigators who found that true vasculitis was a rare finding in patients with SLE and neurologic symptoms. However, many patients may have a vasculopathy that may cause direct injury and can also affect the blood-brain barrier, thereby allowing antibodies to enter the nervous system. This vasculopathy is characterized by a small to moderate perivascular accumulation of mononuclear cells, without destruction (eg, fibrinoid necrosis) of the blood vessel.
• challenge in patients with SLE is to determine whether neurologic symptoms are functional (ie, have a psychologic basis) or are due to an organic abnormality (ie, are due to dysfunction of the central or peripheral nervous system) and, if the basis is organic, whether the symptoms or findings are due to lupus itself (either active or inactive) or are due to other causes.
COMMON CLINICAL SYNDROMES:

- The most common neurologic manifestations of systemic lupus erythematosus (SLE) are cognitive dysfunction, stroke, seizures, headaches, and peripheral neuropathy.
Stroke syndromes:

- SLE may be associated with a significant increase in the risk of stroke and of premature death due to cerebrovascular disease. Strokes have been reported in up to 19 percent of patients with SLE.

- Strokes in the setting of SLE may be particularly severe. In a prospective cohort of patients with SLE, a high proportion, 77 percent, of incident strokes were associated with an NIH stroke scale of >6.

- Other reports in the literature also report a high association between antiphospholipid antibodies and stroke in SLE patients.
• the presence of a combination of anti-cardiolipin/beta2-glycoprotein I and anti-phosphatidylserine/prothrombin antibodies was strongly associated with cerebral infarction, more so than a positive test for a lupus anticoagulant alone.

• hypertension and accelerated atherosclerosis, both associated with chronic steroid therapy, are common risk factors for stroke. Elevated plasma homocysteine levels have been identified as a risk factor for stroke and other thrombotic events in patients with SLE. Other factors, such as infection, vasculitis, valvular heart disease, emboli, and/or thrombosis, can affect large or small blood vessels, thereby causing large vessel occlusive disease and infarction, or transient ischemic attacks (TIAs).
Stroke:
• **CNS vasculitis** due to SLE typically presents with a distinct syndrome of fever, severe headaches, and confusional episodes, with rapid progression to psychotic symptoms, seizures, and coma.

• Evidence of active lupus is usually demonstrable (eg, hypocomplementemia and elevated anti-double-stranded DNA [dsDNA] antibody)

• in our experience, the MRI or magnetic resonance angiography (MRA) is abnormal, with focal defects. Other tests of neurologic function, if performed, are also usually abnormal. This includes electroencephalography (EEG), analysis of the cerebrospinal fluid (CSF), proton emission tomography (PET), single photon emission computed tomography (SPECT) scans, and conventional cerebral angiography.
CNS vasculitis:
Stroke Treatment:

- **For the patient with SLE and persistent elevation of aPL** and with no stroke events, low-dose aspirin 81 mg/day is recommended.

- **For the patient with SLE and an ischemic stroke who has no other identifiable risk factors** (eg, does not have atrial fibrillation, has no vegetations by echocardiography, has no significant extracranial arterial stenosis, has no aPL) and for whom MRI suggests small vessel thrombosis, we recommend use of low-dose (81 mg/day) aspirin.

- **For the patient with SLE and moderate or high levels of aPL**, we recommend anticoagulation with warfarin with an INR target of 2 to 3.

- The administration of glucocorticoids and perhaps cyclophosphamide may be warranted if there is an associated lupus flare (including active vasculitis). By contrast, steroids are not used in patients with a stroke and aPL who have no evidence of active lupus. Steroid therapy is usually ineffective in this setting and may be associated with significant side effects.
• **Libman-sacks Endocarditis:**
  • Use of corticosteroids and cytotoxic agents for acute enlarging vegetation is controversial. Furthermore, steroid usage is implicated in the formation of leaflet thickening and valvular dysfunction.
  • Antibiotic therapy is recommended for prophylaxis of secondary infective endocarditis during procedures.
  • Anticoagulation with warfarin is often indicated for atrial fibrillation, mitral stenosis, mechanical heart valves and thromboembolic events.
  • Valve surgery may be required for hemodynamically significant valvular dysfunction.
Libman-sacks:
Flares:

**Definition** — The clinical course of SLE is variable and may be characterized by unpredictable disease flares and remissions. There is no consensus on what constitutes a disease flare, but most definitions have incorporated a combination of results from serologic measures and disease activity indices.
Seizures:

- Seizures develop in approximately 10 to 20 percent of patients with SLE. Both generalized and partial seizures can occur. The latter may be complex (complex partial seizures) or simple (focal epilepsy). Seizures may be the first manifestation of lupus or may develop during the course of the illness. In one case series, about half of new-onset seizures occurred during the first year after diagnosis.

- **The causes of seizures** are varied and may reflect an acute inflammatory episode or old CNS damage with scarring. Other factors may also contribute, including aPL, metabolic disturbances (such as uremia), hypertension, infections, tumors, head trauma, stroke, medication withdrawal, vasculopathy, or drug toxicity (eg, high doses of antimalarials, nitrogen mustard).
• Risk of seizures has been associated with anti-50 kDa, anti-Sm, and aPL. Other risk factors may include concomitant neuropsychiatric symptoms and other evidence of high disease activity.

• The development of focal seizures in the absence of a clear etiology, with negative angiograms, CT, and MRI, is probably due to a local vasculopathy.
Treatment:

- There are no randomized clinical trials that have specifically examined the treatment of seizures in patients with SLE. A variety of antiepileptic medications can be used depending upon the type of seizures. The evaluation and management of seizures in the setting of SLE does not differ from that in the general clinical setting.

- Antiepileptic drug (AED) therapy may not be necessary in patients with single or infrequent seizures, unless high-risk features for recurrence are present, such as two or more unprovoked seizures occurring within 24 hours, serious brain injury, brain MRI structural abnormalities causally linked to seizures, focal neurological signs, partial seizure, and epileptiform electroencephalography (EEG).
The following observations have been made in series of patients with seizures and SLE:

- In one case series of 75 patients with new-onset seizures in the setting of SLE, seizure recurrence occurred in 40. Eighteen patients required a second AED to control seizure activity.
- While there are case reports of drug-induced SLE in which the drug was an AED (eg, phenytoin, carbamazepine), an alternative explanation in at least some of these cases is that the seizure was the first sign of SLE. **We do not avoid these medications in patients with SLE.**
- If new-onset seizures are thought to reflect an acute inflammatory event or if a concomitant flare exists, a short course of steroids (prednisone, 1 mg/kg per day in divided doses) may be given in an attempt to prevent the development of a permanent epileptic focus.
- The combination of pulse intravenous methylprednisolone and intravenous cyclophosphamide was effective in reducing seizure frequency in a case series of patients with refractory seizures and SLE.
Headache:

- Headache is relatively common in patients with SLE, but there does not appear to be a causal relationship.
- Headache alone in a patient with SLE does not require additional investigation beyond the evaluation that would be performed for a patient with headache who does not have SLE. Migraine and tension headache are most common, although other rarer disorders should be considered in the differential diagnosis. An organic basis for the headaches is suggested by the sudden development in someone previously free of headaches, associated with neurologic changes or changes in personality.
- The treatment of headaches in patients with SLE does not differ from that in patients without this disease unless there are other manifestations of CNS lupus as noted above.
Psychiatric aspects:

- The psychiatric aspects of this disorder, including anxiety, cognitive dysfunction, mood disorders, and psychosis.
- Neuropsychiatric disturbances associated with glucocorticoid therapy may be confused with CNS lupus. The presentation can be varied and include depression, hypomania, and overt psychosis. A systematic review found that glucocorticoid-induced neuropsychiatric disturbances were dose-dependent, with an increased risk with a prednisone equivalent dose of ≥40 mg/day. Symptoms usually occurred during the first six weeks of treatment, and they were more common in women than in men. Neuropsychiatric symptoms generally resolve with discontinuation of glucocorticoids.
Neuropathy:

- Approximately 10 to 15 percent of patients with SLE develop a peripheral neuropathy that is probably due to vasculopathy of small arteries supplying the affected nerves. Autonomic neuropathy has also been reported in some patients, resulting in multiple gastrointestinal, bladder, cardiac, pupillary, and sweating abnormalities.

- Peripheral neuropathy due to SLE is usually asymmetric, mild, may affect more than one nerve (*polyneuropathy or mononeuritis multiplex*), and affects sensory nerves more than motor nerves. A typical presentation may be that of bilateral (but not truly symmetric) paresthesias and numbness of the digits that are often worse at night. **A small-fiber neuropathy** may also occur in SLE, producing painful sensory symptoms in the absence of abnormalities on nerve conduction studies or reflex changes. This may be isolated or may coexist with large-fiber polyneuropathy.
Inflammatory polyradiculoneuropathy, including the acute form resembling Guillain-Barré syndrome and the chronic form resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIPD), has been observed in patients with SLE in a few case reports.

Patients with the acute form present with sudden onset of ascending areflexic motor weakness with no sensory loss. Such patients respond to glucocorticoids within weeks if there has been no neuronal damage. SLE patients with CIPD may present with recurrent episodes of Guillain-Barré syndrome-like symptoms, mononeuritis multiplex, or symmetric polyradiculopathy over a period of weeks to months. Therapy with glucocorticoids and intravenous gamma globulin or plasmapheresis may be indicated. If there is evidence of axonal damage on electrodiagnostic studies or vasculitis on nerve biopsy, then more potent immunosuppressive therapy (eg, cyclophosphamide) is indicated.
Treatment:

- Neuropathies generally respond to therapy with glucocorticoids in moderate to higher doses (eg, prednisone 30 to 60 mg/day), but not all patients improve.
Recommendations:

- If there is **pain or intolerable paresthesia** and if a nerve conduction test is **abnormal**, we recommend glucocorticoids (e.g., *prednisone* at 1 mg/kg per day or equivalent) plus *gabapentin* (initial dose of 100 mg three times daily) or a low dose of a tricyclic antidepressant such as *amitriptyline* (initial dose 25 mg/day). If either of these approaches is ineffective or causes intolerable side effects, we would next utilize *carbamazepine*.

- **Active vasculitic neuropathy** (e.g., mononeuritis multiplex) warrants use of glucocorticoids (e.g., *prednisone* at 1 to 2 mg/kg/day or equivalent) plus *cyclophosphamide* therapy (either oral daily intake at a starting dose of 1.5 to 2 mg/kg/day, or intermittent monthly intravenous doses of 600 to 750 mg/m2), with or without plasma exchange for a six-month period.

- If the nerve conduction test shows **no abnormalities**, then we do not use glucocorticoids for neuropathy and would initiate either *gabapentin* or low-dose tricyclic antidepressants as described above.
UNCOMMON NEUROLOGIC SYNDROMES: Movement disorders

- Movement disorders occur in less than 5 percent of patients. Symptoms may include chorea, ataxia, choreoathetosis, dystonia, and hemiballismus. Dopamine-resistant parkinsonism has also been described.

- Movement abnormalities are thought to reflect lesions in the cerebellum and/or basal ganglia. Brain imaging should be considered when other focal neurological signs are present or to exclude secondary causes of chorea. While some data associated the development of movement disorders, particularly chorea, with antiphospholipid antibodies (aPL), other patients develop SLE chorea without aPL.
Treatment:

- The use of corticosteroids and other immunosuppressive therapy has also been advocated. In our experience, however, this is a self-limited and reversible disorder, and therefore may not require therapy. As an example, we have seen three cases of chorea, each of which resolved within two to six weeks without any specific treatment. Symptomatic therapy with dopamine antagonists or other agents can be effective.
Cranial neuropathies:

- Cranial nerve involvement is usually associated with other manifestations of active SLE. Depending upon the location of the neuropathy, symptoms may include diplopia, nystagmus, ptosis, visual field deficits, trigeminal neuralgia, dysarthria, facial weakness, and vertigo.
- **Eye movement abnormalities** are seen infrequently and are usually transitory.
- **Optic neuritis** in SLE is frequently bilateral. The underlying mechanism may vary along with the acuity of its presentation. Testing reveals aPL, optic nerve enhancement on magnetic resonance imaging (MRI), and other MRI abnormalities in a high proportion.
- **Sensorineural hearing defects** in both low and high frequencies have been noted more frequently in patients with SLE than in the general population.
Optic neuritis in SLE:
The term “lupoid sclerosis” has been given to patients who have MRI abnormalities that are similar to the findings in MS. If not previously tested, patients with lupus and cranial neuropathies should be assessed for the presence of aPL, concurrent Lyme disease, sarcoidosis, myasthenia gravis, and mid-brain or base-of-skull lesions.
Treatment:

- The optimal approach to treating cranial neuropathies is uncertain. Glucocorticoids are generally used first (eg, prednisone 0.5 to 1.0 mg/kg per day). The addition of cyclophosphamide has generally been reserved for those who do not respond to glucocorticoids. The possible value of this approach was illustrated in a small uncontrolled series of 10 Mexican patients with SLE and bilateral optic nerve involvement who had visual impairment that was refractory to steroids. Intravenous cyclophosphamide (0.5 to 1.0 g/m2) was given monthly for six months. Complete recovery of vision occurred in 50 percent of affected eyes, partial recovery in 30 percent, and no improvement in acuity in 20 percent.

- Other case series also support an aggressive treatment of optic neuritis with combined glucocorticoids and cyclophosphamide approach in patients with optic neuritis and SLE.
Recommendation:

- We generally begin treatment of cranial neuropathies with glucocorticoids in a dose of 1 mg/kg per day of prednisone (or equivalent), and we would consider adding cyclophosphamide if visual loss was due to optic nerve involvement.
Transverse myelitis:

- Transverse myelitis has been noted in patients presenting with the sudden onset of lower extremity weakness and/or sensory loss, plus loss of rectal and urinary bladder sphincter control. While symptoms of transverse myelitis may be the initial feature of SLE, the onset usually coincides with other signs of active lupus, including optic neuritis.
- This syndrome is thought to be due to an arteritis, with resultant ischemic necrosis of the spinal cord. It has been associated with aPL in some studies, but other series found no difference in the incidence of aPL in patients with or without transverse myelitis. Myelopathy can also be due to hematomas, tumors, fractures, disc herniations, infections, vascular occlusions, demyelinating conditions, or epidural abscesses.
• **MRI** should be performed to exclude a compressive lesion from infection or another cause. Patients with transverse myelitis and SLE may have localized edema along with T2 hyperintense foci on MRI scan.

• **CSF** should be obtained to exclude infection; in SLE, there is typically an elevated protein level and a moderate lymphocytic pleocytosis.

• **While neuromyelitis optica (NMO) spectrum disorders** (transverse myelitis occurring with bilateral optic neuritis) with seropositive findings for NMO-IgG have been described as occurring in SLE and antiphospholipid syndrome, investigations suggest their presence to be an indication of coexisting NMO rather than a vasculopathic or other complication of SLE.
Myelitis in SLE:
Treatment:

- Transverse myelitis must be treated aggressively and quickly if there is to be significant recovery. We and others have had success in a limited number of patients with the combination of **prednisone** (1.5 mg/kg per day), plasmapheresis, and **cyclophosphamide**.
- In those with transverse myelitis who have aPL, a good outcome may be achieved by combining **warfarin** with glucocorticoids and immunosuppressive treatment.
Meningitis:

- Meningitis may develop due to bacterial infection. A lumbar puncture and testing of the cerebrospinal fluid (CSF) is generally indicated if meningitis is suspected. Based upon the results of the lumbar puncture, those with meningitis can be classified into suspected acute bacterial or suspected aseptic meningitis.
- For patients with suspected **bacterial meningitis** (eg, positive Gram stain, cell count >1000/mm3, glucose <40 mg/dL), antibiotics should be initiated promptly.
- Patients with probable **aseptic meningitis** include those with CSF findings of cell count <500/mm3, >50 percent CSF lymphocytes, protein <80 to 100 mg/dL, normal glucose, and negative Gram stain.
• There are many causes of aseptic meningitis. In SLE patients treated with immunosuppressive agents, opportunistic infections (eg, Listeria monocytogenes, reactivation of tuberculosis, and fungi such as Cryptococcus) should be considered.

• Aseptic meningitis may be due to drugs used in treating SLE, including ibuprofen (and less commonly other nonsteroidal antiinflammatory drugs [NSAIDs], excluding aspirin) and azathioprine.
Treatment:

- Treatment of bacterial, viral, and other infectious causes of meningitis are presented elsewhere.
- Suspected drug-induced aseptic meningitis generally responds to withdrawal of the offending agent.
Reversible posterior leukoencephalopathy syndrome:

- SLE is among the inflammatory autoimmune disorders that are associated with the reversible posterior leukoencephalopathy syndrome (RPLS). Clinical manifestations include seizures, headache, visual disturbances, and altered mental status. Renal failure, hypertension, and immunosuppressive medications are believed to be risk factors.

- While the clinical features of neuropsychiatric lupus and RPLS can overlap, it is important to distinguish between these because treatment approaches differ. MRI is the most helpful diagnostic tool in this regard. In RPLS, MRI demonstrates characteristic vasogenic cerebral edema that is usually most predominant in the posterior cerebral.
• Diffusion-weighted MRI (DWI) can help distinguish between the vasogenic edema of RPLS and the cytotoxic edema more typical of lupus-related infarction.

• MRI is the most helpful diagnostic tool in this regard. In RPLS, MRI demonstrates characteristic vasogenic cerebral edema that is usually most predominant in the posterior cerebral hemisphere and does not respect a specific vascular territory.
PRES in SLE:
certain systemic findings in patients with SLE have been associated with particular neurologic syndromes:

- **Livedo reticularis** has been associated with aPL and an ischemic cerebrovascular disease.
- CNS vasculitis and transverse myelitis have been associated with signs of peripheral vasculitis, such as **Osler nodes and Janeway lesions**.
- Peripheral neuropathies have been associated with unilateral limb swelling, Jaccoud's arthritis, and Raynaud phenomenon.
Levedoreticularis:
Osler node:
Jaccoud arthritis and raynaud:
Immunosuppressive in SLE:

- We consider the use of **intravenous cyclophosphamide** (at an initial dose of 500 mg per square meter of body surface area) in patients with the following characteristics:
  - Acute or recent onset of neurologic symptoms, such as seizures or organic brain syndromes in the absence of another cause.
  - Evidence of active inflammation in the brain, such as increased cells and protein in the cerebrospinal fluid and brain swelling on magnetic resonance imaging (MRI) or computed tomography (CT) scan.
  - Failure to respond to a one- to two-week course of high-dose oral glucocorticoids (e.g., **prednisone** in a dose of 1 to 2 mg/kg per day) or to pulse **methylprednisolone** (1000 mg/day for three days).
• **Azathioprine** and **mycophenolate mofetil** have been used as second-line immunosuppressive agents; good outcomes were noted in the reported cases. Intravenous immunoglobulin administration and plasmapheresis have also been used in SLE patients; however, their role in central nervous system (CNS) lupus needs to be confirmed in randomized controlled trials.

• **Rituximab**, a B cell-depleting monoclonal anti-CD20 antibody, was administered to 10 patients with neuropsychiatric SLE, who were unresponsive to immunosuppressive, plasma exchange, and/or immunoabsorption therapy.

• Stem cell transplantation was studied in a phase I study.
Behçet’s disease:

- The International Study Group (ISG) criteria, which we prefer, were published in 1990. These remain the most widely used and well-accepted criteria among experts in Behçet’s disease. They require the presence of recurrent oral aphthae (at least three times in one year) plus two of the following in the absence of other systemic diseases:
  - Recurrent genital aphthae (aphthous ulceration or scarring)
  - Eye lesions (including anterior or posterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis observed by an ophthalmologist)
  - Skin lesions (including erythema nodosum, pseudo-vasculitis, papulopustular lesions, or acneiform nodules consistent with Behçet’s)
  - A positive pathergy test
The International Criteria for Behçet’s disease (ICBD) were developed in 2006 in an effort to improve sensitivity compared with the ISG criteria, but they are not widely accepted. Each of several findings is assigned a point value; the criteria require a total of at least three points for diagnosis of Behçet’s:

- Genital aphthosis – Two points
- Ocular lesions (anterior uveitis, posterior uveitis, or retinal vasculitis) – Two points
- Oral aphthosis – One point
- Skin lesions (pseudofolliculitis or erythema nodosum) – One point
- Vascular lesions (superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, or aneurysm) – One point
- Pathergy – One point

Validation studies have estimated a sensitivity of 87 to 96.5 percent, a specificity of 88.9 to 97.3 percent, and an accuracy of 74.2 to 85.5 percent for these criteria.
Behcet image:
Neuro Behçet’s disease:

- Neurologic disease occurs in less than one-fifth of patients with Behçet’s disease. It is observed more frequently in men than women. Neurologic disease is classified as parenchymal or non-parenchymal.

- **Parenchymal disease** is subdivided into brainstem disease, multifocal (diffuse) disease (including brainstem, cerebral, or spinal cord disease), myelopathy, cerebral disease (including encephalopathy, hemiparesis, hemisensory loss, seizures, dysphagia, and mental changes such as psychosis and cognitive dysfunction), and optic neuropathy.

- **Non-parenchymal disease** includes cerebral venous thrombosis, intracranial hypertension syndrome (pseudotumor cerebri), acute meningeal syndrome, and uncommonly stroke due to arterial thrombosis, dissection, or aneurysm
• Focal parenchymal lesions and complications of vascular thrombosis are the most common abnormalities. Progressive personality change, psychiatric disorders, and dementia may develop. Unlike many other systemic vasculitic disorders, peripheral neuropathy is not a common feature of Behçet’s disease, though it may develop in a subset of patients.
Parenchymal disease may be due to lesions in the corticospinal tract, brainstem, periventricular white matter, spinal cord, and basal ganglia. Brainstem disease (which may extend to the midbrain, basal ganglia, and diencephalon) including focal lesions or atrophy with signs and symptoms including ophthalmoparesis, cranial neuropathy, and cerebellar or pyramidal dysfunction are more characteristic of Behçet's than multiple sclerosis. Cerebral lesions are often multiple though may be single, are often subcortical, and are not particularly peri-ventricular, as in multiple sclerosis.

Clinical presentation of parenchymal disease is often subacute and manifestations may include headache, behavior changes, and deficits reflecting areas of parenchymal involvement.
Neurobehcet:
Central nervous system manifestations may result from **arterial or venous thrombosis**, including dural sinus thrombosis.

Cerebral venous thrombosis may present with headache, papilledema, sixth nerve palsy, and an elevated CSF pressure. An association has been observed between dural sinus thrombosis and peripheral deep venous thrombosis. Thrombosis of the cerebral arteries may also be observed. One analysis of neurologic Behçet’s from Turkey, involving 26 children and 702 adults, found that dural venous sinus thrombosis was much more common in children than parenchymal neurologic involvement, although parenchymal disease was more frequent in adults.

Venous disease may also be more common in patients with a **positive pathergy test or ocular involvement**.
CVT in Behcet:
Arterial disease:

- Arterial disease is most commonly a small vessel vasculitis, but medium and large vessel disease may also develop.

Large vessel vascular involvement occurs in approximately one-third of patients with Behçet’s disease. In these patients, perivascular and endovascular inflammation may lead to hemorrhage, stenosis, aneurysm formation, thrombus formation in both arteries and veins, and varices. Progression and recurrence are more likely in these patients, and immunosuppressive treatment of this inflammation has been found to be beneficial, though patients may also require vascular surgery intervention.

- Carotid, pulmonary, aortic, iliac, femoral, and popliteal arteries are most commonly involved; cerebral and renal arteries are uncommonly involved.
antiphospholipid syndrome:

- The antiphospholipid syndrome (APS) is defined by two major components:
- The occurrence of at least one clinical feature: vascular event or pregnancy morbidity
- The presence of at least one type of autoantibody known as an antiphospholipid antibody (aPL) on two separate occasions at least 12 weeks apart
- In addition, there are aPL-related clinical manifestations that are not part of the APS classification criteria, such as livedo reticularis, thrombocytopenia, cardiac valve disease, and aPL-nephropathy
Thrombosis:

- The risk of both venous and arterial thrombosis and/or thromboembolism is increased in individuals with positive tests for lupus anticoagulant (LA) activity (odds ratio [OR] of 11) or with medium or high levels of anticardiolipin antibodies (aCL) (OR 1.6). The risk of recurrent thrombosis or thromboembolism may be further enhanced in those with positivity to three aPL activities (LA, aCL, and beta-2-glycoprotein-1) upon repeated testing.
APS is strongly linked to ischemic stroke. The occurrence of livedo reticularis in association with a stroke is known as Sneddon’s syndrome. In the great majority of cases, Sneddon's syndrome is associated with detectable aPL.

A thrombotic stroke occurring in a young patient with no overt risk factors for cerebrovascular disease is the classic setting in which to suspect APS. In one study, aPL were found in 25 percent of patients younger than 45 years of age who presented with a stroke of unclear etiology. In another report, 20 percent of stroke victims under the age of 50 had aPL.

Ischemic stroke may be a manifestation in situ thrombosis or due to embolism arising from valvular heart disease. If routine transthoracic echocardiography is normal, transesophageal echocardiography may be indicated to assess for vegetations due to nonbacterial endocarditis.
APS:
Cognitive deficits:

- Considerable interest, and controversy, has focused on the relationship between aPL and cognitive deficits. The degree of reported cognitive deficits ranges from subtle findings to transient global amnesia to permanent and profound cognitive functioning. The cognitive deficits reported in APS are sometimes but not always associated with white matter lesions.
White matter lesions:

- Central nervous system involvement in APS is associated with high-intensity lesions on MRI that are suggestive of a vasculopathy. These lesions may be difficult to distinguish from those in multiple sclerosis. When present in patients with clinical or serologic features of SLE or APS, these lesions have been referred to as “lupoid sclerosis”.

- A number of patients with multiple sclerosis also have aPL. However, there appears to be no correlation between these antibodies and any clinical features of multiple sclerosis.
• Other neurological associations — Other neurologic disorders with which aPL have been reported include:

• Epilepsy
• Psychosis
• Chorea and hemiballismus
• Transverse myelopathy
• Sensorineural hearing loss
• Orthostatic hypotension
• Migraine
Polyarteritis Nodosa, Churg-Strauss Syndrome, and Overlap Syndrome:

• **Peripheral neuropathy** occurs in up to 60% of patients with polyarteritis nodosa, Churg-Strauss syndrome, or overlap syndrome. Usually a painful mononeuropathy multiplex, at least in polyarteritis, develops during the first year. In others, a secondary polyneuropathy (e.g., from renal failure) may develop. A plexopathy, radiculopathy, or cauda equina syndrome also can develop. Electrophysiological studies and nerve histology are often abnormal even in the absence of clinical evidence of peripheral nerve involvement.

• **CNS involvement** usually occurs later than peripheral involvement in the course of the disease. Common features are headache, which sometimes indicates aseptic meningitis, and behavioral disturbances such as cognitive decline, acute confusion, and affective or psychotic disorders. The electroencephalogram (EEG) sometimes shows diffuse slowing, but neuroimaging studies are generally normal. Focal CNS deficits are uncommon but are typically sudden in onset and may be caused by cerebral infarction or hemorrhage. Angiography may not show the underlying vasculitis. Ischemic or compressive myelopathies from extradural hematomas are rare complications.
Patients with Churg-Strauss syndrome often have asthma and a marked peripheral eosinophilia; typically p-ANCA elevations are present. Nerve or muscle biopsy often shows the necrotizing vasculitis, and angiography reveals segmental narrowing or aneurysmal distention, especially in the renal, mesenteric, or hepatic vessels.

Treatment for these conditions is with corticosteroids combined with cyclophosphamide and has reversed the poor prognosis in this disease. With adequate combined therapy, approximately 60% of patients do well. Some are able to discontinue treatment by 2 years, although a subset will require lifelong therapy.
PAN image:
Wegener Granulomatosis:

- Neurological involvement occurs in up to 50% of patients with Wegener granulomatosis. **Peripheral involvement** is usually a mononeuropathy multiplex; less often, a symmetrical polyneuropathy develops. Direct involvement of the brain may occur by vasculitis or by extension of granulomas from the upper respiratory tract. The associated clinical syndromes are basal meningitis, temporal lobe dysfunction, cranial neuropathies, cerebral infarction, and venous sinus obstruction.

- Among patients with neurological complications, peripheral neuropathy is most common. The neuropathy usually is a mononeuropathy multiplex, but symmetrical polyneuropathies sometimes occur.

- **Cranial neuropathy also may occur (usually involving II, VI, and VII), and multiple cranial neuropathies sometimes develop.** Other neurological features include an external ophthalmoplegia (due to orbital pseudotumor), cerebrovascular events, seizures (e.g., metabolic, sepsis, vasculitis), and cerebritis.
• Treatment includes corticosteroids, often in conjunction with other immunosuppressive agents such as cyclophosphamide or methotrexate
Pachymeningitis in Wegner:
Rheumatoid Arthritis:

- Disorders of the central nervous system (CNS) due to rheumatoid arthritis (RA) include cervical myelopathy, vasculitis, rheumatoid nodules located within the CNS, meningitis, organic brain syndrome, and (rarely) progressive multifocal leukoencephalopathy. Stroke also occurs with increased frequency, but the basis for this association is not well understood.
Cervical myelopathy — Cervical myelopathy (cervical myeloradiculopathy) resulting from atlantoaxial subluxation, atlantoaxial impaction, and/or subaxial subluxation is discussed separately.

Central nervous system vasculitis — CNS vasculitis is rare in patients with RA, with the literature generally consisting of case reports of intracranial arteritis. CNS lesions are also infrequent in patients with systemic rheumatoid vasculitis.

Clinical manifestations — Presenting manifestations of CNS vasculitis include seizures, dementia, cranial nerve palsies, strokes, encephalopathy, intracerebral or subarachnoid hemorrhage, and myelopathy.

Diagnosis — Brain biopsy is the most specific diagnostic test. Cerebral angiography and magnetic resonance angiogram also may be helpful but are less specific. However, some evidence suggests that magnetic resonance imaging (MRI) abnormalities among symptomatic patients with RA cannot be ascribed to vasculitis alone.

Treatment — Therapy of patients with RA and CNS vasculitis is similar to that for patients with isolated CNS vasculitis. This includes high-dose glucocorticoids and cytotoxic agents.
Atlantoaxial dislocation in RA:
• **Rheumatoid nodules** — Rheumatoid nodules have been reported rarely in the central nervous system. Extradural nodules in the spinal canal may cause nerve root compression, spinal cord compression, and spinal stenosis.

• Rheumatoid nodules of the cerebral leptomeninges and within the choroid plexus also have been described.

• Surgical decompression should be performed if a rheumatoid nodule is compressing a vital structure.
• **Stroke**: There is an increased risk of stroke in RA, especially ischemic stroke.

• **Progressive multifocal leukoencephalopathy**: The risk of progressive multifocal leukoencephalopathy (PML), which is associated with the polyoma JC virus, is increased in patients treated with rituximab for RA, but the absolute risk is very small.
PERIPHERAL NERVOUS SYSTEM:

- **Compression or entrapment neuropathy** — Entrapment neuropathies are diagnosed in approximately one-half of RA patients with severe peripheral disease and subcutaneous nodules. Joint deformities and inflamed synovium, ligaments, or tendon sheaths may compress peripheral nerves that are in close proximity to joints or bursae.

- **Carpal tunnel syndrome** — Carpal tunnel syndrome (CTS) is probably the most common neurologic manifestation of RA and can occur at any time during the disease.

- **Tarsal tunnel syndrome** — Tarsal tunnel syndrome, which is less common than CTS, is due to compression of the posterior tibial nerve as it passes near the medial malleolus.
An entrapment neuropathy and symptomatic cervical spine disease with nerve root compression may present concurrently and is termed the "double crush" syndrome.

Treatment of compression neuropathies — Nonsurgical management involves treatment of the underlying disease process. Additional modalities include splints, antiinflammatory medications, and local corticosteroid injections. Surgical decompression is indicated if motor deficits or denervation are present, or if sensory symptoms worsen despite adequate nonsurgical therapy.
• **Noncompression neuropathies**:
  
  • **Distal sensory neuropathy**: Symmetric paresthesias and burning sensations tend to be worse in the feet than in the hands
  
  • **Combined sensorimotor neuropathy** — Combined sensorimotor neuropathy is associated with long duration seropositive, nodular RA, male gender, other extraarticular involvement, systemic constitutional symptoms, and other signs of vasculitis including palpable purpura, livedo reticularis, skin ulcerations, nailfold and digital infarcts, and Raynaud phenomenon.
  
  • **Autonomic neuropathy**: An increased incidence of autonomic neuropathy, as determined by abnormal cardiovascular reflexes, has been reported
  
  • There is no convincing evidence that steroids are helpful or that antimalarials and gold alter the course of disease. Plasmapheresis has been used in refractory cases, but without great
NEUROMUSCULAR DISORDERS:

- **Myopathy** — Myopathic processes, which are subdivided into disuse or denervation atrophy, must be distinguished from a muscular dystrophy, such as myopathy and weakness due to corticosteroid use.

- **Disuse atrophy** — Muscle weakness and wasting with disuse atrophy results from pain due to synovitis. Muscle biopsy reveals type II fiber atrophy; there is no muscle inflammation, necrosis, regeneration, or vasculitis. Effective treatment requires control of joint inflammation and reduction in pain, which is followed by a strengthening exercise program.

- **Denervation atrophy** — Motor nerve demyelination and degeneration due to angiopathic neuropathy, such as mononeuritis multiplex, can lead to muscle fiber atrophy, necrosis, and regeneration, with minimal muscle inflammation on biopsy. Treatment for weakness due to ischemia or infarction of peripheral nerve is directed at control of vasculitis.
- **Muscular dystrophy-like myopathy** — Muscular dystrophy-like myopathy in those with RA is similar to muscular dystrophy both clinically and pathologically. There is loss of muscle tissue, replacement by adipose tissue, fiber caliber variations, and fibrosis without inflammatory infiltrates. Motor innervation is not disturbed. This may represent late chronic myositis.

- **Glucocorticoid-induced myopathy** — Glucocorticoid-induced or steroid myopathy is characterized by proximal muscle weakness without significant serum muscle enzyme elevations. Muscle biopsy reveals type II fiber atrophy. Gradual reduction in the glucocorticoid dose and a muscle strengthening rehabilitation program are the mainstays of treatment.
**Myositis** — With myofiber necrosis and regeneration, there is focal or diffuse infiltration of lymphocytes, plasma cells, and mononuclear cells into the endomysium, perimysium, and perivascular areas. Since it may be impossible to distinguish myositis in RA from idiopathic polymyositis, this process may represent an overlap syndrome. Treatment of myositis complicating RA is similar to the therapy of idiopathic polymyositis.

**Amyloid** — RA may rarely be complicated by secondary amyloidosis, which may result in abnormalities in both the central and peripheral nervous systems. Amyloid deposits have been reported in brain arterioles in four patients with RA and central nervous system (CNS) vasculitis. Peripheral neuropathy can also result from secondary amyloidosis.
DRUGS:

- Nonsteroidal antiinflammatory drugs (NSAIDs) may result in headaches, drowsiness, and aseptic meningitis.
- Glucocorticoids can cause myopathy, depression, psychosis, and benign intracranial hypertension.
- Antimalarials, such as hydroxychloroquine, can cause dizziness, headache, tinnitus, seizures, and neuromyopathy.
- Gold therapy can be complicated by peripheral neuropathy, cranial nerve palsies, and Guillain-Barré syndrome.
- **Methotrexate** can cause headaches and impair the ability to concentrate.
- **Sulfasalazine** and **leflunomide** reportedly cause headaches.
- **Leflunomide** is associated with peripheral neuropathy.
- Agents that interfere with the action of tumor necrosis factor alpha (anti-TNF therapies) may increase the risk of demyelinating disorders of the central nervous system (CNS). Progressive multifocal leukoencephalopathy and peripheral neuropathy also have occurred in patients treated with anti-TNF therapies.
THANK YOU