

Neurological Complications of Systemic Lupus Erythematosus (SLE) and Sjogren's Syndrome

Julius Birnbaum, M.D./M.H.S.
Assistant Professor, Division of Rheumatology and
Department of Neurology
Associate Director, Johns Hopkins Jerome Greene
Sjogren's Center

Overall objectives

Describe the spectrum of peripheral nervous system (PNS) and central nervous system (CNS) manifestations of Sjogren's syndrome and systemic lupus erythematosus (SLE)

Develop a standardized diagnostic approach in the evaluation of specific neurological manifestations of SLE

Understand how such diagnostic paradigms can be applied to understand etiopathogenesis and treatment of neurological syndromes seen in Sjogren's syndrome

Brief review of the peripheral nervous system
manifestations of SLE and Sjogren's syndrome

Step 1: Attribution of neuropathies due to SLE or Sjogren's,
versus a competing co-morbidity

Need to fashion a very broad differential diagnosis.

Challenge: Such a broad differential diagnosis can encapsulate many different syndromes

But such a differential diagnosis can be developed and memorized using the VITAMIN mnemonic

Attribution of neuropathies due to SLE or Sjogren's syndrome, versus a competing co-morbidity

Vascular: Systemic vasculitides, (frequency unknown)

Infection: HIV, Hepatitis C

Traumatic: No

Autoimmune/Inflammatory Disorders: Celiac disease, sarcoidosis, other rheumatic syndrome (frequency unknown)

Metabolic Disorders: Diabetes and impaired glucose tolerance (Need to order a 2-hour GGT!), Vitamin B12 deficiency, hypothyroidism

Inflammatory Disorders: Amyloidosis; Paraproteinemias; Cryoglobulinemia (frequency unknown)

Neoplastic Disorders: Paraneoplastic disorders

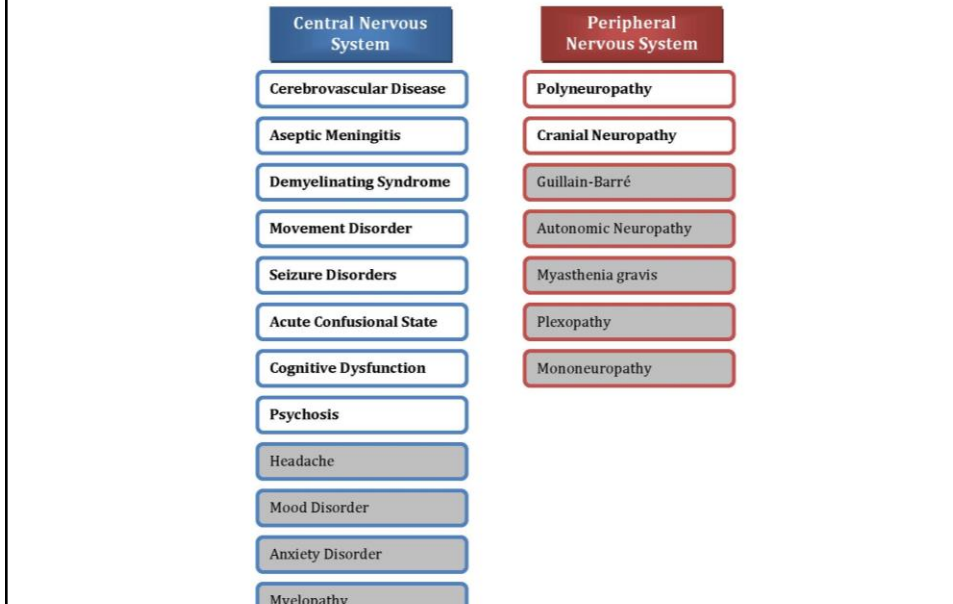
Structural "mimics": Syringomyelia, myeloradiculopathies

Step 2: Define the spectrum of peripheral nervous system manifestations of SLE and Sjogren's syndrome

Many of the peripheral neurological complications of SLE and Sjogren's syndromes, traditionally listed in classification criteria, are sufficiently rare and should be regarded as the manifestation of a distinct and co-incident autoimmune disease.

Figure 2: Utility and Limitations of the 1999 American College of Rheumatology Nomenclature & Case Definition of Neuropsychiatric Systemic Lupus Erythematosus (SLE)

(a.) Current Case Definitions



Step 3: Define the spectrum of the peripheral neuropathies occurring in SLE and Sjogren's syndrome

When rigorously assessed and corroborated using appropriate ancillary testing, peripheral neuropathies have been described between 1 and 10 percent of SLE and Sjogren's patients.

In SLE, approximately 40 percent of peripheral neuropathies will be attributable to non-SLE causes

In Sjogren's syndrome, most neuropathies will be attributable to underlying Sjogren's syndrome

Characteristics of axonal polyneuropathies and mononeuritis multiplex in SLE versus Sjogren's syndrome (SS)

Clinical Pattern	Axonal Polyneuropathies	Mononeuritis Multiplex
Association with disease activity	SLE and Sjogren's: Lower disease activity	SLE and Sjogren's: Higher disease activity
Association with disease-specific autoantibodies and immunological markers	SLE: No Sjogren's: No	SLE: No, but likely reflect mechanisms of ICD Sjogren's: Yes Cryoglobulinemia (type II and type III, Anti-RF, and low C4
Therapy	Contextualized in background of disease activity	Immunosuppressive therapy

Small-fiber neuropathies in SLE and Sjogren's syndrome

A painful neuropathy, frequently described as burning, which targets thinly myelinated A-delta or unmyelinated C-fiber nerves

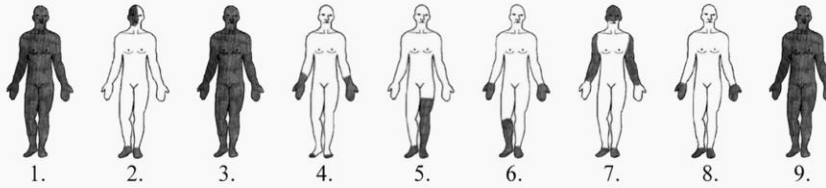
Electrodiagnostic studies are normal!

Require further diagnostic techniques such as a punch skin biopsy

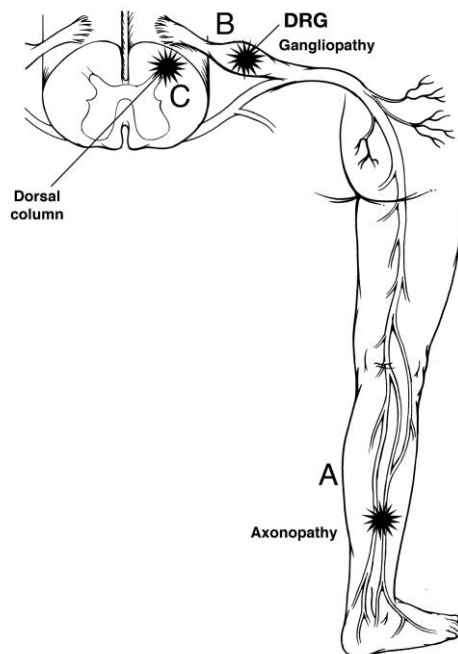
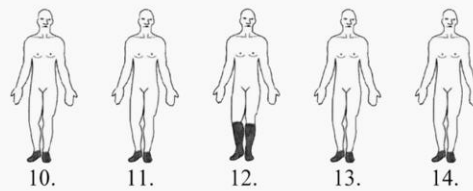
With characterization using skin biopsy studies, small-fiber neuropathies may be as frequent as axonal neuropathies in both SLE and Sjogren's syndrome.

There are two subtypes of SLE small-fiber neuropathies

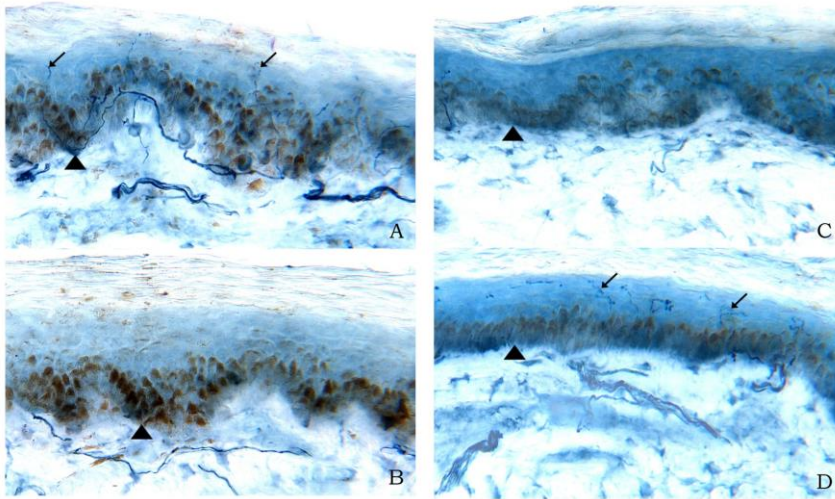
Non-length-dependent, small-fiber neuropathy



Length-dependent, small-fiber neuropathy



The role of skin biopsy in evaluation of small-fiber neuropathies



Summary of PNS manifestations of SLE and Sjogren's syndrome

Importance of identifying competing co-morbidities not due to rheumatic disease: Use the **VITAMINS** mnemonic.

Immunosuppressive therapy warranted for mononeuritis multiplex, but rarely for axonal polyneuropathies.

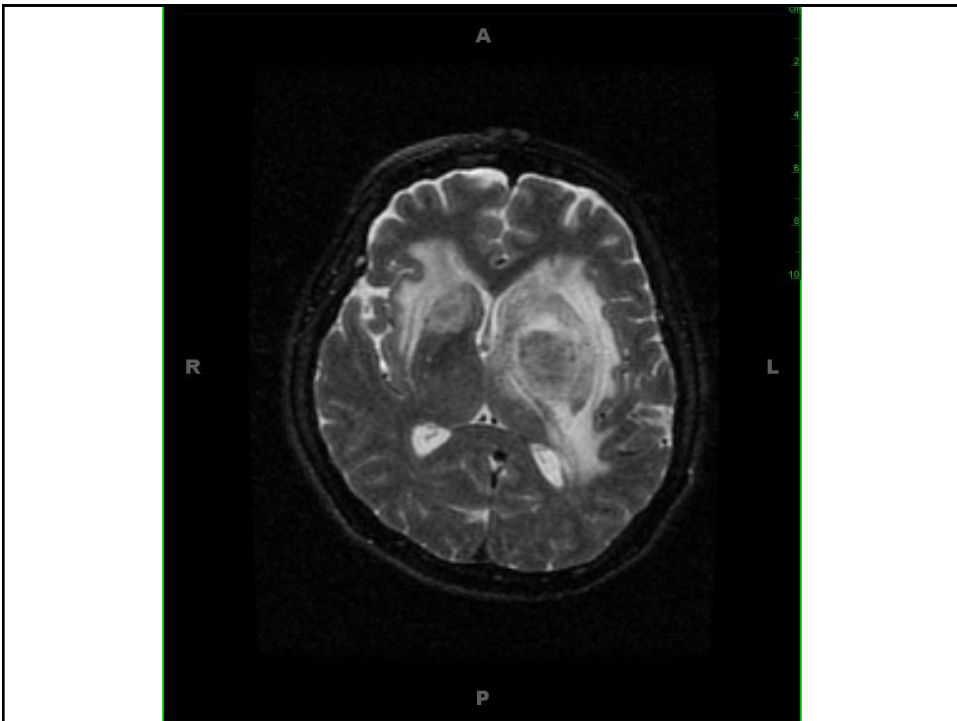
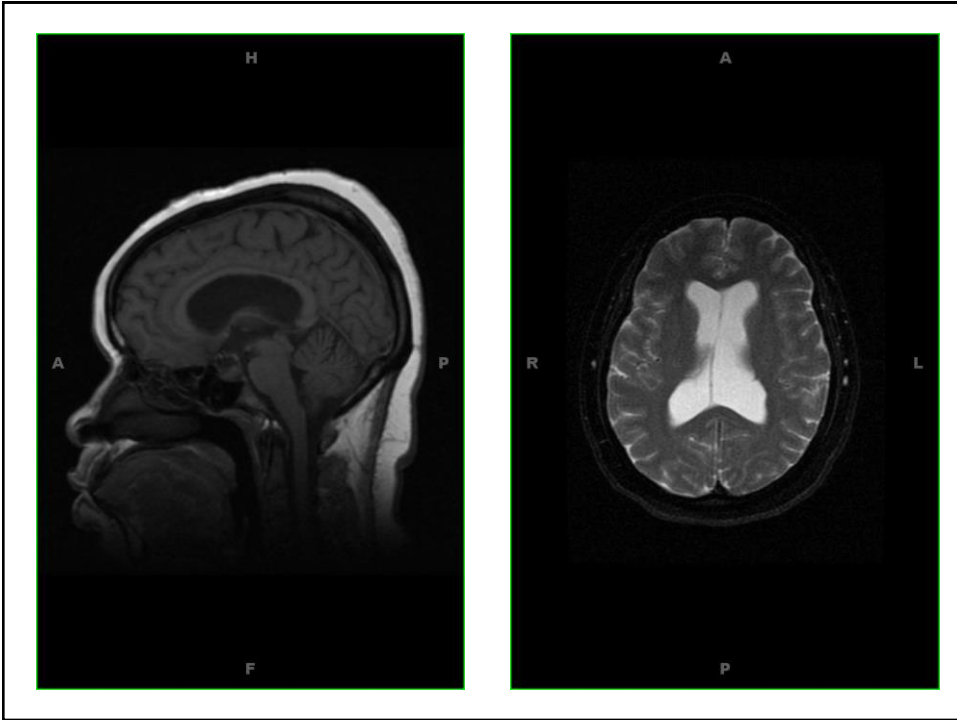
Small-fiber neuropathies are under-recognized

Neuropathic pain without an underlying neuropathy may be a distinct, immune-mediated entity, and warrants identification of novel antibody biomarkers

NEUROPSYCHIATRIC LUPUS

Specific objectives with regard to CNS NPSLE

- (1) Develop a diagnostic approach in the evaluation of CNS syndromes which occur in SLE patients
- (2) Attribute CNS syndromes as due to SLE versus an alternative co-morbidity by once again utilizing the VITAMIN mnemonic
- (3) Understand when to institute immunosuppressive versus symptomatic therapies.
- (4) Use this framework to approach the CNS manifestations of Sjogren's syndrome



Step 1: Identify whether a CNS syndrome is attributable to SLE versus non- SLE causes

Take home point: Always suspect that neurologic disease in a SLE patient is not due to underlying SLE disease!

Between 33% and 50% of SLE patients will have a CNS syndrome which is not due to SLE

Be appropriately paranoid about the lurking possibility of an infection!

Step 1: Use of the VITAMIN mnemonic to develop a differential diagnosis for CNS NPSLE syndromes

Vascular/-strokes: Septic emboli, subarachnoid hemorrhage from mycotic aneurysms, septic thrombophlebitis

Infections

Classification as due to etiology (i.e. Bacterial, fungal, virus)

Classification as due to anatomic region

 Parenchymal: Abscess, parameningeal extension of meningitis

 Meningeal/meningitis

 Vascular: Septic emboli or thrombophlebitis

Traumatic: As per general population

Metabolic: Uncommon. Hyperhomocysteinemia, B12 deficiency

Autoimmune: Other autoimmune or inflammatory syndromes.

Iatrogenic complications: Metabolic (corticosteroids), infections (immunosuppressive) therapy

Neoplastic

Diagnostic strategies which are suggested by using this VITAMIN mnemonic

Routine serological studies (i.e. evaluation for uremia as a cause for encephalopathy or seizures)

Infectious workup which may warrant lumbar puncture studies

Neuroimaging studies: CT scan to exclude a hemorrhage. MRI studies to evaluate for focal disorders (i.e. stroke or abscess), or for multi-focal disease

Diagnostic-specific modalities for distinct CNS disorders (i.e. EEG in the evaluation of seizures)

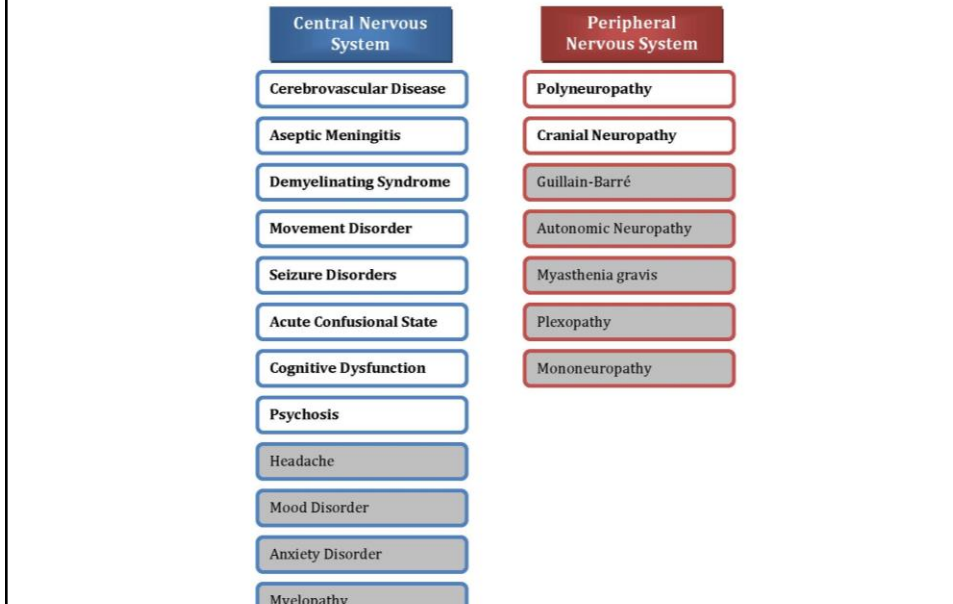
Step 2: Consider the specificity of a particular CNS syndrome for NPSLE

Is a given CNS syndrome specific for SLE versus non-disease controls?

What are limitations of the current ACR NPSLE nomenclature and case definitions for CNS NPSLE?

Figure 2: Utility and Limitations of the 1999 American College of Rheumatology Nomenclature & Case Definition of Neuropsychiatric Systemic Lupus Erythematosus (SLE)

(a.) Current Case Definitions



Limitations of the ACR NPSLE case definitions, and implications for diagnostic care

The following CNS syndromes included in the ACR case-definitions are non-specific, are seen with similar frequency in non-SLE controls, and in **most** cases can be evaluated and treated as if an SLE patient did not have SLE

Headache
 Mood disorder
 Anxiety disorder
Mild cognitive impairment

Epidemiological studies might have limitations when applied to an individual SLE patient

A SLE patient may infrequently have a “non-specific” NPSLE syndrome, which in the appropriate clinical context may still be sculpted by SLE-specific etiopathogenic mechanisms

Examples:

“Lupus headache”

Depression with unusual catatonic features, or exquisite intractability

Can occur, but is exceedingly uncommon

When to institute immunosuppressive versus symptomatic therapy for CNS NPSLE?

Early-onset SLE (<2 years into SLE disease course)	Later-onset SLE (>2 years into SLE disease course)
Associated with higher, extra-neurological SLE activity	Associated with lower, extra-neurological SLE activity
Associated with cumulative organ disease, in the context of SLE activity	Associated with cumulative organ disease, in the context of SLE damage
Immunosuppressive therapy may be warranted for extra-neurological SLE activity	Immunosuppressive therapy not warranted.
Neurological disease more likely to remit, and not require prolonged symptomatic therapy	Neurological disease more likely to persist, and require prolonged symptomatic therapy
Immunosuppressive therapy rarely is warranted for isolated manifestation of CNS disease	Immunosuppressive therapy rarely is warranted for isolated manifestation of CNS disease

Characterization of distinct CNS
manifestations of NPSLE

MYELITIS IN SLE

Is this a singular diagnostic entity?

In SLE, there are two distinct subtypes of myelitis which have recently been defined, which are *never* seen in MS.

Gray-Matter Myelitis	White-Matter Myelitis
Defined by “gray-matter” clinical findings of flaccid paralysis and hypo-reflexia at time of initial examination	Defined by “white-matter” clinical findings of weakness, spasticity, and hyper-reflexia
Hyper-acute onset, evolution to paraplegia in minutes to hours	Acute to sub-acute onset, hours to days/weeks or even months
Associated with highly active SLE	Associated with lower SLE activity
Monophasic	Polyphasic
Increased frequency of anti-dsDNA antibodies	Associated with Ro/SS-A, lupus anticoagulant, and NMO-IgG antibodies
CSF profile indistinguishable from bacterial meningitis	More modest pleocytosis and elevation of total protein
Uniformly poor prognosis of irreversible paraplegia, unresponsive to immunosuppressive strategies	May be responsive to immunosuppressive strategies

Can we prevent catastrophic venous hypertension in gray-matter myelitis?

9 patients sought medical attention, either through PMD or in ER, complaining of inability to void!

Severity: Ranging from subjective complaints of difficulty voiding, to having bladders with greater than 1 Liter of post-void residual!

In animal models of spinal cord ischemia, earlier vulnerability of nuclei affecting micturition compared to sensorimotor tracts

Therefore, unexplained inability to void in a patient with highly active SLE should be recognized as a sign of impending “spinal cord herniation” (i.e. the anatomic equivalent of a blown pupil!), and patients should immediately be treated with pulse intravenous steroids

Gray-matter and white-matter myelitis have clinical features which are **never** seen in MS.

SLE gray-matter myelitis likely represents venous infarction

Recognize unexplained urinary retention as a potentially treatable prodrome

CSF findings indistinguishable from bacterial meningitis

Treatment: 1000 mg IV Solumedrol, while empirically covering for bacterial and viral meningitis meningitis.

White-matter myelitis is a demyelinating entity with some features of NMO/NMOS, and require immunosuppressive therapy at time of first attack.

Cerebrovascular disease

Prevalence of 5 to 15 percent of SLE patients.

VITAMIN mnemonic to exclude infections and other non-SLE causes!

Small-vessel lacunar strokes>embolic strokes>hemorrhagic strokes

For embolic strokes, need to particularly consider Libman-Sacks endocarditis.

Stringent control of “modifiable” risk factors

The lupus anticoagulant is more strongly associated with increased risk of thrombotic events, compared to anticardiolipin or beta-2-glycoproteins

Seizures

Occurs in 5 to 20 percent of patients.

Is particularly important to consider vascular, infectious, metabolic, and structural causes in the VITAMIN mnemonic!

Seizures <2 years into SLE disease may be associated with high extra-neurological SLE disease activity, and eradication of extra-neurological SLE activity does not usually require prolonged anti-epileptic therapy

Seizures >2 years into SLE course are more likely to be associated with SLE "damage," is less likely to remit, and has a higher risk to require ongoing anti-epileptic therapy

Cognitive impairment

Occurs in up to 80 percent of SLE patients

May be present at time of SLE diagnosis in 60 percent of cases!

Is not associated with disease activity, and improves over time.

Therefore, SLE patients should be reassured they don't have a progressive dementia.

Screen for other etiologies of cognitive impairment, including depression, pain, and hypothyroidism.

Depression is the most strongly associated covariate, and may emerge as a modifiable risk-factor.

Psychosis

May occur in up to 5 percent of patients

Need to be especially vigilant to consider syndromes encapsulated in the VITAMIN mnemonic, including infection!

A frequent diagnostic conundrum is whether psychosis is due to high SLE activity, or due to high-dose corticosteroids used to treat SLE activity.

Once extra-neurological, SLE activity has been quenched, it may be necessary to empirically lower the dose of Prednisone, and see whether there is any clearing of the sensorium.

Central nervous system manifestations of Sjogren's syndrome

Specific objectives: The CNS manifestations of Sjogren's syndrome

Using a similar approach taken in the CNS manifestations of NPSLE, define the clinical spectrum of what constitutes the CNS manifestations of Sjogren's syndrome

Contrast mechanisms of NPSLE versus SLE, to further refine the spectrum of Sjogren's CNS disease

Winnowing the spectrum of what constitutes CNS Sjogren's syndrome

Similar to CNS NPSLE, headache, mood disorder, anxiety disorder, and mild cognitive impairment is likely not more frequent in SS patients, versus non-diseased controls

In contrast to NPSLE, a CNS vasculopathy has not been consistently demonstrated to be a mechanism of CNS Sjogren's

Therefore, focal syndromes such as seizures and strokes are not increased in SS patients, compared to other non-SLE rheumatic diseases

Therefore, if we remove non-specific, “diffuse” CNS syndromes and such focal disorders, what is the residuum of CNS Sjogren’s disease?

(1) Cognitive impairment: Well-characterized in cohort studies

(2) Aseptic meningitis,

(3) Acute confusional state;

(4) Movement disorders:

Described mainly in case-reports, and clinicians may need to determine on a case-by-case basis whether there are unusual features which suggest an immune-mediated basis

:

Do I have a progressive, neurodegenerative disease similar to Alzheimer’s disease?

There is a characteristic “**A**” pattern of deficits seen in “cortical” dementias

Aphasia, Acalculia, Apraxia, Alexia, Agraphia: Can be assessed on MMSE

This is not what Sjogren’s patients convey when they describe “brain fog”

Instead, there is a “sludging” of thoughts, difficulty multi-tasking, etc.

The absence of “**A**” deficits means that Sjogren’s patients have *subcortical* versus *cortical* impairments in cognitive functioning

Take home points about cognitive impairment in Sjogren's patients

Sjogren's causes subcortical impairment: MMSE is extremely limited

Symptoms of brain fog are associated with **objective** subcortical findings on neuropsychological testing and functional imaging

Not a progressive, neurodegenerative disease!

Fatigue and pain are correlated with selective domains of subcortical impairment, and further studies are warranted to evaluate whether these represent modifiable risk factors.

Demyelinating Syndromes in Sjogren's syndrome

How to distinguish CNS manifestations of Sjogren's (and other rheumatic diseases) versus MS.

The differential diagnosis of brain lesions in SLE and Sjogren's patients

A 25-year old patient with Sjogren's syndrome presents with multi-focal, evanescent sensory symptoms, which intermittently affects the face and extremities,

Neurological examination is unrevealing.

A brain MRI reveals multiple, subcortical white-matter and periventricular lesions.

"In a patient with SLE syndrome, the differential diagnosis includes vasculitis, Lyme disease, anti-phospholipid syndrome, migraines, and demyelinating disease."

Next diagnostic steps?

Next diagnostic steps:

Spinal Tap

MRI on a 3-Tesla Magnetic

Evaluate for disseminated disease, by performing spinal cord MRI

Evaluate for disseminated disease, by performing Visual Evoked Potential

But in this context, is there an additional diagnostic test which has greater utility than alternative strategies

TELL HER TO TAKE A BATH!

SERIOUSLY!

Demyelinating syndrome in rheumatic disease

For patients to have a demyelinating syndrome, they must have clinical evidence of a demyelinating syndrome

Not enough for vague or otherwise unexplained neurological symptoms

Perform clinical correlate of bath-tub tests.

Optic neuritis?

Myelitis?

Brainstem syndrome?

Cerebellar syndrome?

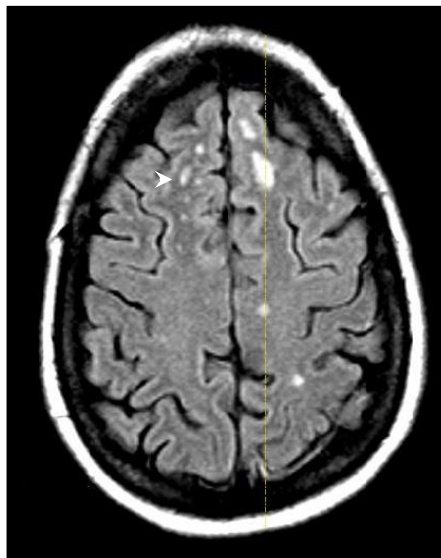
How to distinguish brain and spinal cord lesions in MS from Sjogren's syndrome or from SLE.

First, perform the clinical correlate of a bathtub test! Is there any clinical evidence that the patient has ever had a demyelinating disease?

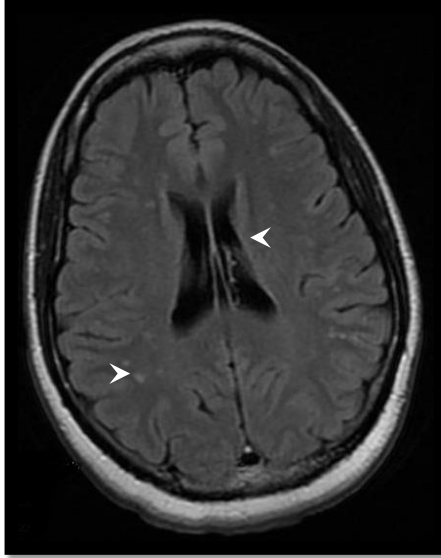
Secondly, can review with interpreting radiologist whether brain lesions satisfy the **Barkhoff criteria**, which have relatively high specificity for MS versus other CNS diseases, and can serve as a surrogate marker for multi-focal CNS dissemination

What follows is such a radiographic potpourri of how to distinguish brain lesions occurring due to MS versus a primary rheumatic disease such as SLE or Sjogren's syndrome

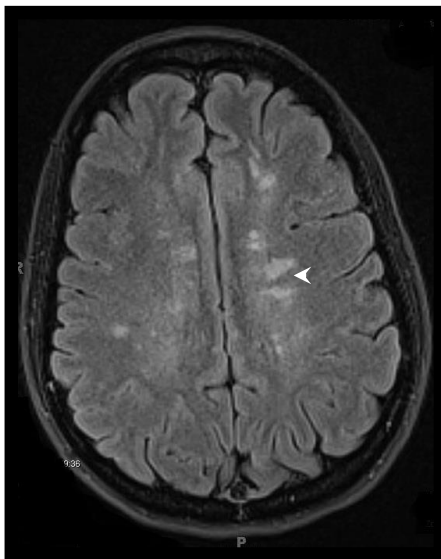
This pattern of T2 hyperintense, ovoid frontal lesions could *potentially* be consistent with MS



But in MS, you wouldn't see this pattern of periventricular sparing



MS Periventricular lesions which radiate perpendicularly from the ventricular surface: "Dawson's Fingers"



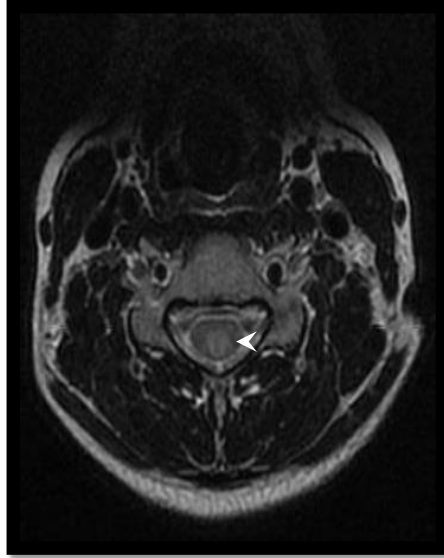
Dawson's Fingers



“Non-specific” periventricular lesions: Seen commonly in Sjogren’s patients, but unfortunately is commonly ordered when patients don’t meet threshold of a “positive” bath-tub test



“Transverse” Myelitis: Can be seen in MS and Sjogren’s



What is neuromyelitis optica (i.e. NMO), also known as Devic's syndrome?

A distinct diagnostic entity from MS, and which has been described in cohorts of SLE, Sjogren's syndrome, and other rheumatic diseases

Similar to MS, is defined by optic neuritis and myelitis

However, have **longitudinally-extensive** myelitis, which is more than 3 vertebral segments, and consequently more clinically severe than MS

Similarly, optic neuritis may be bilateral and more clinically severe

Is associated with a specific, antibody marker which targets aquaporin-4, also known as the "NMO-IgG antibody"

In Sjogren's syndrome, most cases of optic neuritis or myelitis will have features more consistent with Neuromyelitis Optica (NMO), instead of MS

Variables	NMO	MS
Clinical features of myelitis	Motor>sensory	Mainly sensory
Radiographic extent of spinal cord lesions	More than 3 vertebral segments	Less than 3 vertebral segments
Prognosis of untreated disease after 5 years	50% blind or wheelchair-bound	100% ambulatory
Presence of specific serum biomarkers?	Yes, including the NMO-IgG antibody	No

Diagnostic distinction of demyelinating syndromes occurring in rheumatic disease patients versus MS

Clinical equivalent of a bath-tub test, with patients needing to have clinical evidence of a demyelinating disease.

Two subtypes of SLE gray-matter versus white-matter myelitis, never seen in MS.

Most Sjogren's patients with demyelinating disease will have clinical and radiographic features more consistent with NMO rather than MS.

Only rarely will Sjogren's patients have brain lesions with distribution and morphology of MS lesions (i.e. Barkhoff criteria)

Summary of neurological complications of SLE and Sjogren's syndrome

CLINICAL PHENOTYPES=MECHANISMS!

Use VITAMIN mnemonic to distinguish between SLE/Sjogren's versus a competing comorbidity.

Small-fiber neuropathies are under-diagnosed and require skin-biopsy studies.

Neuropathic pain without peripheral neuropathic pain may be a distinct, immune-mediated entity, and requires further anti-neuronal biomarkers

Most SLE and Sjogren's patients have demyelinating syndromes which can be clinically and radiographically distinguished from MS.

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